Image-Guided Stereotactic Radiosurgery

High-Precision, Non-invasive Treatment of Solid Tumors

Harun Badakhshi

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Preface

Image-Guided Stereotactic Radiosurgery: High-Precision, Non-invasive Treatment of Solid Tumors provides an overview on current strategies and available technologies for the treatment of patients with solid tumors, as well as for cranial benign lesions, for primary early-stage cancer, and for cancers with oligometastases. The term oligometastases refers to those cancers that have a limited metastatic capacity, thus a limited volume, number, and occurrence site of metastases.

A decade of work in this field, including clinical routine, scientific investigation, interdisciplinary communication, and targeted publications, was a plausible reason and the motivation for writing this book. The text is a frozen moment of data streams and informational flow that characterizes this highly innovative field of clinical activity and scientific inquiry.

The book is not claiming to cover the entireness of current options of image-guided stereotactic radiosurgery. It is, indeed, based on what is done in the routine of clinics and has really been executed at the moment, in 2016, in large- and middle-sized medical centers in the Western hemisphere and large parts of Asia and Latin America. It should present merely a snapshot of options on how to treat patients with benign and malignant solid tumors by means of a safe and effective non-invasive method that is also verifiably cost efficient.

The text might orient the reader toward possible and realistic options that might, or might not, have valid high-quality scientific evidence base. It is neither a discussion of all likely options nor a prediction of all future perspectives, just a snapshot of the reality.

Technology does not exist for the sake of technology; in the realm of clinical medicine, it has to serve implicitly and explicitly the care of individual patients.

Concepts of conservative and progressive strategies of care get implemented by their intrinsic coherence and rational structure and indeed by the base of scientific evidence, or they get lost in translation.

Image-guided stereotactic radiosurgery as a dedicated technique had been used for a long time. These forerunner technical formats of stereotactic radiosurgery were used in an empiric way. While imaging technologies like computed tomography, magnetic resonance imaging, and especially positron emission tomography emerged and consecutively spread widely, more details in the trajectory of tumorous lesions became apparent. In parallel, the emergence and apperception of new

insights into the complex biology of cancer, metastases, and benign lesions changed the situation.

This coincidence of technologic advancements in imaging methods as well as real transformative shift in image-guided stereotactic radiosurgery technologies with the groundbreaking developments in biology of tumors generally and of cancer with limited metastases especially was the momentum.

Formally, I structured each chapter according to the identical criteria of data validity and information quality of fully published papers. That means that basic assumptions of evidence-based medicine are respected and reproduced so far as they could apply. Simultaneously, it is not a dogmatic and static adoption of a theory but rather a dynamic contextualization of best available literature according to the current practices in the clinics. Any search in the databases, like PubMed and ScienceDirect, was performed systematically and repetitively with identical and consistent criteria that were based on clinical practice and investigational background.

My colleagues of different disciplines such as neurosurgery with Dr. Martin Misch and Professor Peter Vajkoczy, thoracic surgery with Dr. Mahmoud Ismail and Professor Jens Rückert, pulmonology with Professor Christian Witt, and radiation oncology with Dr. David Kaul, Dr. Pirus Ghadjar, Dr. Reinhold Graf, and Professor Wust, to whom I owe a lot, have influenced positively my way of clinical thinking and scientific acting.

I would particularly like to thank Professor Volker Budach, the chairman of my former and formative department, who made clinical radiation oncology as a true cross-section oncologic discipline at the Berlin University's Charité School of Medicine and taught us to be valid and dependable partners in the care of our patients.

And I have to express a huge portion of gratitude to Professor Horst Bredekamp from Humboldt University Berlin, a globally well-recognized art historian and image theoretician, for his inductive thoughts in personal communication and, through his extensive research, how images became operational agents and how imaging became action.

Berlin, Germany Harun Badakhshi

Contents

Part III Radiosurgery for Cancer and Its Metastases

About the Book

This book provides the reader with a detailed update on the use of stereotactic radiosurgery (SRS) in patients with lesions of the brain and other parts of the body. The aim is not simply to explain the application of SRS and document its value with reference to the author's own clinical experiences and other published evidence, but also to contextualize the technology within a new strategic concept of cancer care. When embedded within an appropriate conceptual framework, technology becomes pivotal in changing therapeutic strategies. A new paradigm that is increasingly impacting on clinical practice is the oligometastatic state, on the basis that long-term survival might be achieved in patients with a low volume and number of metastatic lesions. This book accordingly addresses the value of SRS in patients with oligometastases of solid tumors to the brain, lung, spine, and liver. In addition, it examines the use of SRS in patients with diverse brain lesions, early-stage lung cancer, liver cancer, and early-stage prostate cancer. Readers will be persuaded that SRS, using cutting-edge imaging technologies to deliver precisely targeted radiation therapy, represents an exciting non-invasive procedure that holds great promise for the present and the future of cancer care.

Fig. 1 Image-guided oncology I. Monitoring during treatment

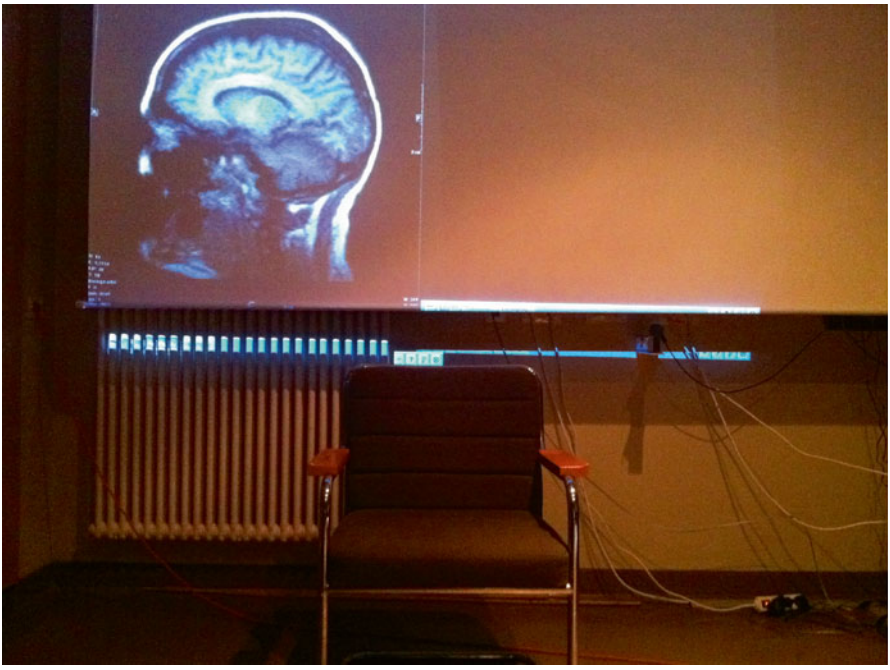

Fig. 2 Image-guided oncology II. The essential void

Abbreviations

AVM	Arteriovenous malformation
BM	Brain metastases
BT	Brachytherapy
CRT	Controlled randomized trial
CK	CyberKnife technology
EBRT	External beam radiotherapy
GK	Gamma Knife technology
IGRT	Image-guided radiotherapy
IMRT	Intensity-modulated radiotherapy
LINAC	Linear accelerator technology
LoE	Level of evidence
LoE Ia	Level of evidence from systematic reviews of randomized controlled trials
LoE Ib	Level of evidence from individual randomized controlled trials
LoE 2a	Level of evidence from systematic reviews of cohort studies
LoE 2b	Level of evidence from individual cohort studies and low-quality randomized controlled trials
LoE 3	Level of evidence from case–control studies
LoE 4	Case series, poor-quality cohort or case–control studies
LoE 5	Expert opinion
NSCLC	Non-small cell lung cancer
PA	Pituitary adenoma
Patients (f/m)	f for female and m for male. In terms of gender mainstreaming
RT	Radiotherapy
RCT	Radiochemotherapy
RCT	Randomized controlled trial
SRS	Stereotactic radiosurgery
SABR	Stereotactic ablative radiotherapy, just another name for SRS
SBRT	Stereotactic body radiotherapy, just another name for SRS
Stage I or II	Stage I or II according to UICC
VS	Vestibular schwannoma
WBRT	Whole brain radiotherapy

Part I

Premises and Context

Introduction

1

Image-guided high-precision stereotactic radiosurgery is a leading and transformative technology in the care of patients (f/m) with solid tumors; this is indeed true for malignant primary cancers and their metastases; while they are limited in volume, number, and occurrence site, it is accurate to state that it is effective and safe also for a variety of benign lesions, especially in the brain and in the base of the skull.

Furthermore, it is important to emphasize at the beginning of this book that stereotactic radiosurgery is explicitly a noninvasive intervention, implicitly supported by image guidance techniques, that could achieve in a vast majority of cases similar, thus equivalent clinical outcome comparable to conventional open surgery or to the so-called minimally invasive surgery.

It has been serving as a niche technique for decades, 1960s–1980s, in dedicated and specialized medical centers with interrelated radiotherapy and neurosurgery departments. The real and long-lasting clinical focus was, at least for the first phase technology of Gamma Knife, on benign cranial lesions or functional intracranial disorders. It should suffice to note that stereotactic radiosurgery primarily was used in a highly pragmatic, empiric setting and with a utilitarian modus operandi. This instance was, among other factors, due to the more mechanistic understanding of the procedures by the protagonists and due to the less developed diagnostic tools available in the period of the 1960s–1980s.

The emerging diagnostic imaging technologies of the 1980s–1990s as they are computed tomography and magnetic resonance imaging, and their widespread availability, have altered the way invasive and noninvasive procedures were executed. Images and imagery changed in a determinant way not only diagnostics but, with more sustainable effects, the interventions.

Interventions, peculiarly noninvasive procedure like stereotactic radiosurgery, became more sophisticated by the advancement at large in computer sciences and informatics, microelectronics, signal technology, material research, and, later on, fundamental transitions in image guidance techniques.

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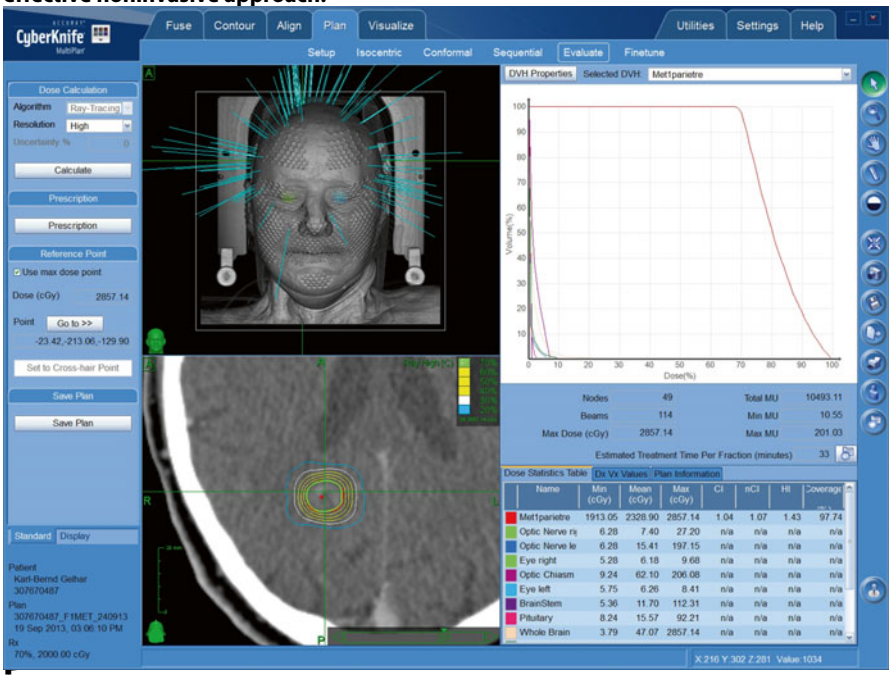
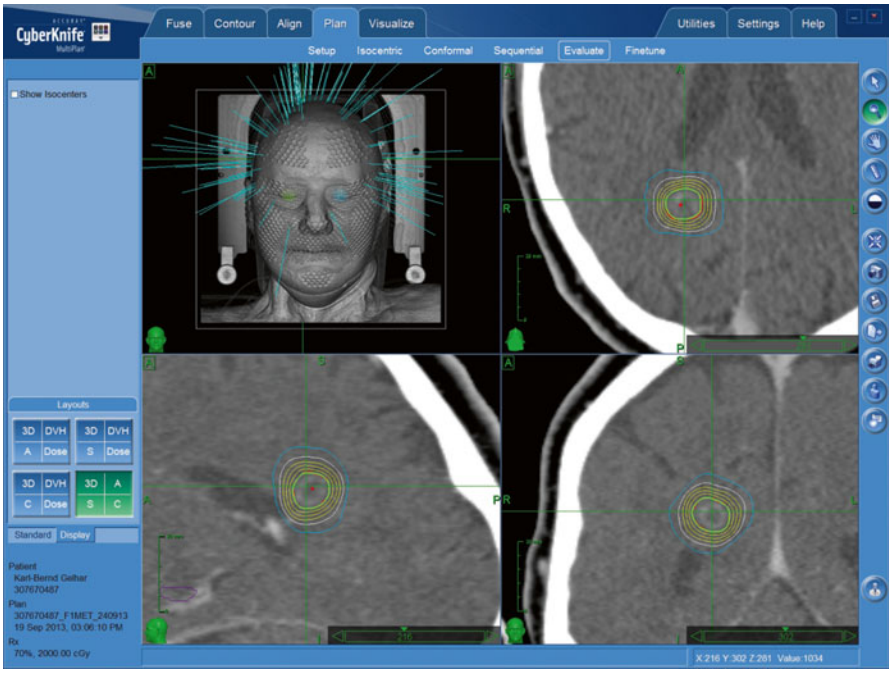
Today, in 2016, image-guided stereotactic radiosurgery in all its technical appearances and in its conceptual context is proved to become, in its essence as a noninvasive, safe, and highly effective method, a innovative approach in treating patients (f/m) with solid tumors. We investigate here with a critical regard the scientific base of image-guided stereotactic radiosurgery.

Cancer challenges medicine more than ever. This is true for lesions in the brain and base of the skull that are benign by histology but behave aggressively.

Radiation oncology as a cross-sectional discipline belongs juxtaposed to invasive surgical arsenal and, in collaboration with systemic drug treatment, to the triad of active agents in the care of patients (f/m) with tumors.

The principle responsiveness of tumorous lesions to the radiation is the empiric and scientific base of radiotherapeutic procedures. The merit of any radiotherapy lies in achieving a significant local control of the tumor, while it is applied in a safe and effective noninvasive approach.

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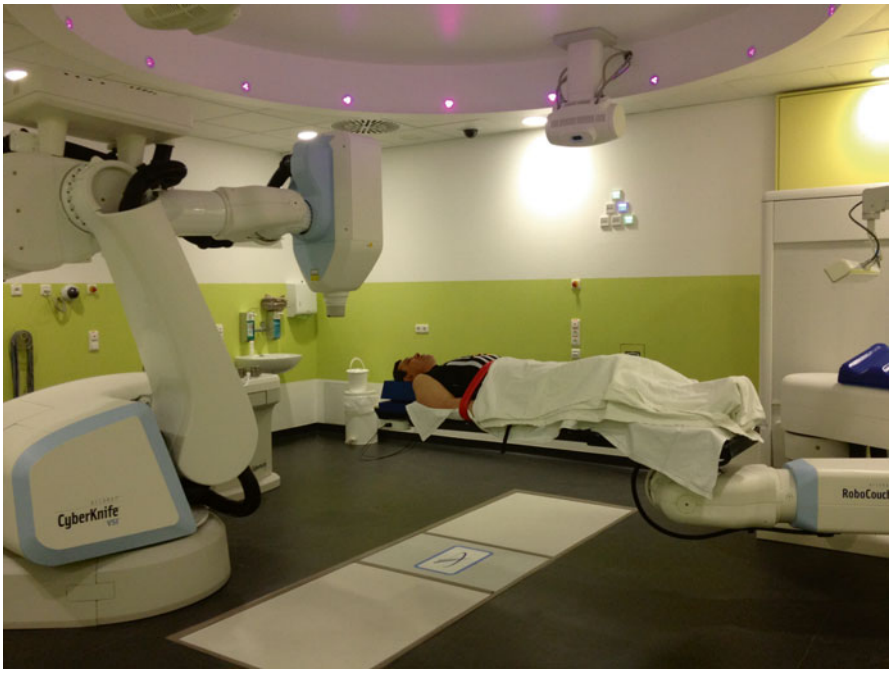
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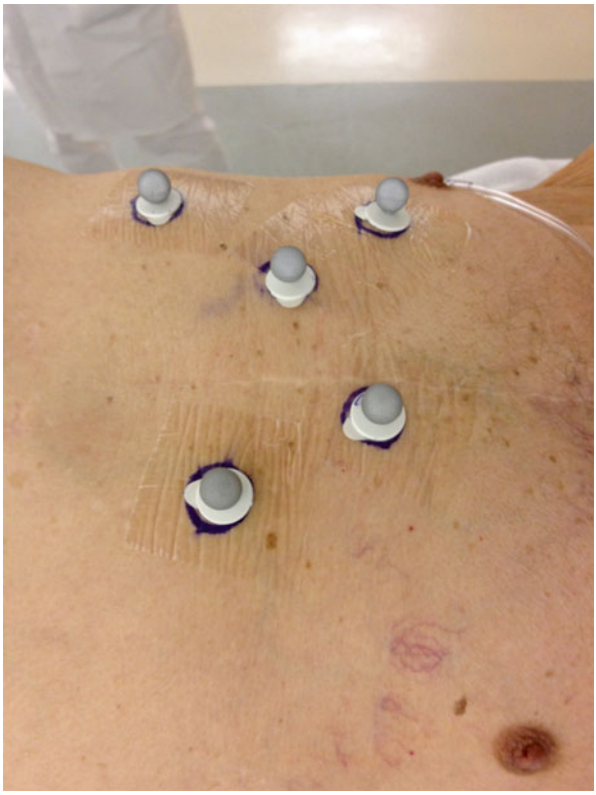

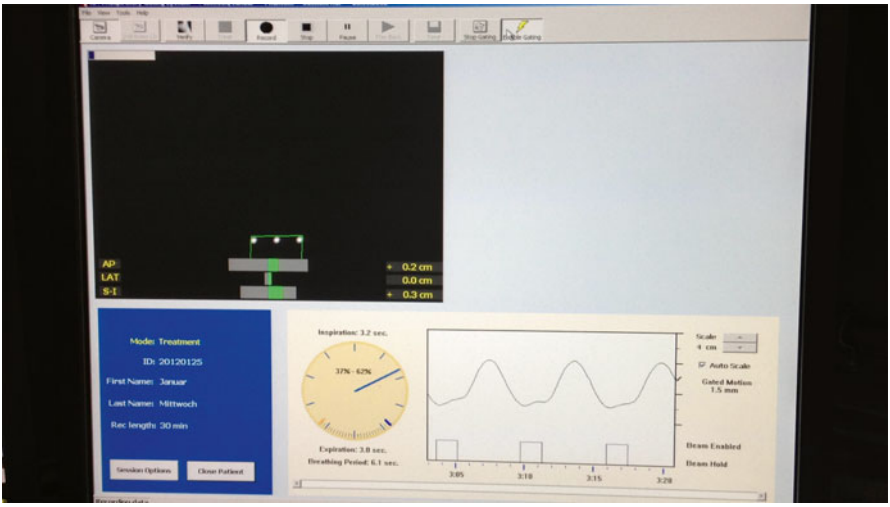
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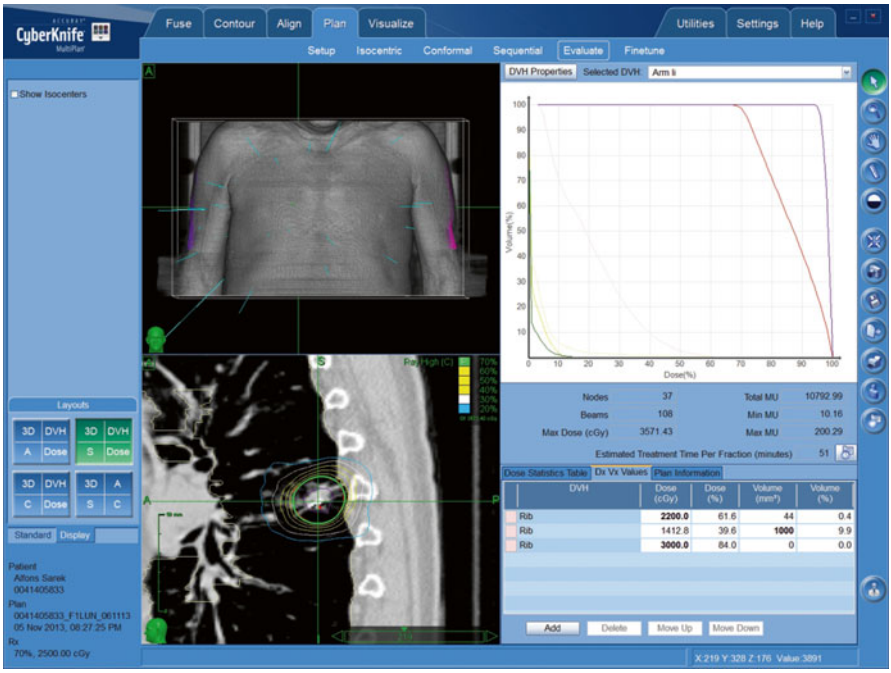
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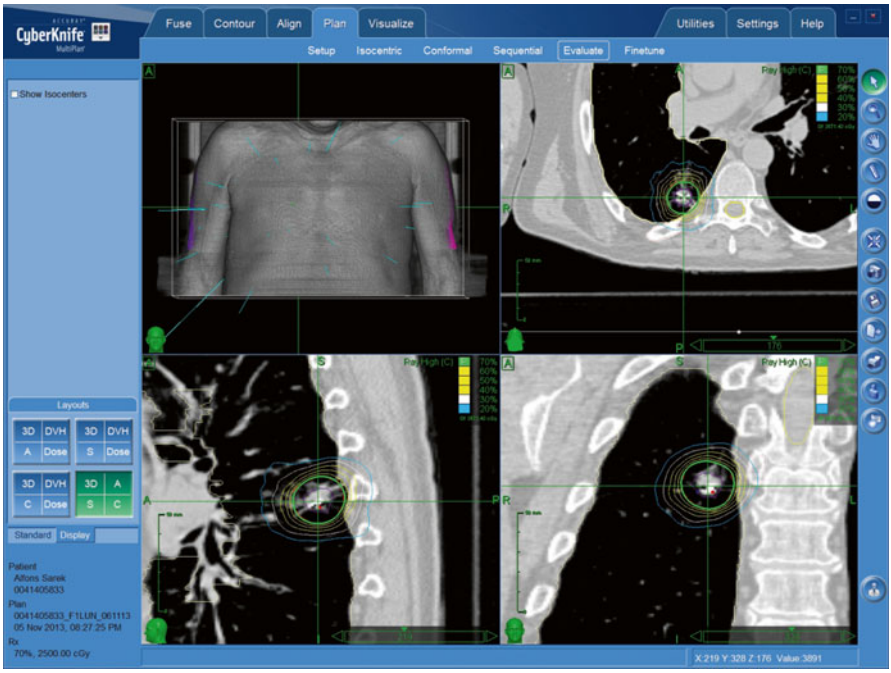
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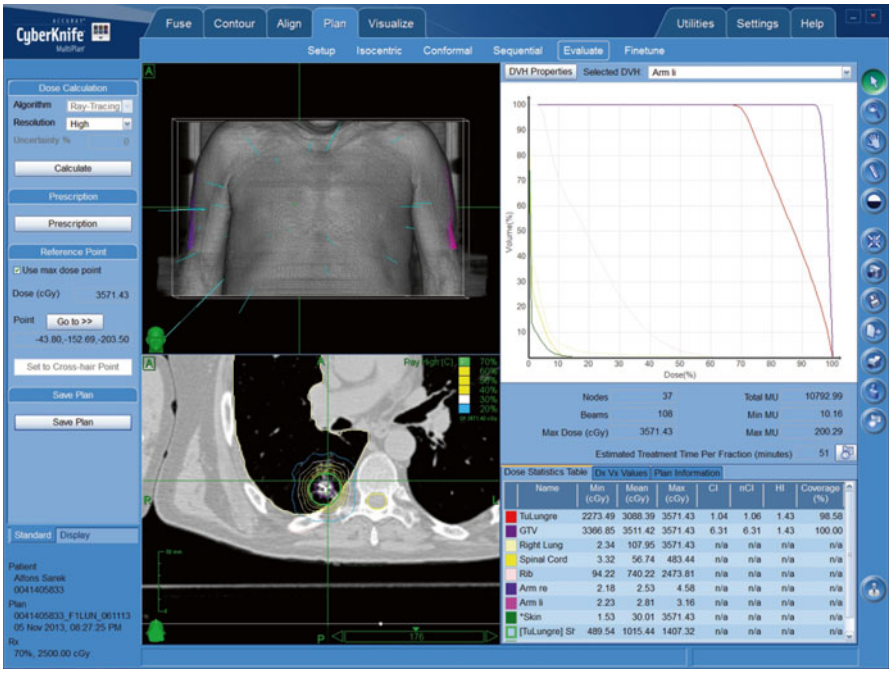
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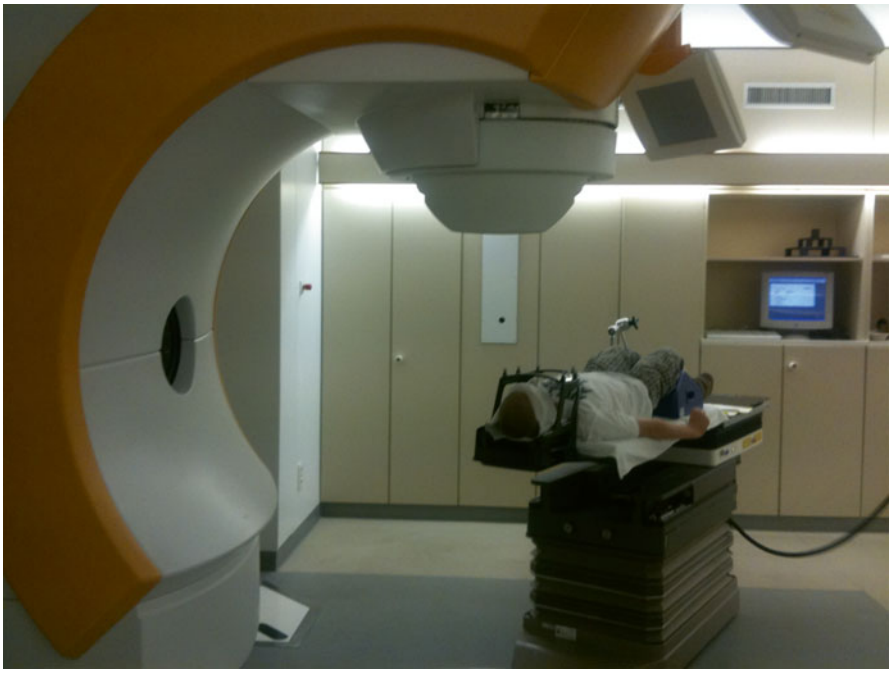


Conceptual Context

2

Abstract

Technology without a coherent concept is merely a tool, an apparatus. This might be, at some stage of its usage, from a benefit to humans; or, indeed, it might harm individual.

Medical technology used without a concept that is rational, empirically reproducible, and verifiable by clinical outcome does not fit to primary ethical premises of physicians.

Cancer with limited metastatic capacity, clinically apparent as metastases, limited by volume, number, and occurrence site, has been called as oligometastases. The concept of "oligometastatic state," introduced in 1995 by Dr. Samuel Hellman, as an intermittent state in the trajectory of cancer diseases presents a new understanding of cancer in the dialectics of cure and palliation.

Oligometastases react to high-dose radiation by stopping their growth. High doses of radiation could be given safely when image-guided stereotactic radiosurgery is executed. Here comes the epistemic cross section or the coincidence of technology and strategy.

Image-guided stereotactic radiosurgery with its multiple labels like stereotactic ablative radiotherapy (SABR) or stereotactic body radiotherapy (SBRT) could affect tumorous lesions by deactivating tumor cells. Consecutively, it demonstrates a noninvasive high-precision and safe technique in treating patients (f/m).

H. Badakhshi, *Image-Guided Stereotactic Radiosurgery*,
DOI 10.1007/978-3-319-39189-2_2

Theory

In the absence of a coherent concept, technology is merely a tool, apparatus, or, more concisely, a contrivance. At some stage of its use, it might represent a benefit to humans; at another stage, it might harm humans.

This idea is true in two respects.

First, this idea is related to the following statements: "Technology is a means to an end" [1] and "technology is a human activity" [1]. Martin Heidegger, the last eminent German philosopher, stated that the utilization of machines, the "used things themselves," and the "need and ends they serve, all belong to what technology is… Technology itself is a contrivance, or, in Latin, an instrumentum" [1]. Heidegger summarized this concept as follows: "The current conception of technology, according to which it is a means and a human activity, can therefore be called the instrumental and anthropological definition of technology" [1].

Technology as a *means and as an activity* refers as to two domains that are intrinsically related.

As a *means*, tools often have an inherent equipment-like functionality, and we also tend to understand them in the context of technical detail. In this context, there remains a will to master and control technology as a *means* to a specific and outlined end.

As a *human activity*, technology induces curiosity about real exertion scenarios that we not only aim to interpret but also, and more importantly, to apperceive empirically [2]. We aim to use technology to solve a proper, concrete problem. Heidegger's attempted explanation in his seminal essay, "The Question Concerning Technology," concluded with the assumption that any technology is first and foremost a revelation of the reality of the world. Thus, the a priori essence of technology is not technical.

Second, any scientific and, in particular, interventional medical activity must be embedded in a specific conceptual framework. This individual conceptual framework enables scientists and physicians to act legitimately under more or less well-defined circumstances in a therapeutic scenario. At a basic level, a recent, traceable body of scientific evidence is needed when using interventional technology in a therapeutic scenario. In other words, our example of stereotactic radiosurgery does not merely concern the technology in and of itself. As stated above, our example concerns the specific conceptual framework that must demonstrate a body of scientific evidence that could legitimize the use of stereotactic radiosurgery in specific medical scenarios. The contrivances and device setup epistemically and urgently require medical concepts, technical plausibility, and, more importantly, a rationale.

In fact, a rationale does exist for the use of stereotactic radiosurgery within a very confined conceptual framework. This concept is solid when visualized through an epistemological lens and currently indicates a pivotal shift in clinical medicine. This concept has been given the name "oligometastatic cancer." The term oligometastases [3] is related to the seeding of a limited number and volume (and thus a limited tumor burden) of metastases of a primary tumor in another tissue structure or organ that are. This may occur synchronously with the primary tumor lesion or consequently after an event such as primary treatment comprising surgery or radiation [3, 4]. We will later return to the details of this concept.

Practice

In fact, metastases are the main cause of death in cancer patients, especially when these metastases are widespread throughout the body, thus affecting multiple structures or organs. This condition is generally described as poly- or multi-metastasized cancer. Clinically, single or multiple organ failure is the most significant cause of death, especially when accompanied by acute infections, complex inflammation, bleeding, and advanced age, all of which render physiologic compensation extremely challenging.

A brief review of the twentieth century discourses and disputes on cancer is necessary in order to understand the historic development and epistemological characteristics [5] of the "oligometastases concept." A few significant epistemological categories must be recapitulated here to contextualize the stories that will be presented later in this text.

Gaston Bachelard, an eminent historian and philosopher of science and a true rainmaker in the vein of Carl Popper, introduced the notion of *discontinuity* of scientific knowledge in the vivid disputes of science and progress that had occurred since the 1940s. A "continuist premise," which presumed a monistic linear fashion, had dominated the philosophy of science for more than a century from August Comte to Emile Meyerson; simultaneously, heavy weight was given to the enduring "science does not think" dispute, of which Martin Heidegger stated: "Science does not think and cannot think; indeed, that is what constitutes its chance" [6].

Bachelard underscored his main ideas using two intertwined notions, epistemological break ("rupture épistémologique") and epistemological obstacle ("epistemological obstacle"), which have been shown to determine each other's processing and to be constitutive for all scientific knowledge typologies. He subsequently employed practical examples to visualize this concept.

A certain specific body of evidence within the realm of scientific knowledge may begin to separate from or contradict an existing common-sense belief system and experience of space that correlates with an object or object collection. This *rupture* is constitutive for upcoming events and processes and determinative for a new and distinctive cognitive structure. The *break* intervenes in the normal realm of experiences by replacing objects of scientific experience with another regimen of categories and axioms that lead to new type of interactions and correlations not yet available to common-sense perceptions. Such breaks apply not only to traditional experiences in a certain area of knowledge but also to ruptures in previous scientific theories in the same area of knowledge. He named it a "new scientific spirit" [7].

A break event suggests that something must be shattered to overcome a hindrance. Bachelard introduced the notion of an obstacle to explain issues of resistance within a given theory complex, doctrine, or highly specialized community dedicated to older concepts and experiences. An obstacle is any tool, mechanism, or discourse that prevents an upcoming and inevitable break. Primarily, common sense is a significant origin of such epistemological obstacles. Bachelard visualized the movement of scientific progress in the dynamics of breaks and rejected stabilities and the overcoming of obstacles.

Although Georges Canguilhem further elaborated this concept, perhaps the work of Michel Foucault has best demonstrated the importance of this concept by extending it beyond the strictly scientific domain employed by Bachelard and Canguilhem. Foucault described epistemological breaks not only in the history of medicine but also in the histories of prisons, sexuality, and psychiatry. Discontinuity thus became a main epistemological category that led to a large array of scientific concepts, particularly with regard to medicine and a greater focus on cancer.

Multiple concepts regarding cancer and its trajectories were presented in the last century. Few have survived enduring academic discourse; these have thus far demonstrated a basic scientific rationale accompanied by sophisticated investigational data and, more importantly, convincing clinical outcomes. Interestingly, the twentieth century was predominated by two major epistemic shifts in cancer concepts.

One likely source of these shifts was Stephen Paget's work on metastases, which was published in 1889 in the *Lancet* [4]. In that work, he assumed a complex relationship between the host organ of the primary tumor lesion and the distant organ to which the tumor had spread at some time in its trajectory; this "theory of the relation between the embolus and the tissues which receive it" was labeled as the "seed and soil theory." Although this Lancet text was a revolutionary inception with a concise but reductive statement, this was a primordial concept rather than the result of solid and valid investigations.

In the 1890s, an impactful scientific evolution was initiated along the East Coast of the USA. This evolution influenced cancer concepts throughout the next century.

In 1894, Dr. William Halsted from Johns Hopkins University Hospital proposed an empirical approach to the evident clinical problem of the distribution of secondary cancer growths, which was later described as process of metastasizing [8]. Dr. Halsted, an innovator in the fields of medicine, surgery, and clinical oncology, outlines his procedures and understanding for a broader medical audience in the *Annals of Surgery* [9]. In subsequent years, he insisted on the postulate "that cancer of the breast in spreading centrifugally preserves in the main continuity with the original growth" and that "the dissemination probably takes place by way of the lymphatics not by the blood-vessels-and the disease holds together without important interruptions" [10, 11]. This marked the birth of the theory of continuity, postulated by Dr. William Halsted, which endured for almost 90 years.

A century later in 1994, Dr. Samuel Hellmann, another innovator at large in the field of breast cancer research, critically summarized the Halsted paradigm in a lecture given in memoriam of David A. Karnofsky [12], writing: "underlying premise is that breast cancer is an orderly disease that progresses in a contiguous fashion from primary site, by direct extension, through the lymphatics to the lymph nodes, and then to distant metastatic sites. It implies that effective treatment must recognize this orderly, contiguous disease spread" [12].

The possibility of attempting a breast-conserving surgical procedure was not widely considered during that lengthy time period [13, 14].

In an overlapping time period that ranged from the end of the 1960s to the 1980s, multiple researchers undertook huge investigational efforts to understand the

biology of breast cancer because and/or despite many theoretical and practical pitfalls of the Halsted paradigm.

In 1980, Dr. Bernard Fisher of the University of Pittsburgh in the USA summarized his excellent scientific work, which was based on a large body of factual results from in vitro experiments and preclinical studies, as well as multiple prospective clinical trials conducted by the National Surgical Adjuvant Breast Project (NSABP) under his leadership, in a significant lecture given in memoriam of David A. Karnofsky [15]. This lecture contained groundbreaking data and, more importantly, long-lasting and influential conclusions. In this historic lecture, Fisher formulated an "alternative hypothesis" of breast cancer biology. Referring to Halsted's very pragmatic concepts of breast cancer behavior, Dr. Fisher stated his new alternative as "diametrically opposite to those considered to be 'Halstedian'" [15]. His arguments were firm, solid, and consistent and demonstrated "that (a) regional lymph nodes do not trap disseminated tumor cells, (b) there is no orderly pattern of tumor cell dissemination based upon temporal and mechanical considerations, (c) patterns of tumor spread are not solely dictated by anatomical considerations but are influenced by intrinsic factors in tumor cells as well as in the organs to which they gain access, and (d) regional lymph node cells are capable of destroying tumor cells" [15].

Fisher labeled his highly innovative work as an "alternative hypothesis." According to Hellman in his Karnofsky lecture some years later, hypothesis "suggests that breast cancer is a systemic disease and implies that small tumors are just an early manifestation of such systemic disease, which, if it is to metastasize, has already metastasized. Nodal involvement is not an orderly contiguous extension, but rather a marker of distant disease" [16].

This rigorous and rich lecture given by Fisher significantly altered the understanding of various aspects of the natural history of breast cancer. Unfortunately, Dr. Fisher combined his "adventure" with a number of speculative conclusions. The most dogmatic and, from an epistemological perspective, most inconsistent assumption was the notion that "operable cancer is a systemic disease" and, and more dramatically, that "variations in locoregional therapy are unlikely to substantially affect survival" [15, 17].

This marked a major step toward a shift in breast cancer treatment strategies. A large-scale, epistemic, and tectonic movement occurred in breast cancer management. This held true even for the so-called breast cancer industry, which initially included emerging markets in the Western hemisphere and later expanded to a global market for the distribution of chemotherapeutic and other systemic drugs that aimed to fight breast cancer according to the "systemic paradigm."

Meanwhile, a large array of solid clinical observations, which had accumulated since the 1970s, suggested the existence of a subgroup of cancer patients that survived metastatic cancer. The key clinical feature of this subgroup was the existence of "few metastases" (oligo), in other words, metastases that were limited in volume and number. This feature was independent of the primary treatment, primary tumor location, and even histology.

Dr. Samuel Hellmann explained this phenomenon thusly: "A third hypothesis considers breast cancer to be a heterogeneous disease that can be thought of as a

spectrum of proclivities extending from a disease that remains local throughout its course to one that is systemic when first detectable. This hypothesis suggests that metastases are a function of tumor growth and progression. Lymph node involvement is of prognostic importance not only because it indicates a more malignant tumor biology, but also because persistent disease in the lymph nodes can be the source of distant disease. This model requires that there are meaningful clinical situations in which lymph nodes are involved but there has not yet been any distant disease. Persistent disease, locally or regionally, may give rise to distant metastases and, therefore, in contrast to the systemic theory, locoregional therapy is important" [16].

Furthermore, Dr. Hellmann analyzed the particular theoretical details in his lecture. He concluded "this end of the century reflection on the natural history of small breast cancers then brings a synthesis to the contiguous-systemic dialectic. Both have some truth, but adherence to either alone is inadequate. The satisfactory synthesis recognizes both, within a spectrum in which for small tumors the disease is usually restricted to the primary tumor site with the possible involvement of a limited number of regional lymph nodes. Larger tumors are more likely associated with systemic disease when first observed" [16]. He additionally made a more general statement: "Halsted became dogma and, more recently, the notion of breast cancer always being systemic has become dogma. Like all dogma in science, both are too restricting. They tend to limit our inquiries and deny the conditional and approximate nature of scientific knowledge" [16].

After extending the action radius of the spectrum paradigm into specific laboratory and clinical research of different types of cancers, in 2011, Hellmann and his coresearcher Ralph Weichselbaum, who both remained in Chicago, published a critical review of the accomplished and unfinished goals of their work. At this time, exhaustive laboratory and clinical data were collected to prove the principle of oligometastatic cancer or cancer with oligometastases. The authors concluded "the metastases that we define as oligometastases have long been recognized as potentially curable but were considered to be rare exceptions to the cancer metastasis paradigm. However, the oligometastatic state is becoming more frequently identified with more-sensitive methods of detecting such oligometastases" [18]. More practically, the "data suggest a potential stepwise progression with intermediate stages of limited metastatic capacity. It seems quite possible that metastases from tumors with such limited capacities might be separated from those much further along in malignant progression. If this seems possible, then clinicians will be able to limit ablative local treatment to only those patients with true oligometastases" [18]. The accumulation, analysis, and review of data have become widespread since 2012. In this context, the author of this book has contributed a small piece of the grand puzzle.

Epistemological Coincidence

For a long time, *stereotactic radiosurgery* has been an emerging technology in the treatment of both malignant and benign brain lesions. When embedded in a conceptual framework, however, this technology gains a solid and valid clinical meaning in the context of strategies for the highly sophisticated treatment of brain and body

Table 1 A selected series of stereotactic radiosurgery for indications other than the brain

Study (*n*)	Site of treatment	Primary tumor site	Dose/fractions	Local control (in %)	Comments
Jereczek-Fossa (2014) (*n*=69)	Oligometastases to lymph node region	Renal cell, prostate, colorectal, breast	24/3	64.3	G 3 toxicity in 2 cases
Navarria (2014) (*n*=76)	Oligometastases to the lung	Colorectal and others	60/3 peripheral,< 2 cm 48/4 peripheral 60/8 central	3-y: 89	G 1 in 80 % of cases
Milano (2012) (*n*=121)	Oligometastases to Liver, lung, lymph nodes and other	Breast, colorectal and other	50/10	6-y: 65	G 3 in 1 case
Wang (2012) (*n*=149)	Oligometastases to the spine	Renal cell, breast, lung	27–39/3	2-Y: 72.4	G 3 in 6 cases
Casamassima (2012) (*n*=48)	Oligometastases to the adrenal gland	Lung, colorectal, and others	36/3	2-y: 90	G 2 in 1 case
Shipani (2012) (*n*=124)	Oligometastases to the spine	Lung, prostate, and others	18/1	a-y: 92	No toxicity greater than G 1
Greco (2011) (*n*=103)	Oligometastases to the spine, lymph nodes Soft tissue	Lung, prostate, and others	18/1	a-y: 92	No toxicity greater than G 1
Rusthoven (2009) (*n*=47)	Oligometastases to the liver	Colorectal and others	36–60/3	2-y: 92	G 3 in 1 case
Norishi (2008) (*n*=34)	Oligometastases to the lung	Colorectal, and others	48/4 60/5	2-y: 90	G 3 late less than 4 %

lesions. Furthermore, stereotactic radiosurgery has become a good example of an *epistemological coincidence* [19], a notion that contains the following implications (Table 1):

First, a primarily technique emerges at a giving time out of urgent clinical necessity. Stereotactic radiosurgery had emerged in the early 1970s as a consequence of pioneering work of a team of curious researchers who came from the first line of clinical medicine; in the case of Dr. Leksell and colleagues, it was neurosurgery.

Second, it establishes its peculiar practical standing within a specific field during a period of decades. It still remains a technique with the status of pragmatic solution for clinical challenges.

In the mean time, new technologies rise in the background and independently, as it was the case for computed tomography and, later on, magnetic resonance imaging. There has been in the first decade no real interlacing between stereotactic radiosurgery and the new imaging technologies in terms of direct cause and effect relationship. Using computed tomography and, later on, magnetic resonance imaging for the purposes of execution of stereotactic radiosurgery happened, again, following practical necessities and technical improvements, rather than a deliberate and pointing entangling of two different technologies.

Third, pioneering theoretic concepts rise in a relative isolationism to the scientific ecologies as they are cancer and metastases research. This was the case for Dr. Samuel Hellman's idea of oligometastases that he declared in 1995. A small minority of investigators took notice from the pivotal work the team of Dr. Hellman did at this time. And the rise of the theoretic concept was independent to the preexisting techniques as it was stereotactic radiosurgery, because of its peculiar epistemic status. Astonishingly, the emergence of the new concept was even more related to laboratory research work than to the digital imaging technologies of computed tomography and magnetic resonance imaging that was in the process of establishing themselves within the realm of clinic.

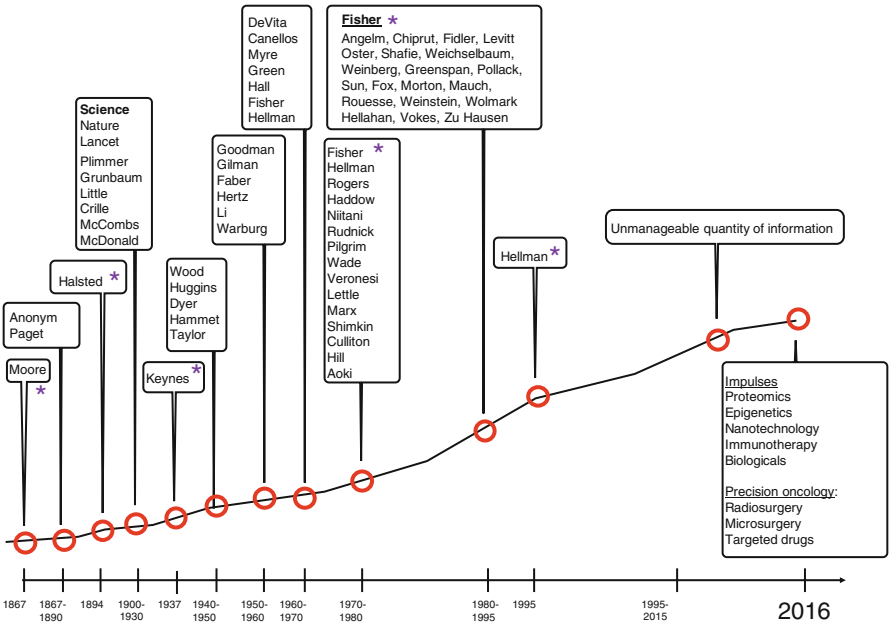
To sum up the prehistory of this unique episode of *epistemological coincidence* [19], stereotactic radiosurgery was implemented in the 1970s as a technique without any epistemic connotation, merely as a technical solution.

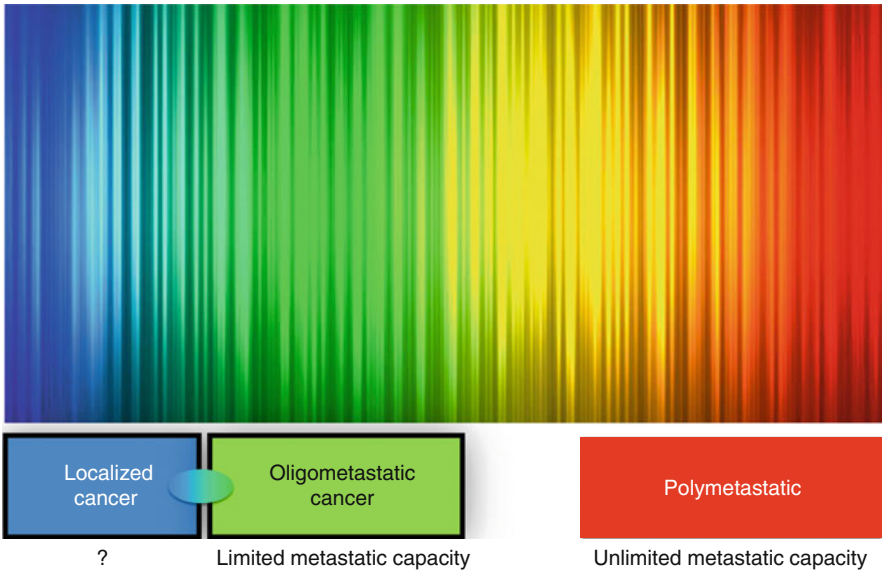
A decade later, digital imaging technologies came up in the 1980s and widespread and transformed clinical medicine during the 1990s. One large-scale effect of new imaging tools was the groundbreaking change in detection and monitoring cancer and its treatment. Almost at the same time, at the mid-1990s, in which digital imaging expanded its operating range, the idea of the existence of a fundamentally different state in the trajectory of cancer was born: the oligometastatic state, described by Dr. Samuel Hellman.

Today the *epistemological coincidence* [19], encompassing stereotactic radiosurgery, digital imaging media technologies, and the hypothesis of "oligometastatic state," instantiates in the reality of the clinic after the convergence of three essentially heterogeneous fields of scientific and practical enquiry.

Substantive better imaging allows to understand cancer's natural history and to detect metastatic lesions earlier and make them allocatable to a noninvasive

method, the image-guided stereotactic radiosurgery that enable oncologists to target oligometastatic lesions with a high degree of reproducible precision; and, finally, there is a consistent concept which makes the "theory of oligometastatic state" as a special compartment of cancers with limited metastatic capacity the object of a process for proofing the principle. This is how science works.





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Methodic Remarks

3

Abstract

This book would like to provide orientation in a rapidly expanding and changing field of clinical activity and scientific inquiry.

This book is *not covering the entireness* of all options to execute noninvasive image-guided stereotactic radiosurgery.

Formally, any search in the databases like PubMed and Science Direct was performed systematically and repetitively with identical and consistent criteria that come from the clinical practice and investigational background. Meeting abstracts and preliminary data are excluded. That means that basic assumptions and rules of the evidence-based medicine are respected and reproduced so far they could apply.

With regard to contents, all clinical chapters are kept, in terms of reproduction, very close to the original papers and their content. It was not my aim to write a formally new prose or to paraphrase, but to mirror the each author's specific view and concrete interpretation, respectively.

Levels of Evidence and the Magnitude of Data

Evidence-based medicine has been the more rational and most plausible approach to the huge and almost unquantifiable body of knowledge available to date. This is true in special regard to the experiences of individual physicians, including their educational background, reading habits, and cognitive predispositions; and it is true when one focuses on collaborative collectives like multidisciplinary tumor boards with their specific group dynamics and horizontal but still complex hierarchies, as the author of this book experienced for more than a decade.

H. Badakhshi, *Image-Guided Stereotactic Radiosurgery*,
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Evidence-based medicine, simultaneously, has been misunderstood as a "box of prefabricated guidelines" [1, 2] that presumably ignores preferences of doctors (f/m) and patients (f/m) and the real-world conditions. The most eminent of any version evidence-based medicine focuses first on "best available evidence" in firm conjunction with physicians' experiences, which must be adjusted to the patient's values and preferences after informed consent.

There are no dogmatic edicts of evidence-based medicine ruling what patients (f/m) and their caregiver have to do rather than individualize treatment for individuals according to the treatment ecology.

We, therefore, go along with the basic principles of evidence-based medicine that grades knowledge by levels of evidence I to V, in order to systematically draw near "best available data" as shown in Table 3.1, without being caught or guided by them.

The selection of literature was based on the decision that should enable the reader to order the validity, plausibility, and thus the quality of the available references selected in this book.

This, so my suggestion, would help to get an impression of the firmness of arguments and of the robustness of individual and collective clinical guidelines for a good clinical practice. Furthermore, it helps to say to the patient (f/m) what is really at stake for her/his individual case.

Regularly, references merely of the last 5 years are quoted in terms of keeping the reader up to date, including more technological and conceptual transformations and, simultaneously, giving her/him the option to read older literature by reading widely available full texts published from 2010 to 2015 quoting studies published earlier than 2010. Where the availability was not sufficient, data elder than 5 years are included.

In each chapter, especially where specific references are quoted, the selection criteria are mentioned. Generally, there will be a "selection pattern" which is based on, first, effectiveness and safety of the treatment; second, the global availability of the machine type for a large population in developing economies and emerging markets, therefore the global option of a giving concept; and, third, not only the number of patients (f/m) but the quality of reports that has been determining the selection process.

Table 3.1 Levels of evidence

Level of evidence	Type of interventional study
1a	Systematic review of randomized controlled trials
1b	Individual randomized controlled trial
2a	Systematic reviews of cohort studies
2b	Individual cohort studies
3a	Systematic reviews of case–control studies
3b	Case–control studies
4	Case series, poor quality cohort, and case–control studies
5	Expert opinion

Formally, we structured each chapter according to the identical criteria of data validity and information quality of published full papers. Meeting abstracts and preliminary data are excluded. That means that basic assumptions and rules of the evidence-based medicine are respected and reproduced so far they could apply. Simultaneously, it is not a dogmatic and static adoption of a theory rather than a dynamic contextualization of best available literature according to the current practices in the clinics. Any search in the databases like PubMed and Science Direct was performed systematically and repetitively with identical and consistent criteria that come from the clinical practice and investigational background.

Terminology and Reaching Out to the Audience

Different terms have been used for the usage of the principles of radiosurgery for lesions of non-cranial anatomy, the so-called body stereotactic procedures.

At the beginnings, presumably in the mid-1990s, it has been called "extracranial radiosurgery." The purpose was, purely, to introduce a newness that was neither a new technology nor a new strategy, but it had been performed for new anatomical sites.

Then, after some years, the label "stereotactic body radiation therapy," acronymized as "SBRT," came up.

This was not really an innovative idea, and it was not a sophisticated strategic move toward other disciplines and patients. It produced and it is producing more confusion than clarity to both groups mentioned.

In case we would intent to embed the principle of "stereotactic radiosurgery" (SRS) within other valid and useful oncologic therapeutic strategies, it would be better to fix one inherently logical category as the term "stereotactic radiosurgery" truly is and to use it consistently.

The intrinsic logic of this format of naming or labeling remains obscure, as if the word "body" is something essentially different than the "head" (synonyms: brain, cranium, cranial), as if the head is not part of the body, and as if the body is outside of the "head." This name confusion seems, to me, to be part of our professional and epistemic distance from humanities, including philosophy and linguistics and social and, especially, cultural studies.

Again, the name "SBRT" that was given to radiosurgery was for the community of radiation oncologists an internal clarification and not a patient-centered activity or the attempt to be understood by other oncology-involved disciplines. "SBRT" did not entail the urgently needed collaborations of oncologists of all involved disciplines. Up to date, the term "SBRT" prevails in publications focused on stereotactic radiosurgery.

The next step in the trajectory of naming and labeling this technological principle that is simultaneously a therapeutic strategy is the introduction of "stereotactic ablative radiotherapy" acronymized by "SABR."

This is a recent move of the radiation oncology community to make things more difficult than they are. The adjective "ablative" should indicate the cell killing effects of stereotactic radiosurgery, a fact that we are aware of for many decades. The inherent problem in this new name could have been forecasted: it distracts from

the mode of conduct of stereotactic radiosurgery that is, essentially, coined as a high-precision image-guided procedure.

The usage of the last two descriptive notions in the current language of publications and conferences is equivalent.

We will use, nevertheless, the word stereotactic radiosurgery, acronymized by SRS, furthermore. This is necessary not only for reasons of consistency of the language used in this book; it is also a useful requisite for interdisciplinary communication in order to avoid more misunderstandings and more confusions.

Explaining Outcome Data by Texts and the Necessity for Tables and Graphs

So far we avoided too many tables and figures, not only that they believe that they visualize facts in a better way is not adequate in our opinion but because they distract from the text and its details embedded in the narrative. The author is convinced that too many tables, too many figures, are as contra-productive as it is to use the software "PowerPoint." All mentioned methods that had been useful at some time are simplifiers at large, which do not serve to the matter discussed in a text.

Personal Comment

What are personal comments?
They are exactly what they express to be, namely, all personal comments that are based on own academic involvement in giving specific and specialized activities. The reflection, which is allowed to be formulated, includes daily routine work also, meaning each physician (f/m) has to reflect on her/his daily work and experiences that accumulate during years.

Medical academia was till the end of the last century yet determined and embossed by eminence-based opinion makers, and, especially in various surgical disciplines, few people independent of their real skills and knowledge had the privilege of to be in authority and to sit on the right seat.

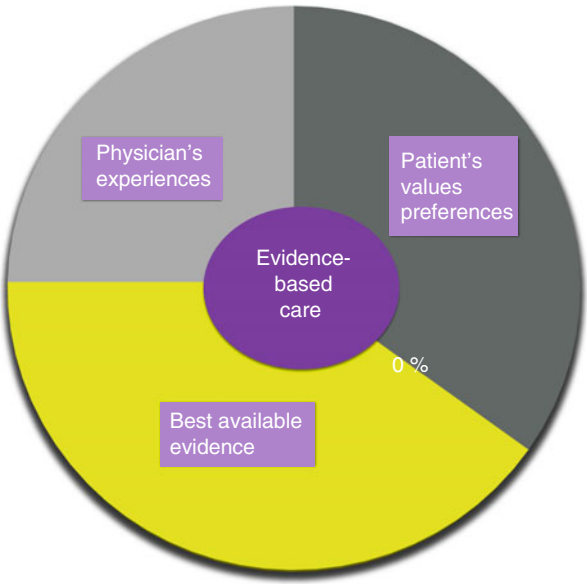
Evidence-based medicine had, then, changed fundamentally the rules. It took a long time to change the rules, written and not written rules, of communication, but it has been now, at least where the author of this book is working, namely, in Germany, another style of speaking and writing and, more importantly, another style of thinking.

The author's personal comments are comments based on her/his experiences and habits and her/his way of communication and basic principles of thinking and reflecting [2].

In the special case of this book, I put personal comments where it seemed to me to be relevant. Evidence-based medicine is not a dogmatic work-up box of rules, but a well-balanced mixture of best available scientific evidence and patient's (f/m) preferences, after receiving latest information on her/his condition, in combination with physician's (f/m) experiences. The latter is the reflection in its pragmatic version.

That is why I used personal comments as a means of communication and not as an ordinance. It is supposed to be understood as an additional stratum of reflection.

And it is indeed an attempt to prove Martin Heidegger, the most influential German grand philosopher of the twentieth century, wrong. He stated that "science is not thinking" (Lecture at Freiburg University at 1951/1952) and this is not legitimate when we do not start to reflect, at least, on a low level, seen from the perspective of philosophy and science theory.



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Radiobiological Postulates for the Effectiveness of Radiosurgery

4

Abstract

The expression of radiobiological hypotheses or clear-cut statements, particularly with regard to stereotactic radiosurgery (SRS), has stymied researchers for a long time. Since the first reported use of Gamma Knife technology in 1968, a wide range of postulates and theorems has been discussed within by a number of protagonists.

Basic research on the molecular effects of *fractionated radiotherapy* yielded a wide range of clinical research, including clinical trials, in the last three decades. Experts undertook huge laboratory experimentation and clinical studies to determine the real meaning of *fractionation* and its effects in clinical practice.

Regarding *single-dose effects*, history took an additional, significantly peculiar course. Clinical investigators have long examined the effects of this type of treatment. The development of postulates like "vascular damage" has to be understood. The role of five R's of conventional radiobiology must be seen differently in the light of the ablative effects of radiosurgery.

Explicitly, a consistent concept of the radiobiological legitimation of radiosurgery is urgently needed.

The expression of radiobiological hypotheses or clear-cut statements, particularly with regard to stereotactic radiosurgery (SRS), has stymied researchers for a long time. Since the first reported use of Gamma Knife technology in 1968, a wide range of postulates and theorems has been discussed within by a number of protagonists among the minority of radiation biology experts who have been involved in issues related to SRS and its molecular agency in tumors. This is true to both malignant and benign lesions.

H. Badakhshi, *Image-Guided Stereotactic Radiosurgery*,
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As a matter of fact, stereotactic radiosurgery refers to the method of delivery of irradiation with a high dose under specific conditions of treatment and technological setup of hardware and dedicated software.

Interestingly, from a science history perspective, a paradox dichotomy exists within the process by which radiobiology has emerged as a scientific discipline. One must assume the parallel existence of two fields of epistemic operations within a common realm that was later named radiotherapy and, subsequently, radiation oncology. The formation of one domain seems to have stymied the other, as if a discursive "obstacle" [1] ("L' obstacle épistémologique," a term introduced by Gaston Bachelard in 1938) had ceased experimental efforts in one field by favoring the other, although not predictable as always. Although this phenomenon is not rare in science history, it has claimed an astonishing epistemic position despite the highly sophisticated and inventive technological changes in the domain of SRS that occurred in the second half of the last century.

Basic research on the molecular effects of *fractionated radiotherapy* yielded a wide range of clinical research, including clinical trials, in the last three decades. Experts undertook huge laboratory experimentation and clinical studies to determine the real meaning of *fractionation* and its effects in clinical practice. These processes are ongoing and characterized by significant scientific intensity.

On the other hand, experimental research has occurred rudimentarily while maintaining a focus on the radiation effects of *single-dose* high-precision radiotherapy and has thus attempted to reveal the biologic essence of so-called radiosurgery.

A review of the history suggests that this epistemic condition is attributable to the lack of validated scientific theorems. From a historic viewpoint, one might claim that compared with single-dose methodology, fractionation research and practice was backed by a stronger lobby within the radiology/radiotherapy research community. In the following statements, I will succinctly summarize the evolution of ideas, theorems, and postulates that constitute our current base of knowledge. In brief, this section will present a distinctive science history of discontinuities and ruptures [1–3].

Regarding *fractionation effects*, researchers in the very early era of clinical radiation oncology observed that the delivery of multiple small doses, in contrast to the application of a single large dose, could effectively enhance tumor cell death. In such studies, tumors were irradiated with 20–70 small doses of 1.2–2.0 Gy over a defined period of weeks [4].

In his seminal work of 1975, Dr. Withers communicated the significance of the so-called four R's of radiation biology [5]: reoxygenation of the tumor, repair of sublethal damage, redistribution of cells in the cell cycle, and repopulation of treated cells. Another pioneer, Dr. Fowler, described in his denotative paper from 1989 a new model for calculating isoeffective doses for fractionated irradiation schemes: the so-called linear-quadratic formula (LQ model) [6]. Last but not least, in 1995 Dr. Brenner and colleagues issued a proposal for an extension of the LQ formula, with the notion of cell cycle redistribution and reoxygenation. The authors labeled this extension the LQ model, as it would enhance the utility of the LQ model [7].

These models and formula remain predominant and have directed clinical radiation oncologists who would subsequently attempt to legitimize the application of *fractionated irradiation* for patients with malignant lesions of the brain and body.

Regarding *single-dose effects*, history took an additional, significantly peculiar course. Clinical investigators have long examined the effects of this type of treatment. The development of theorems and postulates to investigate the possible effects of highly precise, stereotactically delivered radiosurgery is a dynamic and singular adventure. Many authors have not mentioned the historic implications and theoretical issues related to the *single-dose effect* in their writings, whereas a few others have included vague descriptions such as "recent years" or, more imprecisely, "last few decades" [8, 9]. A 2014 text in the *Journal of Clinical Oncology* summarized the deployment of SRS in a historical context by stating a classic example of a paradigm-shifting approach, but did not even mention any radiobiological statements [10].

Explicitly, a consistent concept of the radiobiological legitimation of SRS is urgently needed. SRS is actually neither a strategical nor a technological novel. This novelty, which in one sense is quite old (as demonstrated below), changed the landscape of therapeutic efforts. Reports of the development of SRS extend far back into the middle of the last century. In 1947, Ernest A. Spiegel and Henry T. Wycis of Temple University in Philadelphia began work on a stereotactic system intended to treat brain lesions and subsequently published a paper in science [11].

Prehistory of a Discourse

The technology currently recognized as classic SRS was the result of innovative work conducted in Uppsala and Stockholm in Sweden by Dr. Leksell, Dr. Larsson, and colleagues between 1950 and 1960 [12, 13]. Initially, Dr. Leksell used a cobalt source for SRS^{60}, and in 1968 he constructed a device for this purpose that was given the interesting name of Gamma Knife. This suggested that he had intended to replace surgical knifes with gamma radiation. Gamma radiation is part of the electromagnetic spectrum that exists without mass and is thus either a wave or photon. Co^{60} produces gamma radiation with two distinct energies that reflect two distinct radioactive breakdowns: 1.17 and 1.33 MeV. The most common type of interaction between gamma radiation and matter (e.g., body tissues) is based on the Compton effect. The aim of this method would be to "destroy localized structures" [10] situated deep in the brain parenchyma while providing a potentially high degree of safety for patients. This aim must be achieved by the convergence of multiple beams of ionizing radiation from different geometric angles at a single predefined point in the brain.

The prototype machine used in Sweden was designed and used to treat functional neurological disorders such as pain, movement disturbance syndromes, and even some behavioral diseases that did not respond to current conventional psychiatric treatments. A second machine was built in 1975 and was designated for the administration of therapy for the brain lesion. Nonmalignant malformation of vascular

lesions in the brain comprised one of the few attractive neurosurgical fields at that time. Dr. Leksell later extended the field of indications for the use of this machine to pituitary adenomas and vestibular schwannomas. In 1972, Dr. Steiner and Dr. Leksell and colleagues treated the first patient with arteriovenous malformation with SRS at the Karolinska Institutet in Sweden [14].

In addition to the historic implications and epistemic dynamics, I will attempt to provide a faithful review of a few carefully selected standard texts on SRS from recent years [15–21].

First, I will focus on postulates originating from SRS via Gamma Knife technology because of the historic chronology and accumulated experiences. Next, I will concentrate on linear accelerator (Linac)-based SRS as well as active researchers and their ideas. This describes a well-established action radius of the authors of these texts both within and outside the two radiosurgical communities (Gamma Knife and Linac subgroups). The literature selection was based on textbooks written by active experts and is presented in chronologic order from the current period back to the 1990s [15–21]. I did not aim to provide a comprehensive overview of many issues of different importance, but rather to focus on three essential questions that continue to be discussed intensively at each interventional clinical unit. This review merely presents the *current* discourses on SRS and the methods by which current experts *apperceive the radiobiology* of high-precision radiosurgical approaches.

As such, no explicitly basic research exists on the intrinsic mechanism of SRS. Therefore, we have relied on investigative efforts exerted in the domain of *fractionated radiotherapy* and have sought analogies and a substantial transfer of knowledge into realm of stereotaxy. The main question asks whether the classic four R's of the conventional radiobiological model [5] and the corresponding postulates related to *fractionation effects* could account for the effectiveness of SRS. The second question concerns the utility of the omnipresent linear-quadratic model [6] for the agency of high-dose convergent radiation in tumors. Finally, we address the irrevocable ablative mechanisms or, more concisely, the therapeutic index of dose-escalated highly precise radiation for malignant and nonmalignant lesions in the brain and body.

Research conducted in Northern Europe has officially advanced this clinical field, following the pioneering and genuinely inventive work of Dr. Leksell [12, 13]. One prominent successor in this context, Dr. Jeremy Ganz, also an innovator in his field, described his understanding of radiobiology as related to Gamma Knife effects [15]. With regard to the three questions presented in the previous passage, Dr. Ganz recapitulated the basics of radiobiology, which are well known for *fractionated radiotherapy*, in chapter four of his seminal book on Gamma Knife technology, *Biological Effects of Ionizing Radiation*. What Dr. Ganz failed to mention was the potential effects or possible radiobiological specifics of Gamma Knife-based SRS. Regarding the mechanisms of cellular repair [15], he described two different models, namely, a lethal/potentially lethal model and saturation repair model. Here, too, he provided no direct indication of the special issues of stereotaxy; when labeling the technique, he merely rephrased valid but general information. In the following paragraphs of this 2011 update of a standard textbook, all

issues of radiobiology, such as oxygenation, reoxygenation, dose homogeneity, dose volume, radiosensitivity, tumor volume, and accelerated repopulation, were mentioned without any special regard to the specifics of SRS. The last book, which was coauthored by well-known "celebrities" of the Gamma Knife "scientific scene" (mostly from the "Japanese School" such as Motohiro Hayashi from Tokyo and other international authors), also did not reveal any radiobiological specifics of stereotaxy [16].

One exception, Dr. Jean Régis of Marseille, wrote from a "nonlesional mechanism of action" [16] based on the hypothesis that "low dose radiosurgery applied to normal neuronal tissue, relying on subtle but specific biological changes, may affect some processes while sparing others…" [17]. This hypothesis assumes that beyond the well-described neuronal changes, the effects of radiosurgery may induce distinct reactions at a cellular level in both cycling (e.g., neurons) and non-cycling cells (e.g., glial and endothelial cells). Non-cycling cells appear to respond differently from cycling cells such as neurons; the former can be severely injured [17, 18]. A group of researchers from Pittsburgh described delayed astrogliosis and significant cell loss after Gamma Knife radiosurgery in animals [19]. Theoretically, the loss of glial cells induces the migration of progenitor cells with obviously altered matrix germinal zones. Dr. Régis proposes here a "cockade model," thus implying a *zonal typology* that begins with a necrotic core, a surrounding subnecrotic area lacking coagulative necrosis where cellular differential effects may occur and a neuromodulation zone with more subtle changes and no increase in cell death [17]. Régis stated that inflammatory reactions within the subnecrotic area might be responsible for the functional changes that lead to functional modulation while preserving basic processing. In summary, a biologically destructive effect is not mandatory, but represents a type of functional modulation [17].

The North American group most dedicated to Gamma Knife technology has issued a very wide range of highly scientific themes during the 28-year period since the first machine was inaugurated in 1987 at the University of Pittsburgh department of neurosurgery. The nucleus of this group includes Lawrence Dade Lunsford, Douglas Kondziolka, and John C. Flickinger, who summarized in 1998 their clinical results and some basic postulates of Gamma Knife SRS [19, 20]. Dr. Kondziolka, a pioneer in both clinical and basic science research in this field, began with a statement that might summarize the fundamental "facticity": "Radiosurgery is the precise and complete destruction of a chosen target containing healthy and/or pathological cells, without significant concomitant or late radiation damage to adjacent tissues" [21] (paraphrasing Dr. Leksell). Through his writing, Dr. Kondziolka emphasized that the *destructive effect* might be *total* [21]. Van der Kogel [18] wrote that the effects of SRS did not differ from those of *fractionated radiotherapy*. However, size matters, specifically volume confined within the treatment volume. Dr. Kondziolka suggested that the door leading to the powerful radiobiologic effect of radiosurgery was opened when the "surgeon delivers precise and accurate radiation" [21]. Hereby, he explained his understanding of the relevance of dose homogeneity for Gamma Knife—where the prescription is to the 50 % isodose line and multiple-isocenter plans are applied—and in comparison to LINAC SRS, where the

prescription is to the 80 % isodose line, one- or two-isocenter plans are applied, and more homogenous scenarios are required.

Furthermore, Dr. Kondziolka adopted two distinct factors that influenced the biological effect of Gamma Knife SRS. First, neoplastic cell death caused by high-dose radiation was observed 2–4 weeks after treatment with 20 or 40 Gy in an in vitro nude mouse model [19, 22]. Second, changes in vascularity in abnormal vessels due to a relative sensitivity to radiosurgery were observed in vitro and in vivo after a period of 3–24 months. This time course is, according to Dr. Kondziolka, more consistent with delayed vessel obliteration. "The effects on blood vessels play almost as important role in the radiosurgery response as the effect on abnormal neoplastic or endothelial cell" [21].

Here, at the gateway between older Gamma Knife technology and the subsequent emergence of Linac-based SRS, we will describe differences in the understanding and applications of these technologies [23, 24].

The beginning of the transition from Gamma Knife to Linac-based SRS occurred in Argentina and Italy, where Dr. Betti [25] and Dr. Columbo [26] reported the effective use of Linac in 1982. For many reasons, these reports initiated a wave of acceptance of SRS. First, they addressed the high cost of the Gamma Knife machine. Second, they addressed the limitation of Gamma Knife technology for the delivery of merely intracranial radiosurgery. Finally, they described the rapid and continuously ongoing improvements in imaging technologies.

Current Postulates

Today, a single predominant theorem contains various implications of momentous changes in vessels within and surrounding the tumor that indicate the *radiosurgical effect*. Once again, controversies regarding the classic postulates, namely, four R's and linear-quadratic model, have arisen [27, 28].

Mechanisms of "Vascular Damage"

Evidently, a complex process induces angiogenesis, thus enabling the delivery of nutrients to a tumorous lesion. This process comprises a large array of static and dynamic mechanisms that lead to the formation of a network within and surrounding the tumor; this network is characterized by pure microanatomical changes, with an emphasis on functional transactions involving multiple mediators between different cell types. The vessels must undergo microanatomical neoformation to form new structures that promote tumor survival. Indeed, these vessels can grow into a tumor at a typical velocity in the presence of elevated mediator turnover rate.

De novo emergent vessels are shaped by "sprouting or intussusceptive microvascular growth and vasculogenesis by progenitor and other stem-like cells from the blood and bone marrow," and this is accompanied by the co-option of the preexisting vasculature in tumor-adjacent tissues [30]. The efficacies of different aspects of these dynamics have been demonstrated [31–35]. In a seminal 2003 Nature Medicine

essay, Jain and colleagues stated that the "maturation of nascent vasculature, formed by vasculogenesis or angiogenesis, requires recruitment of mural cells, generation of an extracellular matrix and specialization of the vessel wall for structural support and regulation of vessel function" [36]. In addition, stated the authors, the vascular net must provide nourishment to all parenchymal cells. A highly complex interweaving of ligands and receptors in which "spatio-temporal patterns of expression and concentration are tightly regulated" [36] leads to the formation of *abnormal vasculature*—a hallmark of pathologies such as cancer [36].

This *abnormal vasculature* is the rational basis for a large number of dysfunctionalities and disturbances. The anatomical and physiological features of the tumor and surrounding vasculature network subsist and prevail in a significantly different pattern than that observed in normal tissues and vessels [31, 34, 37–41]. Initially, a net of tumor-infiltrating vessels emerges; these vessels appear immature and capillary-like and are characterized by a single, discontinuous endothelial cell layer in which the gaps are filled by tumor cells. This discontinuous design is marked by the absence of a functional basement membrane. That lack leads to a porous, faulty vasculature network structure within and around the tumor [40].

Second, de novo vessels are distinguished from normal tissue vessels by the lack of a regular nerve organization [30]. This fact has implications for many reaction patterns. First, these vessels do not react adequately (i.e., as normal vessels) to extrinsic stressors. This modified reactivity appears to determine the potential tumor vessel reaction to irradiation. Third, de novo vessels also feature distinctive changes in caliber diameter; these vessels are not merely smaller, but are also tortuous, with numerous breaks, discontinuities, and terminations [30]. These characteristics result in abnormal hemodynamic behavior as blood streams into the tumor, in other words, "sluggish, and intermittently stationary" [30]. This abnormal bloodstream within the tumor further suggests that alternative vascular paths, such as arteriovenous shunts, are sought, which might partly explain the high incidence of thromboembolic events. Finally, interstitial pressure within the tumor is likely to increase because of the deficient lymphatic drainage system and the leaky tumor blood vessel anatomy, which can lead to the intermittent or permanent collapse of smaller "capillary-like" tumor blood vessels [30].

This *abnormal tumor vasculature structure* and functional defects might differ with respect to a slower growth pace than that observed in rapidly infiltrating and expanding lesions.

Overall, the aforementioned features and aspects of *abnormal vasculature* within tumors might be responsible for the acidic, normally hypoxic intratumor microenvironment with nutrient deficiencies, which is more peculiar for tumors [30, 39, 42, 43].

Regarding the effect of radiation on the tumor vasculature, all of the abovementioned statements account for the heterogeneous responses to ionizing radiation. A large body of preclinical evidence indicates a consistent pattern of intratumoral hemodynamics; as human tumors are exposed to *conventional fractionated radiotherapy*, "the blood perfusion tends to increase during the early period of treatment, but returns to the pre-irradiation levels or declines to the levels lower than that before the treatment toward the end of treatment" [30, 44, 45].

Regarding *high-dose radiosurgery*, a vast proportion of the available knowledge is based on in vitro or animal experimental settings (i.e., animal model xenografts). The exposure of a tumor xenograft cell to a dose of 10 Gy (or higher) in a single session causes sustained changes in the vasculature of xenografts [46, 47] or animal lesions [29, 41, 48, 49].

A group in Minnesota, comprising Dr. Levitt, Dr. Song, Dr. Park, and other colleagues, has contributed significantly to research involving *high-dose radiosurgery* under real-world conditions. Suggestive data have led us to believe in the existence of a *temporal design* within the dynamics of (possible) tumor vasculature reactions to *high-dose radiosurgery.* The Minnesota group researchers described precisely and figuratively those "changes in tumor volume, intravascular volume (vascularity) and the rate of extravasation of plasma protein (vascular permeability) in the Walker 256 carcinoma of rats after irradiation with 30 Gy in a single dose. The tumor weight or size continuously increased for 7–8 days after irradiation and then markedly decreased until 15 days after irradiation. The vascular volume significantly decreased within 1 day after irradiation and further decreased for about 12 days and then began to recover. The extravasation rate of plasma or vascular permeability significantly increased soon after irradiation, declined thereafter until 12 days post-irradiation and then began to recover. The continuous increase in tumor size for several days after irradiation with 30 Gy may be ascribed to delayed disintegration of dead cells and induction of edema as a result of increased vascular permeability" [30].

The authors further assumed that "the tumor vasculature began to recover 2–3 days prior to the recovery of tumor size suggesting that proliferation of tumor cells and recovery of vasculatures are closely related" [30]. The notion of stem-like cells might also be important in the context of vascularity (vascular volume) recovery after radiation exposure [30]. In fact, functional vascularity decreases within hours after exposure to *high-dose radiosurgery* (e.g., 10–15 Gy). This obviously results from the phenomenon of endothelial cell death [38, 48]. The aforementioned early changes in interstitial fluid pressure within the tumor, which are caused by the extravasation of plasma proteins, might also play a role [30]. These reactions appear to characterize the early phase.

Late tumor and tumor vasculature reactions might occur in differential causal sequences. A late decrease in functional vascularity has been suggested after approximately 12 days. This might be attributed "not only to the direct effect of radiation on the tumor vasculatures but also to the disorganization in vascular networks resulting from the shrinkage of tumor volume" [30]. Blood vessels appear to react differently depending on location. Vessels in central tumor areas appear to be destroyed [30]. Importantly, smaller-caliber vessels might be more sensitive to high-dose radiation.

Consequences of the Postulate of "Vascular Damage" for High-Dose Radiation Therapy

The trajectory of cancer, which includes genesis, proliferation, and progression, as well as of any solid malignant or nonmalignant tumor, depends on blood supply. The means by which the vascular network provides nourishment to the parenchyma

has been well studied [36]. However, the mechanism by which this occurs within a tumor and related heterogeneous cell subpopulations remains under investigation [31, 32, 34]. The best available evidence, with a focus on morphology and functionality, leads to a reasonable prediction that severe changes in vasculature consequent to *high-dose radiosurgery* will cause cell death in a solid tumor.

Denekamp and colleagues stated that a single endothelial cell could maintain a segment of a tumor containing as many as 2000 tumor cells [50]. Vessels are well known as serial tissues, and thus severe damage, particularly with regard to morphology and functionality, could hinder blood flow from the periphery to the center of a tumor. If the postulate of "vascular damage" were correct, this would lead to serial tumor cell death, at least along the damaged vessel.

The core plausibility of this hypothesis can be interpreted in two ways.

First, we must look at the clinical outcome data. The amount of valid, high-quality clinical data is too high to count, and there has been an exponential increase in data on SRS since its incorporation into the model of oligometastatic cancer [51, 52]. For the first time in decades, SRS has become a conceptual strategy that extends beyond the borders of mere technology. It has, so to speak, gained color or a specific therapeutic context with perspective [53, 54].

This is true for the treatment of brain tumors. SRS is the best option for the treatment of oligometastatic cancers with brain metastases; in this context, SRS has come to represent a paradigm shift [51, 55–58]. In fact, SRS has become almost a "traditional" therapy for benign cranial tumors; outcomes have been consolidated for patients with meningioma [59–62] as well as for those with vestibular schwannoma [63–65]. Other severe "benign" diseases, such as cranial vascular malformation, have been treated with a high degree of sophistication [66].

Patients suffering from spinal lesions are among those who benefit from SRS [67–70].

Patients with extracranial lesions, who have traditionally received palliative systemic therapy, might now gain the opportunity to undergo a "quasi curative" (copyrights reserved to the author) approach. Non-small cell lung cancer has been well studied in both its early stages and the oligometastatic state [71, 72]. Solid oligometastatic cancers with limited liver lesions appear suited to SRS [73, 74]. The effectiveness of this approach has been demonstrated for some lesions with peculiar behaviors, such as glioblastoma, hepatocellular carcinoma, pancreatic tumors, and even prostate cancer [75–78].

Second, we must review the currently available preclinical data and models, even if they appear contradictory at times. Although the clinical outcome data reveal 2- and 3-year local control rates exceeding 85 % for some entities, one might believe the existence of a mechanism that can overcome the hypoxic tumor cell milieu. Brown and colleagues estimated the effects of high-dose radiosurgery in the laboratory [79]. These authors calculated that exposure to 25 Gy (high dose) would reduce cell survival by 3.3 logs, whereas exposure to 20 Gy in three fractions would reduce cell survival by 7.7 logs, assuming that the a/b ratio of the tumor cells is 10 and that 20 % of the tumor cells are hypoxic. Fowler and colleagues conducted experiments to determine the dose required for appropriate cell death that would explain the above clinical data. Their calculations suggested that to control tumors with sizes of

1–10 g, three fractions of at least 23 Gy would be needed to reduce the viable hypoxic tumor burden to 10^{-10} to 10^{-11} if one assumes 20% hypoxic cells, a so-called oxygen enhancement ratio of 3, and no occurrence of cell reoxygenation or repopulation during treatment.

One might thus guess that different mechanisms are employed in the contexts of cranial and extracranial SRS. The ability overcoming hypoxic resistance must be determined by mechanisms other than direct tumor cell death via DNA damage, such as immune responses and vasculature damage [79, 81]. Following this assumption, Kirkpatrick and colleagues and Kocher and colleagues concluded that total cell death in tumors treated with high-dose SRS is a product of direct tumor cell death and that indirect tumor cell death might be caused by radiotherapy-induced vascular changes.

Last but not least, we must mention the concept of supposedly radioresistant stem cells that might exist in a perivascular niche [30, 83]. The vascular damage hypothesis is considered a possible explanation for the effects of high-dose radiosurgery. Again, Song and colleagues stated that "it is therefore conceivable that eradication of cancer stem cells as a result of death of endothelial cells and destruction of vasculatures might be an additional explanation why extreme hypofractionated radiotherapy with relatively small total doses, e.g., 20 Gy, are capable of inducing tumor control" [30].

The Four R's of Radiobiology

Reoxygenation

A fraction of clonogenic tumor cells within a hypoxic milieu remains radioresistant. During the treatment of tumors via fractionated radiotherapy comprising small doses given at definite 24-h intervals, some of these cells will transition to an oxygenated state [4]. The radiosensitivity that results from this process is considered a major benefit of *fractionated radiotherapy*. The reoxygenation of a formerly hypoxic cell subpopulation in the tumor is a result of normoxic cell death and consequent decrease in the oxygen demand, thus enabling the diffusion of oxygen from vessels to hypoxic intratumoral areas. Damage to the tumor vasculature and surrounding tissues would constrain any reoxygenation of hypoxic cells within the tumor. This means that reoxygenation may not occur in the scenario of high-dose radiosurgery and possible consecutive vascular damage [30]. It is therefore likely that some percentage of hypoxic cells, as well as normoxic cells, would be killed during a second high-dose radiation treatment.

Repair of Sublethal Radiation-Induced Injury

The repair process during *fractionated radiotherapy* is negligible. On the other hand, because the delivery of high-dose radiation usually occurs over a longer

period, substantial sublethal damage repair may occur during treatment [30, 80]. A 10 % loss of biological effectiveness is attributed to injury repair during radiotherapy sessions with durations exceeding 30 min (e.g., SRS).

Redistribution

No change in cell cycle distribution is observed after an application of a 20-Gy radiation dose; cells die in the cell cycle phase in which they were exposed to high-dose radiotherapy. These observations imply that interphase tumor cell death will prevail when tumors are treated with high-dose radiotherapy [30].

Repopulation

The duration of a SRS session is less than 5 days; accordingly, there is no reason to suggest repopulation.

How Viable Is the Linear-Quadratic Model?

In 1989, Dr. Fowler described in a denotative paper a new model for calculating isoeffective doses for fractionated irradiation schemes: the so-called linear-quadratic formula (LQ model) [6]. The LQ model encompasses two components, alpha and beta, which represent non-repairable and repairable cell injuries, respectively. This model assumes that the real biologic effect of fractionated radiotherapy is directly proportional to the total dose and fraction number and that the a/b ratio indicates the sensitivity of tissues to different fraction sizes. Radiation-induced cell death and sublethal damage repair are incorporated in this model.

The viability of this model has long been discussed [82, 84, 85, 86]. However, a conclusive recommendation does not yet exist. One concern is whether the dose–response survival curves determined by this formula will shift downward in high-dose areas, whereas experimental dose–response curves remain linear. The question is whether the LQ model overestimates cell death or underestimates cell survival at high radiation doses [30]. Song and colleagues argued that cells that proliferate rapidly in culture exhibit behaviors different from those of tumor cells in patients, which are affected strongly by the microenvironment and cytokine milieu. "It is conceivable that the a/b ratio of cells in such environment may be unnaturally high rendering the survival curve remain linear at high doses" [30]. Brenner subsequently argued that application of the LQ formula is a "notably robust procedure" [84]. In contrast, Song and colleagues again stated that radiotherapy with "doses higher than 10–12 Gy in a single exposure is likely to cause significant vascular damage followed by indirect cell death." They concluded that the "LQ model may become increasing inaccurate" for high-dose radiotherapy (e.g., 10–12 Gy) [30].

Where to Go from Here?

High radiation doses, when applied in one or a few sessions, defy conventional knowledge in the field of traditional radiobiology in terms of the strategic context and specific technological settings of SRS.

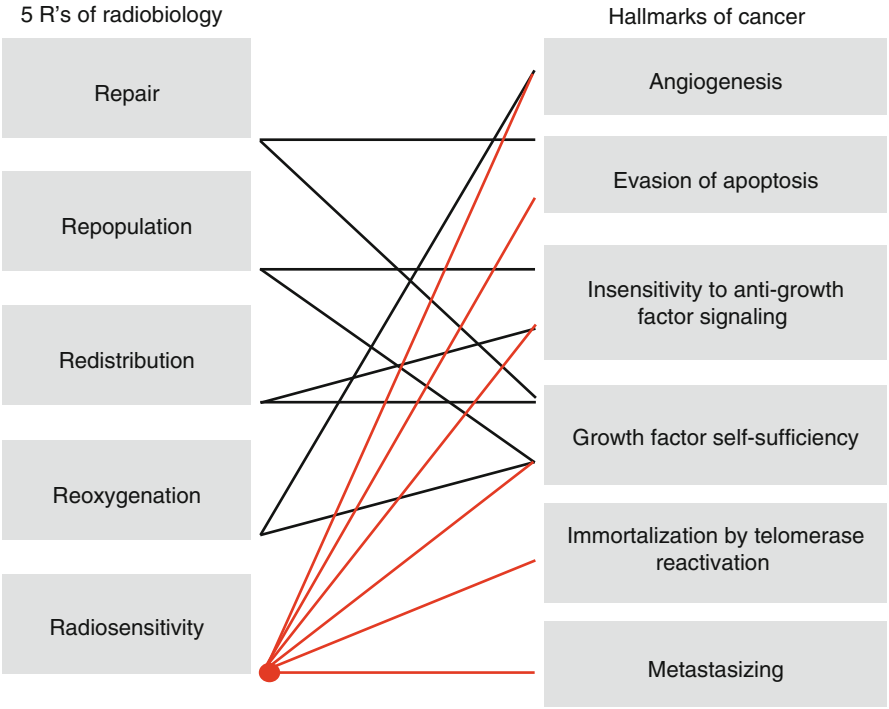
Basic research on the molecular effects of *fractionated radiotherapy* has yielded a wide range of clinical research, including clinical trials, in the last three decades. The experts in this field undertook huge efforts with regard to laboratory experimentation and clinical studies to understand the real meaning of *fractionation* and its effects in clinical practice. These processes are ongoing and characterized by significant scientific intensity. On the other hand, experimental research has been rudimentary, with a focus on the radiation effects of *single-dose* high-precision radiotherapy; in other words, all work has attempted to reveal the biologic essence of so-called radiosurgery.

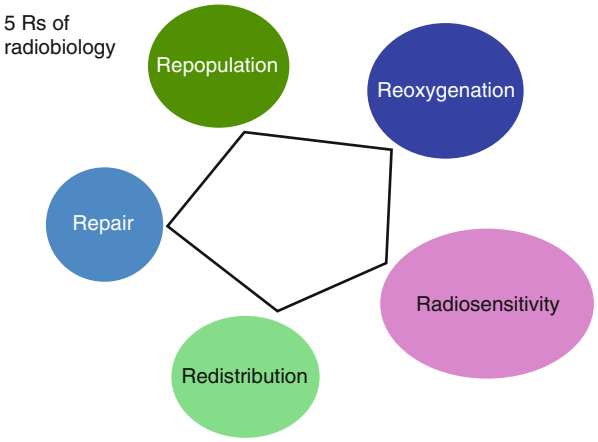
The abovementioned dichotomy persists, even as we have attempted to synthesize different layers and aspects of the current body of knowledge of radiotherapy effects when comparing normofractionated radiotherapy to high-dose radiosurgery. The clinical outcome data, which were generated in the realm of SRS and from a rapidly increasing number of publications, contradict almost all arguments from opponents of SRS. First, the empiric basis substantiates the outcomes of SRS with a high degree of scientific consistency. Second, the point of no return has been reached worldwide in clinical routines and the design of standard operating procedures for SRS.

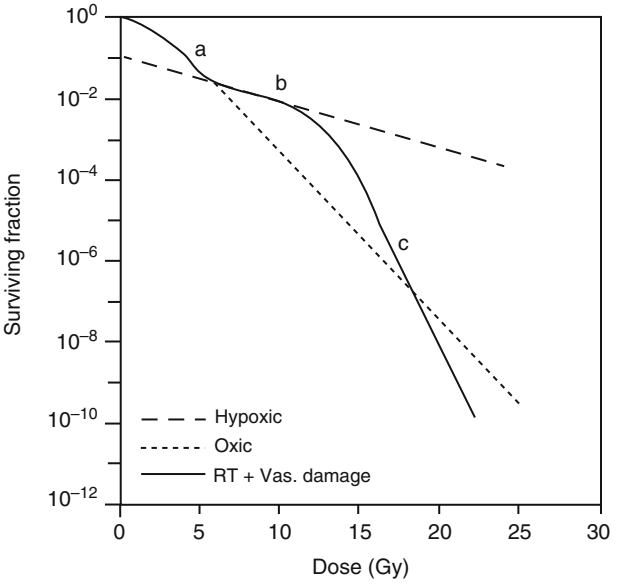
The opposition, which is few in number, continues to support its theorems and postulates at conferences and meetings. This group claims that high-dose radiosurgery does not utilize the full potential of reoxygenation that occurs between dose fractions, leading to the potential for cell cycle redistribution. Furthermore, this group repeats the notion that conformal plans calculated for radiosurgery do not cover potential microscopic tumor cell extension. Arguments against these suggestions have been formulated above.

The orthodoxy, which is large in number, maintains a relaxed attitude toward the urgent need for consistent and rational scientific discourses.

To summarize all the connotations of “integrated and apocalyptic” [86], as mentioned by the proponents, we currently know that disruptive events, including inflammatory disturbances and endothelial cell apoptosis (or “vascular damage”), may work together with DNA damage to enhance tumor cell death in a more ablative scenario.


5 R's of radiobiology
Repair
Repopulation
Redistribution
Reoxygenation
Radiosensitivity
Hallmarks of cancer
Angiogenesis
Evasion of apoptosis
Insensitivity to anti-growth factor signaling
Growth factor self-sufficiency
Immortalization by telomerase reactivation
Metastasizing


5 Rs of radiobiology
Repopulation
Reoxygenation
Repair
Radiosensitivity
Redistribution



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Current Available Technologies

5

Abstract

There is a reciprocal and tight relationship between the capabilities of existing technologies and possibilities of medical strategies. At times, one of the sides introduces innovations at a strong and consistent pace; however, the other side merely waits for an event to trigger its dynamics. Alternatively, an outburst of technological innovation induces immediate transformative evolution in the realm of medical ideas and interventions and vice versa.

The very dialectics of strategy and technology in medicine deploys processes and, indeed, motivates clinicians and caregivers to seek fundamental improvement in the lives of their patients. There appears to be no underlying principle of "who came first," but an exchangeable force field of actions and reactions we call innovation.

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In the following chapter, we will focus on those technologies that are available in the vast majority of countries and medical institutions. We do not aim to provide a perfect or comprehensive overview of all existing technologies and options, but

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rather a focused and reductive practice-based collection of the latest machine types that are currently in the market. It is evident that radiosurgery takes place in a routine setting merely in the Western hemisphere and in selected Asian and Latin-American countries. Hadron therapy and other state-of-the-art technologies belong to their respective research fields and are not likely to be described in practice-oriented books.

The text is oriented to the latest information provided by the respective industry or company with no or minor changes. The reason is to take the technologic essence of the respective machine type into account without significant changes and, still, not to discover the wheel new. This is an attempt to mirror current state of affairs from the perspective of those who produce machines and its software and to avoid additional prose that distracts from high-tech essentials.

We try to avoid any kind of good and bad "propaganda" for any industry or company by adding too much of very specific information, including details on location, places, countries, or logos, first, because there is no need for that and, second, because all details are provided by the websites of industries and companies.

For an update, please take a look in the websites of the industry or companies.

Dedicated Linear Accelerators

The Prehistory of an Unprecedented Innovation

Today, we retrospect a three-decade-long history of emerging linear accelerator (Linac) technology for stereotactic radiosurgery. Within this period of development, numerous stories offer a view of impulsive and dedicated scientific efforts for improving clinical outcomes for patients with certain diseases. The term "dedicated" must apply to the innovators and generators of ideas, including physicians, physicists, technologists, and other caregivers.

The first published dispatch on using a Linac came from Spain, when Dr. Barcia-Salorio described the radiosurgical treatment of a carotid-cavernous fistula [1]. His team used a Co^{60} unit in combination with a special collimator. Soon after this pioneering innovation, other researchers have joined the emerging community. Dr. Betti from Argentina reported radiosurgical treatment using a 10-MV-energy Linac operated with a Talairach localization system. In that study, patients were seated on a moveable chair and were attached to a rotating head frame, designed at the same institution, fixed on the anatomical area of frontal and occipital regions of the skull [2]. Dr. Colombo from Italy had also contributed significantly to this effort of experimental innovation. His team used a 4-MV-energy Linac with no accessory collimators for treating 2–4-cm-wide cranial lesions with 40–50 Gy beams in two treatments separated by a large temporal gap. The European efforts were continued in Germany by Dr. Hartmann from Heidelberg [3]. Meanwhile in the USA, Ginsberg and Houdek addressed the issue for the first time in 1985. These researchers employed a custom-made localization system with a 10-MV-energy machine, although it was a fractionated treatment [4].

At that time, the lack of mechanical precision and system stability of commercial systems urged innovative researchers to improvise. Lutz and colleagues in the USA, at Harvard Medical School, proposed a floor-standing solution. At the same time [5], Podgorsak in Canada, at McGill University, designed collimators with small circular fields in which gantry and couch moved simultaneously [6].

Linac Arrangements

Novalis® Radiosurgery by BrainLab

Novalis is one of the existing platforms for delivering stereotactic radiosurgery. It provides an advanced configuration of specialized tools dedicated to precise and targeted radiosurgery. Since 2004, this technology has been paving the way to introducing fully dedicated Linac-based stereotactic radiosurgery.

The indications obtain the treatment of small-sized nonmalignant [7–12] and malignant lesion tumors [13–19] as well as arteriovenous malformations. The field of functional radiosurgery dealing with functional neurological disorders belongs to the action radius of Novalis.

To obtain the dose falloff necessary for treating challenging localizations, this machine features a dedicated high-definition beam shaping.

Cranial targets are usually much smaller than lesions that are treated by conventional radiotherapy and are often located near critical structures that demand increased conformity. All of the arrangement centers share access to an integrated collimation and treatment planning solution designed and commissioned for delivering high-accuracy treatment. A high-resolution multi-leaf collimator accurately mirrors the contours of the tumor and of organs at risk. It happens to constantly adapt the beam shape with a steep dose falloff at the lesion boundaries with leaves in the 2.5–4 mm range that help to reduce the dose administered to the healthy tissue.

Software

The system is operated by running a comprehensive software suite that expands treatment planning capabilities using high-performance tools and straightforward, automated clinical workflows. It allows clinicians to achieve fast contouring and consistency with Atlas-based structure segmentation in a short time (1 min). This tool is capable of automatically labeling major cranial and spinal structures, with an additional access to the head, neck, lung, and prostate.

The “iPlan RT Planning Software” allows clinicians to simplify complex planning routines of stereotactic radiosurgery and provides access to sophisticated planning options for reaching eloquent areas. In addition, template-based workflows designed by accounting for clinical experience facilitate straightforward planning and allow clinicians to offer reliable and patient- and case-based treatments. The system allows saving treatment configurations, prescriptions, and constraint settings acquired by experience.

The system allows to establish specific clinical protocols and reproduce and practice these protocols for different lesions and machines. The software facilitates collaborative planning and exchange of information for the same patient, helping to expedite the entire planning process.

The core Monte Carlo dose algorithm generates faithful dose distributions within seconds, while algorithms for conformal beam and dynamic arc treatments are generated within minutes. Seamless integration allows using the system with all existing major types of Linacs and multi-leaf collimators (MLCs), virtually eliminating treatment area restrictions associated with conventional dose calculation algorithms. The system is characterized by a proven accuracy that has been verified by specific medical physics measurements and EGSnrc and BEAMnrc algorithms. Advanced integration of hospital-specific clinical configuration of Linac and MLC modeling is possible for achieving highest customization. As is well known, the Monte Carlo algorithm considers the Linac head geometry, the secondary electron dose effects, and tissue inhomogeneities. iPlan RT automatically adjusts the dose grid to allow for accurate dose calculation, even in the case of very small structures. Intelligent scaling of the adaptive dose calculation grid in the function of the object volume ensures precise dose distributions without compromising the calculation speed. It tackles time-consuming contouring challenges with multiple-phase 4D computed tomography (CT) by elastically morphing and matching object contours between different respiratory phase CT scans. Internal target volumes are generated with one click, to support informed free-breathing versus gating treatment decision-making for moving targets.

In this context, dynamic conformal arcs efficiently control and optimize the dose to critical structures while maximizing the target volume coverage by an automatic leaf adaptation to the tumor's contour. During treatment, the MLC field shape is continuously optimized to match the shape of the target in function of the rotating gantry. The beam's eye view allows for better control and intuitive planning of dynamic conformal arcs. HybridArc™ treatment planning allows the provision of proven accuracy alongside the clinical flexibility of treating complex tumors precisely and effectively anywhere in the body. It automatically blends advanced radiosurgery techniques to find the best match given the individual patient circumstances. Within several minutes, this technique flexibly weighs arcs and beams for optimized coplanar and noncoplanar volumetric dose delivery while shaping doses for concave regions and large structures.

Hardware

The advantage of this dedicated machine is the ability to perform meticulous dose plans for high-resolution micro multi-leaf collimators and smaller, irregularly shaped targets.

ExacTrac® is an in-room X-ray based monitoring system that detects intrafractional tumor motion during the treatment delivery, regardless of the couch angle or gantry position. Instantaneous X-ray imaging with proprietary 6D fusion provides fast and highly accurate positioning information and reduces the possibility of geographical miss owing to the patient's motion or internal anatomical shifts.

Monitoring patients provides clinicians with a unique position verification tool based on the patient's internal anatomy. Deviations or unintended shifts from the prescribed treatment position are automatically detected during the treatment delivery and are immediately displayed to the user. It, too, complements the existing IGRT solutions by adding the possibility of detecting intra-fraction motion, regardless of the couch and gantry angle. It allows the patient's initial position, set by the Linac-based IGRT system, to be continuously verified by using X-ray imaging, throughout the entire process of treatment delivery. Even at noncoplanar couch angles and during beam-on, ExacTrac may detect potential misalignment of the patient.

This frameless system offers accurate delivery of single- or multi-fraction treatment without a conventional, invasive head ring. A patient-friendly head-to-shoulder mask facilitates an easy workflow, overcoming the restrictions of frame-based radiosurgery and improving scheduling flexibility for imaging and treatment.

One method for improving the treatment efficiency is to provide a more automated approach to the patient's setup. The optional automatic positioning packages for ExacTrac allow the user in the control area to remotely adjust the patient's position. Positioning packages are available for either 4D or full 6D robotic alignment.

In treatment indications, where visualizing the tumor may be difficult, or where there is a need to compensate for tumor motion owing to respiration or random motion, fiducial markers may be implanted prior to treatment. ExacTrac offers a simple, automated approach to visualize, detect, and register implanted markers by using a proprietary software solution and 6D fusion.

The volume of interest (VOI) tool improves clinical accuracy and confidence in image fusion by focusing on the most relevant anatomy. The user can exclude areas such as the ribs, adjacent vertebrae, or other non-rigidly correlated objects from the 6D fusion, ensuring a precise patient's setup. The defined VOI is automatically used for subsequent imaging during setup and for monitoring intra-fractional motion.

Collaboration with Other Systems

The arrangement might allow compatibility with BrainLab surgical and third-party radiation therapy solutions.

The partnership between Elekta and BrainLab combines the seamless integration of ExacTrac with Elekta Linac: Versa HD™, Axesse™, Infinity™, Synergy®, and Precise. Working in synergy, these state-of-the-art technologies determine positioning and treatment accuracy for treating cancer patients. By streamlining the treatment workflow, ExacTrac and Versa HD increase the patient's positioning efficiency and provide a highly accurate solution for frameless stereotactic radiosurgery. The accuracy is further enriched with the ability to detect and manage intra-fractional patient's motion during the treatment delivery.

The company BrainLab collaborates with the company Varian on the integration of ExacTrac. The system provides an integrated workflow with Varian LINAC, ranging from Unique™ Performance, Clinac®, and Trilogy® to the TrueBeam™ platform. ExacTrac software ensures that the same treatment plan is automatically loaded into

both systems and provides DICOM RT export of the ExacTrac positioning data to ARIA®. This allows any detected patient setup errors to be corrected with the Varian couch and BrainLab Robotics in an integrated and automated process.

Edge™ Radiosurgery System by Varian

Edge offers advanced tools designed for delivering highly conformal dose distributions to tumors of the lung, brain, spine, and other areas of the body, where radiation is indicated.

The system tracks the patient's tumor in real time for intracranial and extracranial treatments, precisely calculates the patient's motion for all six degrees of freedom, and monitors respiratory motion. By integrating the highest dose rate (2400 MU/min) with nonionizing, direct, and real-time guidance for target location, Edge offers surgeons and clinicians the ability to pinpoint the target and deliver highly focused treatments, in fewer sessions and at a noticeably fast rate, while minimizing the dose received by surrounding healthy tissues.

As an all-in-one, single vendor radiosurgery solution, Edge's real-time system architecture helps to coordinate imaging, patient positioning, motion management, beam shaping, and dose delivery technologies. Potentially reducing the overall time and resources required for surgery, compared with traditional methods, can lead to an increase in the volume of procedures performed and lower per procedure costs for the hospital. In an effort to advance radiosurgery treatments, clinics worldwide have already adopted Edge to help advance the way cancer is treated.

The system is an end-to-end, clinical turnkey solution. The technological components have been specifically designed and chosen to ensure that the SRS requirements of a clinic are met. As an all-Varian integrated system, the system allows clinicians to exert control over their technology and resources. Every application, every feature, and every piece of technology reflects performance that drives productivity. It is the seamless fusion of form and function that is designed to fit into the existing high-energy vaults without the need for additional retrofitting. At the same time, treatment planning modules provide treatment delivery decision support tools to help streamline decision-making in advance. As a result, clinical resources may be optimized on the day of treatment. In addition, the system's digital architecture provides an optimized planning and delivery platform for enhanced automation. Simplified so it is easy to learn, treatment processes feature prompts, messages, and an amplified safety system that guides therapists step by step through each treatment. User-friendly features help to streamline advanced performance for imaging and treatment procedures. In addition, innovative tools such as Smart Segmentation, real-time target tracking, and precise dose delivery give clinicians confidence throughout the entire treatment cycle.

Hardware

Accurate delivery of highly conformal dose distributions and steep gradients is the hallmark of the Edge radiosurgery system. Every step of the Edge treatment is characterized by high-level accuracy, enabling high-confidence delivery of treatments.

Calibrated to perform accuracy checks every 10 ms, the Edge treatment process is characterized by precision, with treatments delivered safely and with confidence. Monte Carlo equivalent algorithms for dose calculations, extra-fine 2.5-mm-wide MLC leaves for beam shaping, real-time tracking for direct target localization, and beam specifications that are among the tightest in the industry all combine to yield a unique experience of Edge-based treatment. A streamlined evolution from traditional surgery, Edge offers QA tools to help ensure faster delivery and conformity while minimizing the dose received by surrounding healthy tissues. Dedicated to quickly and accurately delivering radiosurgery, Edge integrates the highest dose rate with nonionizing, direct, and real-time guidance for target location. The large dose level is designed to maximize the amount of radiation to the targeted area while minimizing the amount of time patients spend being treated. Advanced automation helps clinicians guide and maintain the accuracy of treatment delivery by continually tracking patient movements and adapting treatments as the target moves. This feature can potentially decrease the risks of unwanted dose to surrounding healthy tissues. The reliability and precision of Edge radiosurgery allow every patient to feel confident because they are treated according to their plans.

Leveraging the highest dose rate in the industry, 2400 MU/min, Edge treatments allow for short treatment times, enhancing patient comfort. The use of RapidArc radiosurgery technology makes it possible to use the Edge system to deliver SRS and SBRT treatments typically in a standard radiotherapy treatment slot. Clinicians may deliver precisely sculpted 3D dose distributions to single lesions or multiple metastases for stereotactic ablation of inoperable and high-risk operable tumors. RapidArc radiosurgery, powered by the Eclipse™ treatment planning system, enables planning specifically for radiosurgery treatments with automatic, easy-to-use contouring tools. As a result, fast, accurate treatment delivery cannot only help improve the patient's comfort by reducing the amount of time a patient spends on the treatment couch but may also result in a lower overall peripheral dose.

Edge's real-time system architecture enables a high level of coordination between the functional capabilities of the gantry, collimator, and couch. Having a carefully guided workflow automation using intuitive visual cues to enhance safety and reduce operation times, Edge optimizes the patient's throughput. By streamlining imaging and patient's positioning, Edge enables more treatment flexibility for treating a wide variety of pathologies throughout the body, wherever radiation is indicated. The power to not only treat quickly but also to deliver highly accurate dose rates is a hallmark of the Edge system.

Software

Eclipse is designed to increase productivity for clinicians using simplified data settings and easy drag and drop functionality. Using leading edge automated tools, Eclipse opens the door for clinicians to create, import, and optimize plans across numerous multiple Linacs.

"Eclipse™ Treatment Planning System" is an open, dynamic planning environment, continually advancing the speed and accuracy of dose calculation and integrating new

developments as they become clinically available. Eclipse incorporates different algorithms that are optimal for different treatment modalities.

Using photon scatter kernels in multiple lateral directions, the anisotropic analytical algorithm dose calculation accounts for the tissue heterogeneity.

The Acuros XB advanced dose calculation algorithm addresses two strategic needs of external photon beam planning: accuracy and speed. Acuros XB uses a sophisticated technique to solve the linear Boltzmann transport equation and directly accounts for the effects of heterogeneities in dose calculations.

Eclipse Registration and Smart Segmentation® helps to address the time-consuming and challenging aspect of treatment planning contouring. Without going back and forth between standalone equipment, its integrated tools eliminate non-value added steps from the planning workflow. The knowledge-based contouring used by Smart Segmentation streamlines workflow, facilitating the definition of targets and organs at risk, in an efficient and consistent manner.

Versa HD™ Manufactured by Elekta

An all-in-one system from classic radiotherapy to advanced stereotactic precision, equipped with sophisticated conformal beam shaping technology and high-dose rate mode delivery, Versa HD is a dedicated Linac.

At the same time, Versa HD gives cancer management professionals the flexibility to employ conventional therapies for treating a broad spectrum of tumors throughout the body. Proven in its application, Versa HD is a system that unlocks the potential of high-dose rate delivery owing to its market-leading leaf speeds and ultra-low leaf transmission.

In addition, it reduces treatment times by employing rapid leaf speeds and high-dose rate delivery, provides the potential to deliver SBRT/SRS in a standard time slot, lowers nontherapeutic doses for protecting organs at risk and thus potentially reduces the risk of secondary cancer, and, ultimately, exploits the full potential of high doses for advanced therapies by eliminating previous leaf speed limitations. The system enables custom configurations for unique clinical needs and utilizes contemporary imaging technology to allow soft tissue visualization during treatment.

Versa HD features Agility™, Elekta's revolutionary multi-leaf collimator. The "Agility collimator" system utilizes 160 fine-resolution leaves, a 40 cm × 40 cm treatment field and leaf speeds more than twofold faster than those offered by other MLC systems. The patented Rubicon™ leaf-positioning technology of the Agility collimator system verifies leaf movement in real time, providing extreme precision, high reliability, and enhanced conformance for a broad range of cases.

With the ability to perform imaging during treatment delivery, Versa HD provides an opportunity to reduce treatment time slots for improving clinical efficiency. Combining imaging with treatment delivery also reduces the likelihood of patient movement and changes in internal organ position during the treatment session. This means that patient care is further enhanced while giving clinicians the flexibility to provide a patient-specific workflow.

Furthermore, "Versa HD" delivers state-of-the-art 4D soft tissue visualization to manage respiratory motion and accurately target mobile lung tumors—a difficult task before the introduction of this advanced technology. 4D image guidance technology allows clear visualization of moving targets to enable margin reduction for setting new standards in lung treatment.

The system is supported by Elekta's integrated software solutions for providing immediate access to clinical and patient information. Rapidly accessing this data enables multidisciplinary teams to make more informed treatment decisions. MOSAIQ enables clinicians to effortlessly coordinate the patient's entire continuum of oncology care. Through a powerful combination of clinical and patient data available at the user's fingertips, personalized treatments can be created across multiple modalities specific to each patient's disease. Advanced workflow customization and automation supports faster, more effective patient throughput, leading to a greater efficiency and paperless practice.

With sophisticated tools to make the process of planning easier, reproducible, and clinically reliable, Monaco® redefines treatment precision and conformance, enabling the delivery of the most advanced 3D CRT, IMRT, VMAT, and SBRT therapies. Powered by the Monte Carlo algorithm, the most accurate dose calculation currently available, Monaco leads the way in dose conformity, delivery efficiency, and sparing of organs at risk. Combining these capabilities with modern architecture technology, Monaco sets a new standard in accuracy and speed, reducing planning and treatment times and improving the plan quality.

CyberKnife by Accuracy

CyberKnife® System follows the target throughout the treatment, intelligently delivering treatments with submillimeter precision. Designed by using a true robotic manipulator and a compact, lightweight Linac, the CyberKnife System is versatile and can deliver beams from thousands of noncoplanar, isocentric, or non-isocentric angles. Treatments demonstrate excellent tumor coverage, steep dose gradients, and tight dose conformity, regardless of the target shape. The system tracking capabilities eliminate the need for gating techniques and restrictive head frames, providing greater comfort for the patient.

Motion Management

Continuously adapting the treatment to the target motion is a challenge, but the CyberKnife® System offers an expanding set of options that help track tumor types anywhere in the body—including the head, prostate, lung, spine, liver, pancreas, and other extracranial tumors. Our treatment delivery software provides an automatic, intuitive user interface for efficiently controlling all interactions between the robotic manipulator, treatment couch, and imaging system. The software quickly and automatically processes live images acquired throughout treatment at user-defined intervals, calculates

offsets based on digitally reconstructed radiographs, and sends offset data to the robotic manipulator for immediate and automatic motion compensation.

Depending on the type of tumor being treated, the CyberKnife System uses different targeting and tracking methods:

6D Skull Tracking System: Renders invasive stereotactic head frames obsolete, by using the bony anatomy of the skull to continuously track intracranial targets and automatically correct even for a slightest translational or rotational target shift during the treatment delivery.

Synchrony Respiratory Motion Tracking System: This solution continuously synchronizes beam delivery with the motion of the target resulting from respiration, without the need to interrupt the treatment or move the patient. It allows clinicians to significantly reduce margins while eliminating the need for gating or breath-holding techniques.

Xsight® Spine Tracking System and Xsight Spine Prone Tracking System: Use the bony anatomy of the spine to automatically locate and track tumors, eliminating the need for surgical implantation of fiducials and making radiosurgery in and near the spine more precise and less invasive. With the Xsight Spine Prone feature, the benefits of noninvasive spine treatments can be extended to patients in the prone, as well as the supine, position.

Xsight Lung Tracking System and 1-View Tracking System: Works together with the Synchrony® Respiratory Motion Tracking System to eliminate the need to implant fiducials. These solutions directly and noninvasively track lung tumors independently of their position.

InTempoTM Adaptive Imaging System: Uses the CyberKnife System's time-based image guidance to assist with tracking and correcting non-predictable intra-fraction target motion.

Lung Optimized Treatment is an integrated suite of tools that provides a complete fiducial-free clinical solution for lung cancer patients and optimizes noninvasive lung stereotactic radiosurgery treatments. Lung Optimized Treatment consists of the following features:

Simulation Application is a workflow-based application that automatically recommends the optimal choice for fiducial-free treatment of lung tumors based on specific clinical conditions.

1-View is a tracking method that works in conjunction with Synchrony Respiratory Tracking System. 1-View tracks lung tumor motion in one of two X-ray projections, allowing accurate dose delivery with radiosurgical margins in the tracked direction. In this scenario, ITV expansion is applied in the non-tracked X-ray projection.

0-View is a treatment method that is used in situations in which a lung tumor is not clearly visible in either X-ray projection. 0-View uses ITV expansion in two X-ray projections and Xsight Spine Tracking System to track the patient's position.

The CyberKnife System, the premier solution for full-body robotic radiosurgery, now extends its accuracy and precision to radiation therapy, allowing you the freedom to choose the very best treatment for each of your patients, with confidence and without compromise.

The CyberKnife® M6™ Series has the capabilities and efficiency required for every radiation oncology practice—for the treatments accepted today, providing the foundation for treatments of tomorrow. It is the only truly robotic system on the market, developed to meet the evolving needs of the most demanding radiation oncology programs.

Benefits of the CyberKnife M6 Series

Unmatched clinical excellence, patient-focused design, and capabilities to treat more patients and expand practice.

With the new InCise™ Multileaf Collimator (optional on the FI version), the CyberKnife M6 Series is the only clinical solution that combines the benefits of the MLC beam shaping with continual image guidance and non-isocentric, noncoplanar treatment delivery. Precisely sculpting dose to spare healthy tissue while maintaining submillimeter accuracy—even for targets that move during respiration—the CyberKnife M6 Series is the clinical solution you require when accuracy, flexibility, and efficiency are essential.

Created to make personalized treatments an option for your patients, the CyberKnife M6 Series offers a comprehensive set of clinical features. Indication-specific tumor tracking with automatic correction throughout treatment, true robotic mobility, and advanced collimation integrate seamlessly into the only system to automatically stay on target despite patient and tumor motion. It enables you to treat tumors anywhere in the body with confidence and without compromise.

Designed with the patient in mind, the CyberKnife M6 Series enhances the patient's comfort and improves the patient's experience in a number of ways: soothing environmental elements, easy and efficient treatment, and being frameless and noninvasive.

The CyberKnife M6 Series introduces clinical capabilities that are not achievable by using other treatment systems. With the flexibility of the InCise™ Multileaf Collimator and robotic delivery, tumors previously thought to be untreatable with radiosurgery and SBRT can now be treated efficiently and with unrivaled accuracy and tissue sparing. You have the freedom to choose the very best treatment for each of your patients, expanding the field of radiosurgery with unmatched possibilities.

The CyberKnife M6 FIM System with full-body robotic radiosurgery and radiation therapy offers an advanced system geometry, fixed collimators, Iris™ Variable Aperture Collimator and InCise™ Multileaf Collimator, brain clinical package, prostate clinical package, lung and prone clinical package, and clinical efficiency package.

Gamma Knife

Leksell Gamma Knife® Icon™ Manufactured by Elekta

Leksell Gamma Knife® Icon™ is a precise radiosurgery device on the market, limiting radiation dose to healthy tissue. Icon is the only technology with image-guided stereotactic radiosurgery capabilities, allowing for the treatment of virtually any target in the brain with ultrahigh precision.

Icon introduces a number of new innovations, such as integrated imaging and software for the continuous control of dose delivery. It also makes it possible to treat patients without a minimally invasive fixation while assuring the same highest level of precision.

Addressing the growing radiosurgery market, Icon makes Gamma Knife radiosurgery more flexible and easier to use, allowing more clinics to establish cranial radiosurgery programs.

One of the features of this technology is the "real-time motion management." With Icon, a similar level of precision can be achieved with frameless immobilization as with the frame. The high-definition motion management system monitors the patient in real time during treatment with an accuracy of 0.15 mm, which is six times better than the industry standard. If the patient moves outside the preset threshold, the system's gating functionality instantly blocks the radiation.

Online Control of Dose Delivery

The unique integrated stereotactic cone beam CT is a new addition to Icon. Calibrated with respect to the patient positioning system, it determines stereotactic coordinates in three dimensions by using bony anatomy. After co-registration of images from cone beam computed tomography and magnetic resonance imaging (MRI), the treatment plan adapts automatically to any needed correction in the patient's position. Owing to the unique dose delivery characteristics of Leksell Gamma Knife, the system automatically adapts for the patient's rotation online, shot by shot, without any mechanical movement.

Online dose evaluation enables you to compare the dose distribution that is about to be delivered to the planned dose. The comparison is performed at the console and, if needed, the plan can be adapted online, quickly and easily.

Leksell GammaPlan®: Simplifying

With Leksell GammaPlan, a full treatment plan can take just a few minutes to complete, even for complex cases. Inverse planning automatically optimizes the plan. Dose sculpting enables precise handling of complex targets, and with dynamic shaping, critical structures are protected. The convolution module accounts for different

tissue types when the dose is being calculated. For Leksell Gamma Knife Icon, the seamless integration between GammaPlan, the stereotactic CBCT, and the delivery unit makes GammaPlan more than a treatment planning system—it is a treatment management system.

Frameless treatments with similar level of precision as frame-based treatments. The manufacturer provided following details that the average accuracy in clinical setting is 0.15 mm, high therapeutic dose with maximal precision, and lowest dose to healthy tissue: 2–4 times lower dose to the intact brain. Additionally, doses for non-cranial are supposed to be 10–130 times lower.

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Part II

Radiosurgery for Benign Brain Lesions

Vestibular Schwannoma

6

Abstract

Vestibular schwannomas arise from the vestibular branch of the vestibulocochlear nerve, the 8th brain nerve. This nerve branch transmits spatial and temporal balance information to the central processing areas of the brain, and the other branch is juxtaposed to it, and because of the vicinity to the facial nerve (7th brain nerve), all functions of brain nerves 7th and 8th become defective when a tumorous lesion is growing in the tight meatus acusticus internus. This leads to severe clinical problems, and it reduces the quality of life of patients (f/m).

Image-guided stereotactic radiosurgery in its multiple technological appearances as the Linac, Gamma Knife, or CyberKnife radiosurgery could affect substantially the lesion by stopping its growth and improving relevant clinical symptoms. Consecutively, it demonstrates a noninvasive high-precision and safe technique in treating patients (f/m) with traceable improvement of quality of life. Image-guided stereotactic radiosurgery could be performed in outpatient setting and is cost-efficient.

Background

These benign lesions arise from the Schwann cells that form the myelin, which comprises the protective sheath that surrounds nerves. Hypothetically, schwannomas can sprout anywhere in the body. However, in particular locations, these lesions can induce significant problems that deteriorate the quality of life of patients (f/m). Schwannomas may develop in the bony base of the skull, specifically in the tight "meatus acusticus internus," where the 8th brain nerve, or vestibulocochlear nerve, is located. Vestibular schwannoma (VS) is so named because it arises from the vestibular branch of the vestibulocochlear nerve. All nerve function might therefore be influenced by the development of a VS. This nerve transmits spatial and temporal balance

H. Badakhshi, *Image-Guided Stereotactic Radiosurgery*,
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information to the brain, and a defect in this process might be the first indication. If growth occurs within the auditory canal or expands outside of the canal, other functions, such as hearing, might be disturbed. Facial paralysis may occur because of the vicinity to the facial nerve (7th brain nerve). Tumor progression may even lead to compression of the brainstem, dysfunction in cranial nerves, and hydrocephalus [1].

These lesions have been previously described as acoustic neuromas, acoustic neurilemmomas, or acoustic neurinomas; however, a global understanding and minimal consensus of these lesions as VS have been reached because of the cellular origin and functionality [1].

The prevalence of clinically diagnosed VS has been estimated at 1–2 per 100,000 people [1]. The true prevalence of symptomatic VS is likely greater. The actual dynamic has shifted since magnetic resonance imaging (MRI) amplified the initial diagnosis rates among asymptomatic individuals [2–4].

Diagnosis of VS is established via MRI scans and confirmed using audiometric and audiologic tests. These are not necessary but are optional for patients (f/m) at high risk or those with a diagnosed arterial obstructive disease that could cause arterial obstruction in the vertebral artery, leading to similar symptoms [1].

Because of the slow-growing nature of VS, three care options are available. The first is watchful waiting. This might depend on age, comorbidities, and patient's (f/m) preferences and should include MRI scans at regular time points. Second, microsurgery is frequently used because of the lack of available stereotactic radiosurgery (SRS) equipment and/or experience at specific medical centers. The goal of microsurgery is to remove as much of the tumor as possible while preserving hearing, balance, and other cognitive functions. Various anatomic approaches are available, including the retrosigmoid, translabyrinthine, and middle fossa approaches. In the translabyrinthine technique, the operator makes an incision behind the ear and enters through the mastoid and semicircular canals to reveal the most lateral aspect of the tumor. The semicircular canal is a set of fluid-filled chambers involved in balance control. However, a loss of hearing is one consequence of this procedure. It is therefore reserved for patients with no useful hearing in the affected ear. However, this approach minimizes damage to the facial nerve, and surgical removal is not limited by the tumor size. The middle fossa method includes entrance via an incision in front of the ear. The bone covering the top of the internal auditory canal is removed to expose the tumor. This approach yields the best outcomes for tumors <2 cm in diameter. Although this approach provides the best chance for hearing preservation, it is limited to smaller acoustic neuromas. Complete removal is often achieved with this procedure. In the retrosigmoid technique, also known as keyhole craniotomy, the surgeon makes a small incision behind the ear, which allows access to the cerebellum and brainstem. This minimally invasive surgical approach is effective for preserving hearing, removing tumors of all sizes, and decreasing spinal fluid leakage. However, it is more difficult to completely remove tumors that extend too laterally, and there is an increased risk for postoperative facial weakness.

Independent of the magnitude of the surgical team and operator, microsurgery is an invasive method with an enormous cost when comparing to SRS.

SRS, a noninvasive method, is used in various contexts [5]. The differential approach may involve age, comorbidities, patient's (f/m) preferences, and the

noninvasive and cost-effective nature of the procedure. The author and his colleagues have collected experiences with the different scenarios, with the potential for reflection. The use of SRS for VS was first described by the Swedish neurosurgeon Leksel [6], and it represents an alternative to microsurgical resection in patients with small and moderately sized lesions [7]. Lesions up to 3 cm in diameter (including the internal auditory canal in the measurement) can be successfully controlled with this technique in the majority of patients, although most studies that have reported the control of lesion growth included patients without documented lesion growth before treatment initiation.

Best Available Data

A sufficient number of available publications have described the use of SRS for patients with VS. These publications could be used to promote a fair, patient-centered, and objectively differential approach to the recommendation and discussion of innovative treatment options that are safe, noninvasive, effective, and beyond the traditional method of microsurgery. This does not mean that the patient's preferences should be influenced, but rather that patients should be able to provide informed consent based on the best available data from recent years.

Below, the degrees of validity and quality of the available data concerning the initial, postoperative, or hybrid usage of SRS are presented in question and answer format.

Are plausible and valid data available at the "level of evidence 1a" with particular regard to the initial usage of SRS?
No, data from meta-analyses of prospectively designed randomized controlled trials (RCTs) are not available.

Are plausible and valid data available at the "level of evidence 1b" with particular regard to the initial usage of SRS?
No, data are not currently available from prospectively designed randomized controlled trials (RCTs) on this issue.

In summary, it is clear that the overall quality of the available data is not sufficient to draw robust conclusions and firm recommendations.

Are plausible and valid data available at the "level of evidence 2a" with particular regard to the initial or hybrid usage of SRS?
In 2014, Muzevic and colleagues published a systematic review of cohort studies within the institutional frame of the Cochrane Collaboration. However, the extremely strict inclusion criteria meant that no studies were included in the qualitative analysis [1].

The levels of comprehensiveness and consistency of the search methodology used in this systematic review are unclear.

Because this systematic review was the most recent, the fine details must be evaluated. First, the inclusion criteria for the study type were "randomized controlled trials" that might evaluate the efficacy of SRS for VS.

Second, the inclusion criteria defined the type of patients (f/m) as those with a cerebellopontine angle lesion up to 3 cm in diameter that was presumed to be VS. Third, the types of interventions were defined as SRS versus microsurgical resection, SRS versus observation, and SRS versus any other possible treatment or combination of treatments. Fourth, the types of outcome measures defined the proportions of patients in whom the lesion had not grown and whose symptoms (e.g., hearing loss, facial function, tinnitus, balance disturbance) had not deteriorated (a) at 12 months, (b) at 2 years, and (c) over the long term. Additionally, the secondary outcomes were tumor growth, changes in hearing, changes in facial function, changes in tinnitus, and changes in balance disturbance. Furthermore, the quality of life and reported side effects of SRS had been predefined.

The authors stated that they could not perform a data synthesis, as no studies were included in the present version of the review.

They excluded two prospective studies because of a lack of randomization [8, 9].

Both studies had compared SRS with microsurgical resection. In the study by Myrseth and colleagues, patients were allowed to select treatment after receiving information about all treatment alternatives. Patients in the study conducted by Pollock and colleagues also selected treatment after discussing the options.

One study was a prospective RCT that compared two SRS modalities. This study, however, did not report the treatment outcomes required for inclusion in the systematic review. However, the study evaluated irradiation time, treatment time, treatment room occupation time, dose-planning parameters, dosimetry measurements on the patient's body, workflow, patient comfort, and quality assurance procedures in patients with various intracranial pathologies, 79 of whom had acoustic neuromas [10].

In addition to this recent review, three other reviews/meta-analyses were published in the last 5 years [11–13]. The authors of the abovementioned review formulated their agreements and disagreements with the other three reviews as follows: as in this review, no randomized controlled trials were identified. The main body of evidence comes from non-randomized trials or observational studies. Bassim and colleagues [11] concluded that the lack of uniform reporting criteria for tumor control, facial function, and hearing preservation, as well as the variability in follow-up times, makes it difficult to compare studies of radiation treatment for VS; they recommend that consideration be given to using standardized reporting for describing VS resection results. Gauden and colleagues [12] state that the most common quality of life measure used is the 36-item short form health survey (SF-36), although it has not been validated for patients with VS. The problem of selecting uniform outcome measures is also evident in our review (characteristics of excluded studies). All studies emphasize the need for well-designed, randomized prospective research, which is in concordance with our conclusions.

This mission was impossible according to the abovementioned entrance criteria for this systematic review alone. Any expert in the field would know the validity and magnitude of the preexisting information about SRS for VS. The authors' conclusion that there is a "need for well-designed, randomized prospective research" was reached previously by all three earlier reviews. The fact that the other three reviews

were performed only 4, 2, and 1 year before the most recent review [1] leads to some inevitable questions: first, why was a new review needed in 2014? This is unclear, given the knowledge that nothing had been communicated at large-scale conferences and relevant meetings in the previous 4 years. Second, the authors reflected on the "problem of selecting uniform outcome," as if the fact that a real consensus is lacking among the neurosurgery community or between the neurosurgery and radiation oncology communities is a new issue.

Personal Comments

The investigators' assumption that valid evidence exists at the level of evidence 1 clearly demonstrates the investigators' poor understanding of both the radiation oncology and neurosurgery communities.

Everyone who is aware of the realities of the clinical care of VS in the Western hemisphere, including interdisciplinary, financial, and reimbursement issues, would not wonder why this systematic review failed to retrieve sufficient data, as no existing data meet this level of evidence. Traditional methods such as surgery, despite all of the advancements in the last decade and the availability at almost all large medical centers worldwide, would not be compared cleanly and methodologically with an emerging noninvasive technology such as SRS, and this is a matter related to infrastructure and the affinities of hospital administrations for these technologies.

Are plausible and valid data available at the "level of evidence 2b" with particular regard to the initial or hybrid usage of SRS?

Yes, such data are available [5, 7, 14–22].

These ten studies were not arbitrarily selected. After systematically reviewing data at the levels of evidence 1 and 2a, we hereby attempted to define the following reasonable selection criteria:

Time factor (e.g., "length of follow-up")
Type of machine (e.g., "Gamma Knife method")
Dose comparison
Dedicated accelerator (e.g., "Novalis [BrainLab]")

It was also considered valid to select studies with a real "prospective database" and quantity factor (e.g., a large "number of patients (f/m)") as well as issues related to the quality of life and to account for emerging technologies such as CyberKnife.

It was necessary to consider these criteria, which might demonstrate the merits and weaknesses of these data. A large body of literature meets this level of evidence.

For the "length of follow-up," we selected a recent study with a 10-year follow-up period that was published by Lopez and colleagues in 2014 [14].

In that study, Gamma Knife and linear accelerator (Linac) SRS were compared. Doses of 12–13 Gy were applied. Radiation was administered between 1999 and 2010. The reported outcomes included lesion variables and the length of follow-up. The tumor growth control rate exceeded 90 %. The main reason for clinic visit (65.71 %) was unilateral and progressive hearing loss. After treatment, 34.28 % of

patients experienced hearing loss. Cranial nerve (V–VII) involvement was transitory in 100 % of cases. Gamma Knife SRS was used in 82.85 % of patients (f/m). The authors concluded that SRS could be used as a valid alternative to microsurgery in select patients (f/m), particularly elderly patients and those with comorbidities, a small tumor size, and hearing loss.

In this setting, SRS, which was executed using Gamma Knife and Linac in 82 % and 18 % of patients, respectively, was found to be effective after 10 years in the entire group. This is a relevant and significant length of follow-up.

This study featured the disadvantages of a neither prospective nor randomized design.

In addition, it was not obvious why SRS should be limited for elderly patients, as the mean age of the study's patients (f/m) was 58 years.

In addition, it was not obvious why patients (f/m) with relevant comorbidities should be allocated to the SRS group. Perhaps each individual patient (f/m) should instead receive the best available information and then make decisions with their team of physicians (e.g., neurosurgeons and radiation oncologists).

For the "Gamma Knife method" type of machine, we selected a recent study published by Flickinger and colleagues in 2013 [15].

The stated goal of that study was to demonstrate tumor control and complications following SRS. The study included 190 patients (f/m). The median follow-up duration was 30 months (maximum, 85 months). The marginal radiation doses were 11–18 Gy (median, 13 Gy), the maximum doses were 22–36 Gy (median, 26 Gy), and the treatment volumes were 0.1–33 ccm (median, 2.7 ccm). The actuarial 5-year clinical tumor control rate (no requirement for surgical intervention) for the entire series was 97.1 % ± 1.9 %. The 5-year actuarial rates for any new facial weakness, facial numbness, hearing level preservation, and preservation of testable speech discrimination were 1.1 % ± 0.8 %, 2.6 % ± 1.2 %, 71 % ± 4.7 %, and 91 % ± 2.6 %, respectively. Facial weakness did not develop in any patient who received a marginal dose <15 Gy ($n = 163$). Hearing levels improved in 10 (7 %) of 141 patients who exhibited decreased hearing (Gardner–Robertson [GR] classes II–V) before undergoing radiosurgery. According to a multivariate analysis, an increasing marginal dose correlated with an increased incidence of facial weakness ($p = 0.0342$) and decreased preservation of testable speech discrimination ($p = 0.0122$). The authors concluded that SRS via the Gamma Knife method was associated with a sustained high rate of tumor control and lower rates of morbidity [15].

Additionally, for the "Gamma Knife method" type of machine and a large number of patients (f/m), we selected a very recent study published by Boari and colleagues [22].

Of 523 patients treated for VS between 2001 and 2010, the authors included 379 who underwent Gamma Knife SRS as the primary treatment. These patients were not affected by type 2 neurofibromatosis and were subjected to a clinical follow-up of at least 36 months. All patients were subjected to clinical follow-up (mean and median durations of 75.7 and 69.5 months, respectively), whereas audiometric and quantitative radiological follow-up examinations were performed for only 153 and 219 patients, respectively. The patients' ages ranged from 23 to 85 years (mean, 59 years). The mean tumor volume was 1.94 ± 2.2 ccm (median, 1.2 ccm; range, 0.013–14.3

ccm), and the median margin dose was 13 Gy (range, 11–15 Gy). Parameters considered as determinants of the clinical outcome were long-term tumor control, hearing preservation, and complications. Clinical outcomes were correlated with radiological tumor features, dose-planning parameters, and patient characteristics through a statistical analysis. The results revealed that tumor control was achieved in 97.1 % of the patients treated with Gamma Knife SRS. In 82.7 % of the patients, the tumor volume had decreased at the last follow-up, with a mean relative reduction of 34.1 %. The complication rate was very low; most events involved a transient worsening of preexisting symptoms. Patients with vertigo, balance disorders, or facial or trigeminal nerve impairment usually experienced complete or at least significant symptom relief after treatment. However, no significant improvement was observed in patients who had previously reported tinnitus. The overall rate of functional hearing preservation over a long-term follow-up was 49 %; in patients whose hearing met the criteria for GR class I, this value was 71 %, with a rate of 93 % among the subset of patients younger than 55 years. Again, Gamma Knife SRS was found to be a safe and effective treatment for VS, with tumor control in 97.1 % of cases and a very low morbidity rate. Younger GR class I patients had a significantly higher probability of retaining functional hearing even at the 10-year follow-up; for this reason, the time between symptom onset, diagnosis, and treatment should be reduced to achieve better outcomes with regard to functional hearing preservation [22].

For the "robotic Gamma Knife method" type of machine with a large number of patients (f/m), we selected a very recent study published by Lipski and colleagues [17]

The objective of that study was a longitudinal evaluation of volumetric changes in lesions treated with SRS. From 2003 to 2007, this study enrolled 133 patients (f/m). The mean marginal dose was 11.5 Gy (range, 11–12 Gy). In total, 126 cases with a minimum post-SRS follow-up of 2 years (range, 2–7 years; median, 4 years) were analyzed. Temporary enlargement was noted in 25 % of tumors at 6 months after radiosurgery. At 3 years of follow-up, tumor shrinkage, stabilization, and volume increase were observed in 73 %, 23 %, and 4 % of cases, respectively. All progressing lesions later spontaneously stabilized and did not require additional management. In 3 % of patients, marked transitory facial nerve function impairment was observed; however, neither permanent dysfunction nor trigeminal neuropathy attributable to treatment was noted. Hearing impairment relative to the pretreatment level was observed in 4 %, 12 %, 13 %, and 16 % of patients at 6 months, 1 year, 2 years, and 3 years after radiosurgery, respectively, and this trend was statistically significant ($p = 0.0042$). Overall, 77 % of patients with serviceable hearing before treatment maintained this level after 3 years. In conclusion, robot Gamma Knife SRS provided effective and safe treatment for patients (f/m) with VS. Nevertheless, possible temporary tumor enlargement, delayed growth arrest, transient cranial nerve dysfunction, and gradual hearing deterioration after irradiation should be always taken into consideration [17].

From among few recent studies with a real prospective database, one study was selected because of its intrinsic plausibility and the fact that the author of present book was knowledgeable about the database structure. In 2012, Roos and colleagues at the Royal Adelaide Hospital published their findings, which were based on a prospective database [16].

The aim of the study was to access the long-term clinical outcome data of 51 patients (f/m) treated from 1993 to 2000. For 44 patients treated with primary SRS for sporadic (unilateral) lesions, the median age was 63 years, the median maximal tumor diameter was 21 mm (range, 11–34 mm), and the marginal dose was 14 Gy for the first four patients and 12 Gy for the remaining 40 patients. The crude tumor control rate was 97.7 % (one patient required salvage surgery for progression at 9.75 years). Only 8 (29 %) of 28 patients ultimately retained useful hearing (interaural pure tone average ≤50 dB). In addition, although the Kaplan–Meier-estimated hearing preservation rate at 5 years was 57 % (95 % confidence interval: 38–74 %), this decreased to 24 % (95 % confidence interval: 11–44 %) at 10 years. New or worsened V and VII cranial neuropathy occurred in 11 % and 2 % of patients, respectively; all cases were transient. No cases of radiation-induced secondary neoplasms were observed. The long-term follow-up data of patients treated with low-dose (12–14 Gy) Linac SRS confirm the achievement of excellent tumor control and acceptable cranial neuropathy rates, but also demonstrate a continual decrease in hearing preservation for ≥10 years [16].

For the quantity factor (i.e., a "large number of patients [f/m]"), we preferred a population-based study published by Klijn and colleagues in the Netherlands [18].

The authors of this study sought to assess local tumor control and complication rates in a large cohort of patients who underwent Gamma Knife SRS and to identify predictors of tumor control. The records of 420 patients treated with a median marginal dose of 11 Gy were retrospectively analyzed. Patients with neurofibromatosis type 2 or who had previously undergone treatment for VS were excluded. The authors assessed tumor control and complication rates via chart review and used the Cox proportional hazards model to identify predictors of tumor control. The preservation of serviceable hearing, defined as GR classes I–II, was evaluated in a subgroup of 71 patients with serviceable hearing at baseline and available follow-up audiogram data. In that study, the median VS tumor volume was 1.4 ccm, and the median duration of follow-up was 5.1 years. The actuarial 5- and 10-year tumor control rates were 91.3 % and 84.8 %, respectively. Only tumor volume was a statistically significant predictor of the tumor control rate. The tumor control rate decreased from 94.1 % for tumors <0.5 ccm to 80.7 % for tumors >6 ccm. Thirteen patients (3.1 %) developed new or increased permanent trigeminal nerve neuropathy, four (1.0 %) developed new or increased permanent facial weakness, and five (1.2 %) exhibited new or increased hydrocephalus and thus required a shunting procedure. The actuarial 3-year and 5-year hearing preservation rates were 65 % and 42 %, respectively. The authors concluded that the 5-year actuarial tumor control rate of 91.3 % in this cohort was slightly unfavorable when compared with the rates reported for other large studies, although the complication and hearing preservation rates in this study were similar to those in previous reports. Various factors might contribute to the observed differences in reported outcomes. These factors include variations in the treatment indication and the definition of treatment failure as well as a lack of standardized terminology and evaluations of complications [18].

Quality of Life

For issues related to the quality of life of patients (f/m), one very recent study that was truly dedicated to the quality of life theme was shortlisted. Carlson and colleagues published their data in 2015 [19].

The majority of studies comparing treatment modalities have focused on a narrow scope of technical outcomes, including facial function, hearing status, and tumor control. These studies have addressed differences between individual treatment groups, and none have used a disease-specific quality of life instrument. A simple questionnaire using the SF-36, 10-item Patient-Reported Outcomes Measurement Information System (PROMIS-10) short form, Glasgow Benefit Inventory (GBI), and the Penn Acoustic Neuroma Quality-of-Life (PANQOL) scale. Additionally, a pool of adults from the general population was surveyed to provide a non-tumor control group for comparison. The results revealed that a total of 642 respondents were analyzed. The overall response rate of patients with VS was 79 %, and the mean time interval between the treatment and survey was 7.7 years. A multivariate regression analysis found no statistically significant differences between management groups with respect to the PROMIS-10 physical or mental health dimensions, SF-36 Physical or Mental Component Summary scores, or the PANQOL general, anxiety, hearing, or energy subdomains. Patients who underwent SRS or observation reported a better total PANQOL score and higher PANQOL facial, balance, and pain subdomain scores than did patients subjected to microsurgery ($p < 0.02$). For the majority of measures, the differences in scores between the non-tumor control group and patients with VS were greater than the differences observed between individual treatment groups. In summary, the authors stated that the differences in quality of life outcomes after SRS, observation, and microsurgery for VS were small. Notably, the diagnosis of VS, rather than the treatment strategy, most significantly affected the quality of life. With the understanding that many VS do not grow after discovery and that intervention does not confer a long-term quality of life advantage, small- and medium-sized VS should be initially referred for observation, and intervention should be reserved for patients with unequivocal tumor growth or intractable symptoms that are amenable to treatment [19].

To account for emerging technologies such as CyberKnife, we selected a study published by Vivas and colleagues in 2014 [20].

From 2005 to 2011, 73 patients (f/m) were treated. The mean follow-up duration was 40 months. Tumor control, defined as ≤2 mm linear growth or <20 % increase in tumor volume (TV, cubic centimeters) after a minimum of 12 months of monitoring, audiogram profiles, Tinnitus Handicap Inventory scores, and Activities-Specific Balance Confidence Scale scores were measured. The results revealed that among those treated with CyberKnife as the primary modality, 83 % had 0- to 2-mm growth (tumor control or stability), whereas 17 % exhibited growth >2 mm. Of the stable tumors, 29 % shrank by ≥2 mm. A volumetric analysis found that 74 % of patients exhibited a <20 % increase in TV, whereas 26 % exhibited a ≥20 % increase in TV. Of the tumors deemed stable, 65 % had a ≥20 % decrease in volume; in addition, 95 % of patients did not require additional surgical intervention, whereas three required salvage surgery and one underwent additional radiosurgery. The majority of patients began the study with class D hearing; of those with class A or B hearing before treatment, 53.5 % maintained serviceable hearing at 3 years of follow-up. The pretreatment and post-SRS median Tinnitus Handicap Inventory grades were both 1. The pretreatment and post-SRS Activities-Specific Balance Confidence scores were unchanged at 81 %. In conclusion, Linac-based CyberKnife SRS (18 Gy in three

fractions to the 80 % isodose line) provides tumor control rates comparable to those achieved with other forms of radiosurgery. The analysis of tumor growth yielded positive rates of 17 % using maximum linear diameters and 26 % with a volumetric workstation. This discrepancy is consistent with previous reports in which volumetric models were found to be more sensitive for establishing growth. Serviceable hearing was comparable to that of previous SRS reports, with an overall hearing preservation rate of 53.5 %. This rate was 77 % among those with pretreatment class A hearing. SRS did not affect pretreatment tinnitus or vestibular function [20].

Dose Comparisons

For the issue of dose comparison, we selected a recent study by Puataweepong and colleagues [21].

This study compared observations between single-dose SRS and fractionated stereotactic radiotherapy (FSRT), including hypofractionated stereotactic radiotherapy (HSRT) and conventional fraction stereotactic radiotherapy (CSRT). From 1997 to 2010, a total of 139 consecutive patients with 146 VS lesions were treated with X-Knife at Ramathibodi Hospital, Bangkok, Thailand. SRS was selected for 39 lesions (in patients with small tumors ≤3 cm and non-serviceable hearing function), whereas HSRT (79 lesions) and CSRT (28 lesions) were selected for the remaining lesions that were not suitable for SRS. With a median follow-up duration of 61 months (range, 12–143 months), the 5-year local control rates were 95 %, 100 %, and 95 % in the SRS, HSRT, and CSRT groups, respectively. Hearing preservation was observed in 75 % of patients after SRS, in 87 % after HSRT, and in 63 % after CSRT. The cranial nerve complication rate was low in all groups. There were no statistically significant differences in local control, hearing preservation, or complications between the treatment schedules. Given these results, the authors concluded that HSRT might be preferable to CSRT for patients with serviceable hearing because of the shorter duration of treatment [21].

Technology Comparisons

For usage of the principle of SRS via a dedicated accelerator, such as Novalis (BrainLab), we present our own published data [7].

We assessed local control and functional outcomes after Linac-based SRS for VS. Between 1998 and 2008, 190 patients with VS were treated with SRS. All patients had tumors with diameters <2 cm. Patients received a tumor margin dose of 13.5 Gy prescribed to the 80 % isodose line. The primary endpoint was local control. The secondary endpoints were symptomatic control and morbidity. The median follow-up duration was 40 months. Local control was achieved in 88 % of patients. No acute adverse reactions exceeded a severity of grade I. Trigeminal nerve dysfunction was present in 21.6 % of patients ($n=41$) prior to SRS. After treatment, 85 % ($n=155$) had no change, 4.4 % ($n=8$) experienced symptom relief, and 10.4 % ($n=19$) developed new symptoms. Prior to treatment, some patients exhibited facial nerve dysfunction: paresis, 12.6 % ($n=24$) and dysgeusia, 0.5 % ($n=1$). After treatment 1.1 % ($n=2$) reported improvement, and 6.1 % ($n=11$) experienced new symptoms. Hearing problems were present in 69.5 % of patients before SRS ($n=132$). After treatment, 62.6 % ($n=144$) had no change, 10.4 % ($n=19$) experienced improvement, and 26.9 % ($n=49$) became hearing impaired. We concluded that this series of SRS for small VS yielded similar local control rates as microsurgery, and thus, SRS is an effective, noninvasive image-guided

procedure. The observed functional outcomes indicate the safety and effectiveness of Linac-based SRS. Patients may now be informed of the clinical equivalence of SRS and microsurgery [7].

Summary

Stereotactic radiosurgery is a safe, effective treatment method for patients (f/m) with vestibular schwannoma. With special regard to the quality of life of patients (f/m) independent of age, this noninvasive method is a good alternative to any surgery, so far the lesions are small in size (<2.5 cm) and are not invading into the bony structures in the base of the skull (Tables 6.1, 6.2, and 6.3).

Stereotactic radiosurgery is indeed cost-efficient too.

The nonarbitrary selection of the best available scientific evidence, in this case it was "level of evidence 2b," noninvasive image-guided stereotactic radiosurgery

Table 6.1 Prospective series without active treatment for vestibular schwannoma

Study (*n*)	Follow-up (mean) in months	Growth, number of cases	Useful hearing Begin	Useful hearing End	Quality score
Varughese (2012) (*n* = 193)	43	52	114	82	7
Godefroy (2009) (*n* = 70)	40	25	31	21	7
Di Maio (2009) (*n* = 47)	27.1	8	12	8	6
Stangerup (2008) (*n* = 636)	48	178	314	154	7
Hajioff (2008) (*n* = 72)	121	29	–	–	6
Stipkovits (2001) (*n* = 44)	42	8	–	–	6
Mirz (2000) (*n* = 64)	43	15	–	–	6

Varughese et al. [23], Godefroy et al. [24], Di Maio and Akagami [25], Stangerup et al. [26], Hajioff et al. [27], Stipkovits et al. [28], Mirz et al. [29]

Table 6.2 Prospective series with active treatments for vestibular schwannoma, functional comparison

Study/year	Follow-up (mean) in months	Growth, number of cases	Useful hearing Begin in %	Useful hearing End in %	Quality score
Myrseth (2009) *n* = 60 RS *n* = 28 S	24	*n* = 1 RS *n* = 0 S	27 for RS 44 for S	17 for RS 0 for S	7
Pollock (2006) *n* = 46 RS *n* = 36 S	42	*n* = 1 RS *n* = 0 S	65 for RS 61 for S	61 for RS 5 for S	8
Régis (2002) *n* = 97 RS *n* = 110 S	48	*n* = 3 RS *n* = 10 S	49 for RS 72.7 for S	54.2 for RS 5 for S	8

Myrseth et al. [9], Pollock et al. [8], Régis et al. [30]
RS radiosurgery, *S* surgery

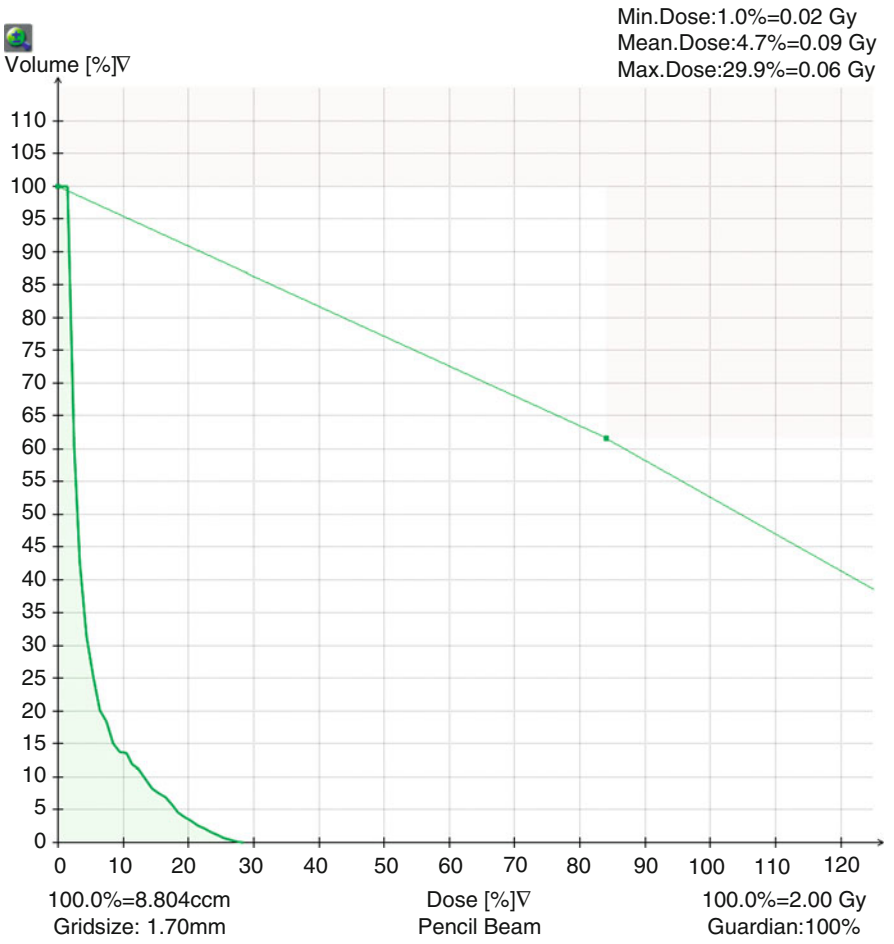
Table 6.3 Prospective series with active treatment for vestibular schwannoma

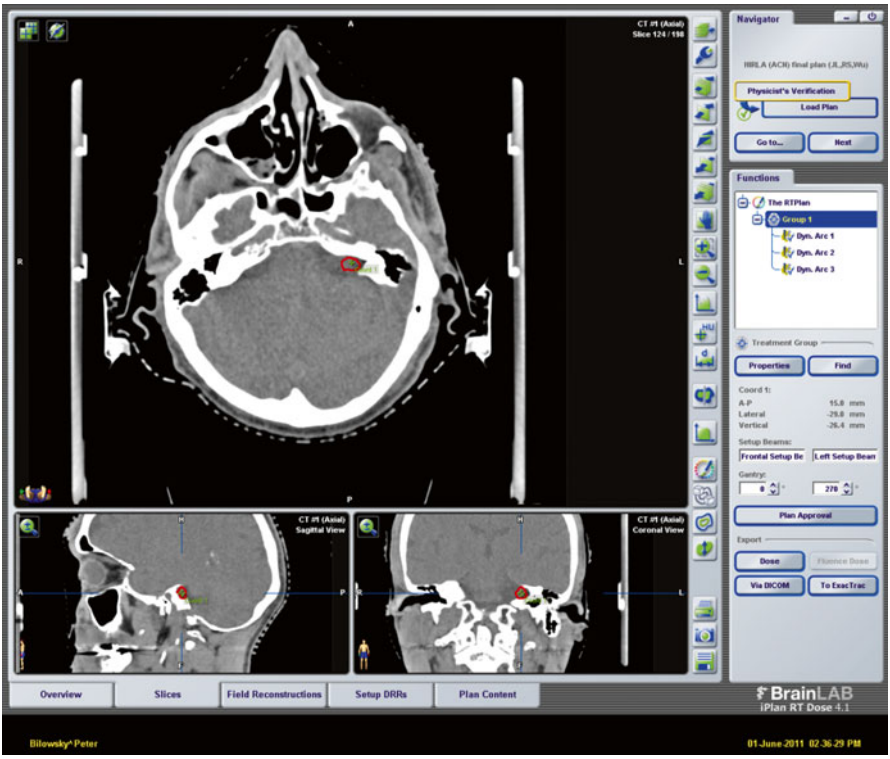
Strategy	Tumor local control (%)	Useful hearing (%)	Complications (%)
Radiosurgery	60.2	60.2	1
Surgery	94.3	4.3	2
Wait and see	71.8	56.3	1

Outcome probabilities

appears to be safe and effective, independent of the selected study type. This was particularly true with regard to the time factor (e.g., "length of follow-up"), type of machine (e.g., "Gamma Knife method"), elected studies with a real "prospective database," quantity factor (e.g., a large "number of cases"), issues related to the quality of life, emerging technologies (e.g., CyberKnife), and dose comparison.

This was also true for the use of noninvasive image-guided stereotactic radiosurgery via dedicated accelerators such as Novalis, as we have demonstrated in large cohorts by our own experiences.

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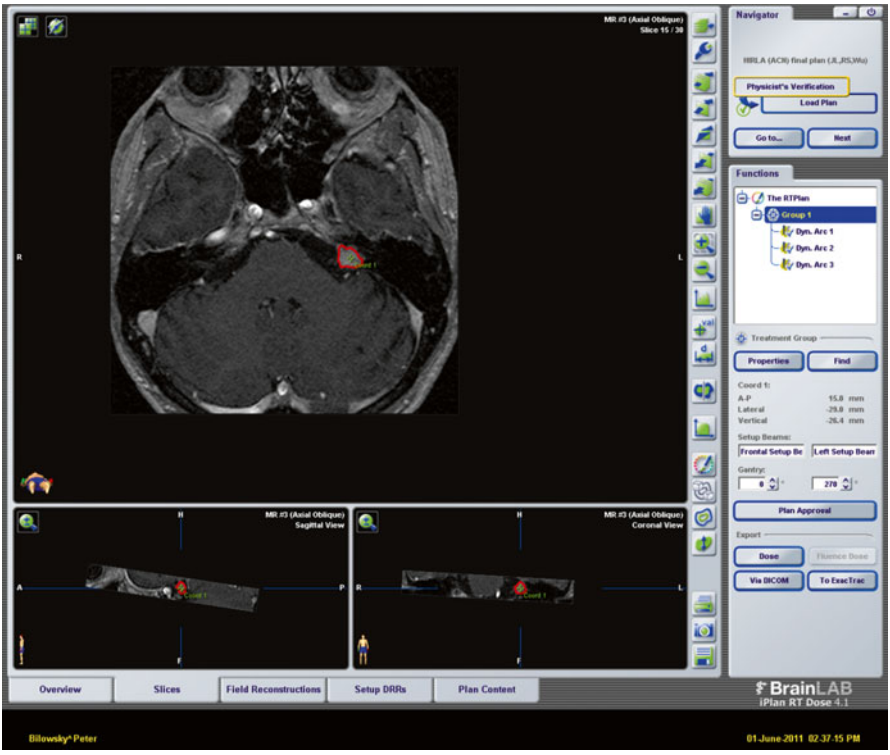
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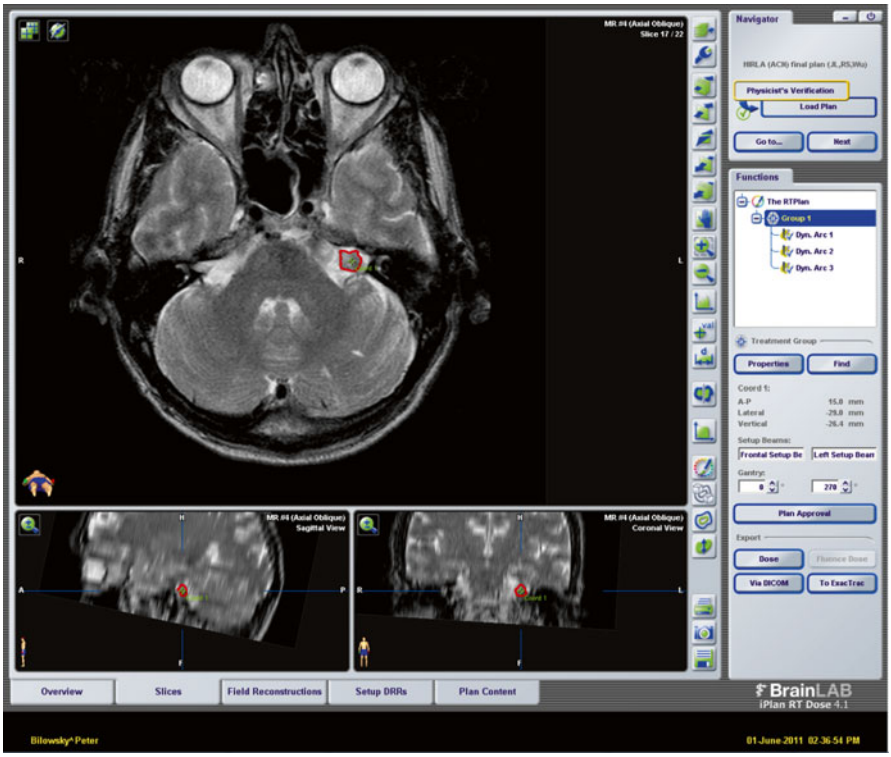
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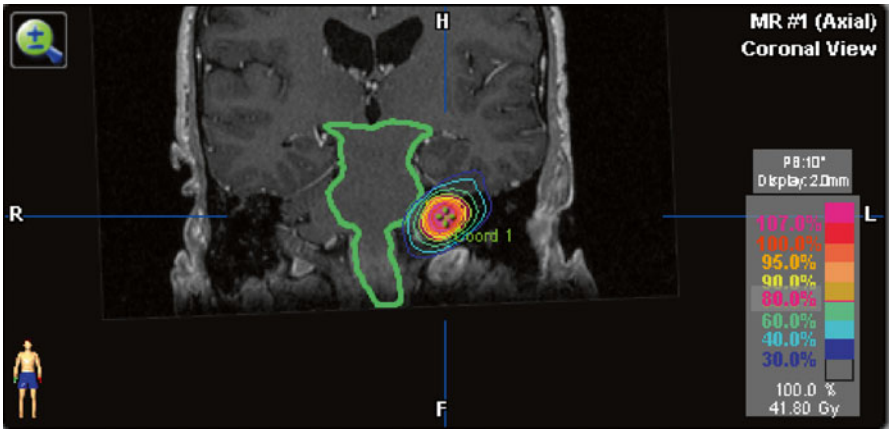
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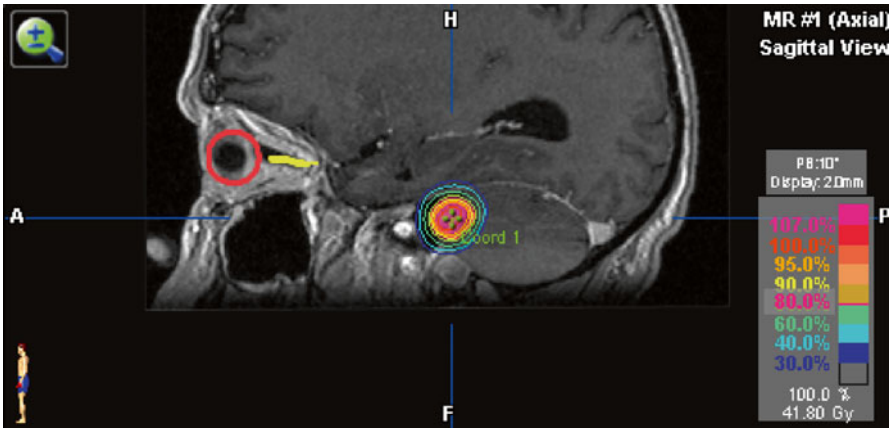
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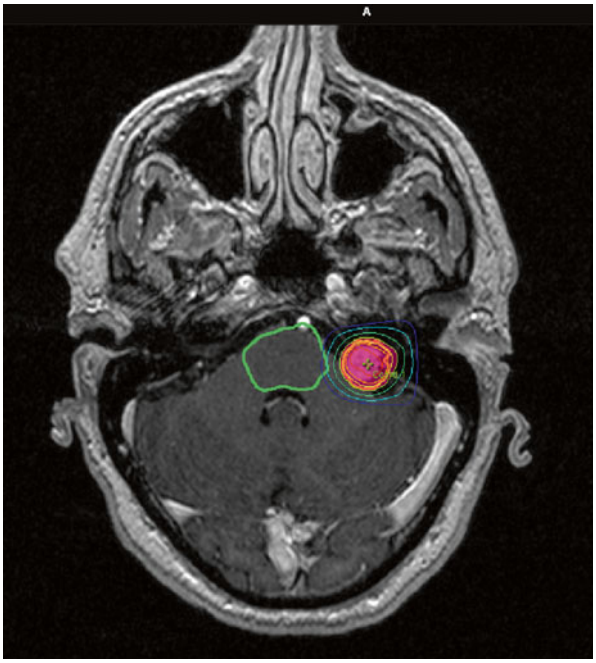
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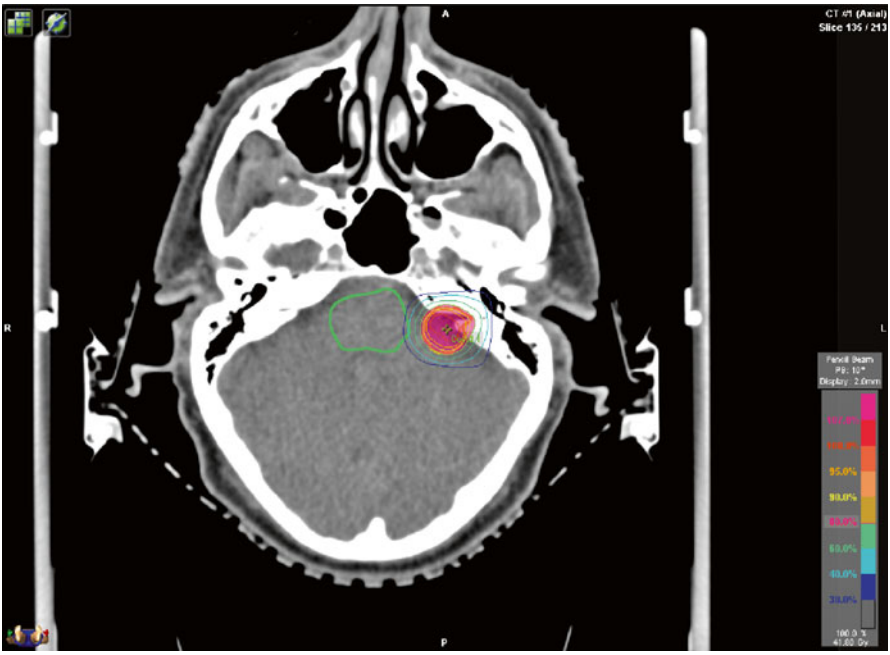

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Meningioma

7

Abstract

Meningiomas arise from the covering cells of the arachnoid layers of the dura mater. While mostly benign, as the second most common cranial tumor they still represent a significant challenge. Dependent on the occurrence site, for example, the base of the scull or sinus cavernous or convexity, and whether they appear uni- or multifocal, the lesions may lead to mild or even severe clinical problems, and it reduces the quality of life of patients (f/m).

Invasive surgical procedures seem to be the method of choice. Image-guided stereotactic radiosurgery in its multiple technologic appearances as the are Linac, Gamma Knife, or CyberKnife radiosurgery; on the other hand, could effect substantially the lesion by stopping its growth and improve relevant clinical symptoms, when performed after surgery or alone.

Consecutively, it demonstrates a noninvasive high precision and safe technique in treating patients (f/m) with traceable improvement of quality of life. Image-guided stereotactic radiosurgery could be performed in outpatient setting and is cost-efficient.

Background

Intracranial meningiomas are tumors that arise either from the cells that cover the arachnoid layer of the dura mater or from the intraventricular choroid plexus. Although these tumors are mostly benign, they still represent a major challenge to the physicians involved with therapeutic management. Meningioma is the second most common type of primary brain tumor [1–3]. Typically, patients with neurofibromatosis type 2 (NF2) and most other patients with spontaneous meningiomas harbor mutations on chromosome 22; however, other chromosomal aberrations (1p, 6q, 10, and 18q) have also been noted. In addition, environmental factors such as ionizing radiation have been established as causative factors [1, 4].

H. Badakhshi, *Image-Guided Stereotactic Radiosurgery*,
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In the 1970s, symptomatic tumors were discovered at a rate of 2 per 100,000 people, whereas asymptomatic tumors occurred at a rate of 5.7 per 100,000 people, for a total incidence of 7.7 per 100,000 people. Notably, the discovery of asymptomatic meningiomas has tripled with the advent of modern sophisticated imaging systems such as computed tomography (CT). High-dose ionizing radiation exposure is an established risk factor for meningioma, and lower doses may also increase the risk; however, the responsible types and doses remain controversial or poorly understood [3]. Because women are twice as likely as men to develop meningiomas and because these tumors express hormone receptors, an etiologic role for hormones (both endogenous and exogenous) has been hypothesized. The extent to which immunologic factors influence the etiology of meningiomas has been largely unexplored. An increasing emphasis on brain tumor research, coupled with the advent of new genetic and molecular epidemiologic tools, promises advances in knowledge about the causes of intracranial meningioma [5, 6].

Small lesions are usually asymptomatic and are discovered incidentally at autopsy. Larger tumors may cause symptoms depending on the size and location. Focal seizures may be caused by meningiomas that overlie the cerebrum [7].

Progressive spastic weakness in the legs and incontinence may be caused by tumors that overlie the parasagittal frontoparietal region. Sylvian tumors may cause myriad motor, sensory, aphasic, and seizure symptoms depending on the location. Increased intracranial pressure will eventually occur. Diplopia or an uneven pupil size might occur if tumor-related pressure causes nerve III and/or VI dysfunction in the brain [8, 9].

To ensure correct treatment planning, doctors must obtain as much information as possible about the type, position, and size of the lesion. Initially, a neurological examination is conducted to assess any effect of the lesion on the nervous system. A magnetic resonance imaging (MRI) scan must be conducted to determine the exact position and size of the lesion(s). MRI scans are the most widely used diagnostic tests because they can very effectively identify even small meningiomas. MRI scans usually include the injection of contrast agent in order to determine the exact position and size of the lesion. Occasionally, an angiogram will be performed, wherein a dye is used to highlight the blood vessels in the brain and their relationships with the meningioma. A biopsy or sample of cells is taken from the tissue to confirm the exact tumor type.

Meningiomas are divided into three categories. Grade I or benign meningiomas are slow-growing tumors that often do not affect the surrounding normal brain. Benign meningiomas are the most common type, accounting for 70–80 % of all meningiomas. Many benign meningiomas do not require treatment. Most treated benign meningiomas do not recur. Grade II or atypical meningiomas usually grow more rapidly than benign meningiomas and have a higher risk for recurrence after treatment.

Grade III anaplastic, or malignant, meningiomas are a form of brain cancer and are most likely to recur after treatment. These tumors are rare, accounting for approximately 2–3 % of all meningiomas.

Surgery is the method of choice for the treatment of meningiomas [10]. Although complete tumor elimination, usually via resection including the associated dura and bone (Simpson grade I), is the optimal management for most meningiomas, not all such tumors are amenable to safe surgical resection. Conservative medical therapy

has been discussed, and indications of effectiveness and long-term control have been observed in selected cases [9]. Other interventional but noninvasive options, such as stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (FSRT), are recommended for some patients. Meningiomas are suitable for either adjuvant or primary SRS, which requires minimal or no brain invasion when administered to the usual regular lesion borders [11–14].

Stereotactic Radiosurgery for Meningioma

The main SRS modalities used at most centers include linear accelerators or Gamma Knife units; both are suitable for SRS administration to a variety of targets, including vestibular schwannomas and, of course, meningiomas [1, 2]. CyberKnife is an image-guided SRS technique that is currently included in the therapeutic arsenal against meningioma [15, 16].

SRS, which was initially used for the management of skull base meningiomas [2] that were difficult to resect, has emerged as a valuable modality in the management of meningiomas in other locations and has yielded good local tumor control with a tolerable side effect profile [17–20].

During long-term follow-ups, primary SRS was shown to provide good local control rates that are equivalent to those achieved with Simpson grade I resection for small- and medium-sized meningiomas (diameter, 3.5 cm) [4, 21–24].

Adjuvant SRS is also beneficial, as it promotes improved progression-free survival; Condra and colleagues demonstrated that adjuvant radiosurgery after subtotal resection resulted in a superior 15-year progression-free survival when compared with gross total resection without SRS [25].

Studies that have reported the outcomes of Gamma Knife or Linac protocols have demonstrated local control rates varying from 86 % to 97 % and 89 % to 96 %, respectively, over a mean/median follow-up of at least 5 years [17, 18, 26, 27].

Overall, few reports in the literature describe more than 10 years of follow-up. In addition, CyberKnife device outcome reports are limited; Colombo and colleagues reported a local control rate of 96.3 % and an adverse radiation event rate of 3.7 % over a 2-year follow-up period [28]. Although these numbers are promising, long-term outcomes are needed to establish efficacy.

The results of SRS primarily depend on the lesion location, World Health Organization (WHO) grade, and lesion diameter/volume. Other factors reported to affect outcomes include age, genetic and molecular markers (e.g., vascular endothelial growth factor), and timing of SRS with respect to initial surgical resection.

Role of the Lesion Location

Meningioma locations are classified as either skull base or others (e.g., posterior fossa, convexity, parasagittal, parafalcine) [4].

Complete microsurgical resection of some skull base tumors is associated with significant risk, with combined morbidity and mortality rates as high as 67 % in

specific studies [29–33]. In addition, the long-term progression-free survival rates are limited when microsurgical resection is the sole utilized modality—particularly if total resection is not attained—with recurrence rates of 30–40 % in follow-up periods of 5 and 10 years [34, 35].

Convexity lesions and those located in the cavernous sinus are also associated with a higher surgical risk, with mortality and permanent morbidity rates ranging from 10 to 29 %, depending on the specific study [23, 24, 36, 37].

Consequently, SRS is often considered as the primary approach or adjuvant therapy after a planned subtotal resection, particularly when a total resection is not safe. The post-SRS outcomes, however, differ according to the lesion location.

Base of the Skull

Good results have been observed following the treatment of skull base meningiomas with noninvasive image-guided stereotactic radiosurgery or fractionated radiosurgery (F-SRS) [30, 32, 38].

In 2009, McGregor and colleagues reported the particular challenges associated with tumors arising from the dura of the skull base. Advances in radiation therapy, including stereotactic techniques, could expand the available treatment options in these situations. These techniques may be used as adjuncts to surgery or as alternative modalities for the treatment of these complex tumors [39]. In 2011, Onodera and colleagues published [40] the long-term outcomes of 27 patients (f/m) treated with F-SRS for benign intracranial skull base meningiomas. This study featured median follow-up durations of 90 months after initial treatment and 63 months after treatment. The median biological equivalent dose, calculated using an alpha/beta ratio of 2.0 Gy, was 82.0 Gy (range, 60–106 Gy). The 5-year overall survival rate was 95.7 % (95 % confidence interval [CI], 87.3–100 %) after initial treatment and 96.2 % (95 % CI, 88.8–100 %). The 5-year overall survival and local control rates of patients who received F-SRS alone were both 100 %. The 5-year progression-free survival and local control rates after F-SRS were both 100 % with a tumor volume of <9.1 cc and 68.2 % (95 % CI, 37.2–99.2 %) and 75.8 % (95 % CI, 45.2–100 %) for tumors 9.1 ccm, respectively. The differences in the progression-free survival rate ($p = 0.022$ [41]) and local control rate ($p = 0.044$) were significant. The local control rate was significantly worse in patients who received fractionated radiosurgery for recurrent tumors ($p = 0.01$). No late radiation damage was observed during the follow-up period. The authors concluded that F-SRS is a safe and effective treatment for benign intracranial skull base meningiomas, especially in patients with tumors <9.1 cc or those intended to receive fractionated radiosurgery with or without surgery as the initial treatment [40].

A study published in 2012 by Shen and colleagues demonstrated the beneficial effects of fractionated radiosurgery for the treatment of cranial neuropathies in a retrospective cohort study of 225 patients with skull base meningiomas [42]. Patients (f/m) were treated with a standard dose of 54 Gy. Symptoms at the time of fractionated radiosurgery were classified based on the affected cranial nerve. The

median follow-up time was 4.4 years. In 92 % of the cases, patients were symptomatic at the time of fractionated radiosurgery; the most common symptoms were impaired visual field/acuity (58 %) or extraocular movement (34 %). After treatment, durable improvement in at least one symptom occurred in 57 % of cases, including 40 % of those with visual acuity/visual field deficits and 40 % of those with diplopia/ptosis deficits. Of all symptomatic patients, 27 % experienced improvement in at least one symptom within 2 months of the end of treatment. The authors concluded that this method is "very effective in achieving improvement of cranial neuropathies from skull base meningiomas, particularly visual symptoms. Over half of treated patients experience a durable improvement of at least one symptom" [42]. One of the largest cohorts was treated in Heidelberg, Germany. Combs and colleagues published their data in 2013 [38]. The aim of that study was to evaluate the long-term outcomes of SRS in 507 patients with skull base meningiomas. At the time of treatment, most patients presented with clinical symptoms, including double vision, headache, nausea, trigeminal or facial nerve dysfunction, or exophthalmos. Prior neurosurgical intervention involving a partial resection or biopsy was performed in 266 patients (54 %). Treatment was delivered using a 6-MV Linac or a TomoTherapy system. Fractionated radiosurgery was applied in 376 patients (74 %), and intensity-modulated radiotherapy (IMRT) was applied in 131 patients (26 %). A median total dose of 57.6 Gy (range, 25–68 Gy) was prescribed in a dose range of 1.6–5 Gy. To evaluate long-term toxicity, as well as the quality of life (QOL), we sent detailed questionnaires comprising specific questions regarding the skull base locations of tumors. A particular focus was placed on long-term sequelae, including visual deficits, cranial nerve deficits, headaches, fatigue, or any other symptoms that would impair the overall quality of life. The median follow-up time was 107 months (range, 1–270 months). Overall, the treatment was well tolerated. The local control rates for the whole cohort were 95 % at 5 years and 88 % at 10 years. Patients with a benign histology had a significantly higher local control rate than did those with high-grade meningiomas. For benign meningiomas, the local control rate was 91 % at 10 years. For high-risk meningiomas, the local control rates were 81 % at 5 years and 53 % at 10 years. The quality of life was unchanged in 47.7 % of the patients, and 37.5 % showed improvement. Most patients reported either symptom improvement or steady state; only a few patients experienced worsening of their disorders over time or side effects. Accordingly, this study demonstrated that fractionated radiosurgery or IMRT leads to long-term tumor control with minimal side effects and also preserves the quality of life of patients with skull base meningiomas [38].

Another group focused on toxicity associated with Gamma Knife SRS. Bir and colleagues presented their data in 2014 [43]. Of 136 patients, 68 had recurrent or residual tumors after microsurgical resection; the remaining 68 patients underwent Gamma Knife SRS alone. The study population was evaluated clinically and radiographically after Gamma Knife SRS treatment. Following treatment, significant variations in meningioma growth control were observed (decreased size in 69 patients [50.7 %], arrested growth in 47 patients [34.6 %], and increased tumor size in 20 patients [14.7 %]). Progression-free survival rates at 3, 5, and 10 years after

Gamma Knife SRS were 98 %, 95 %, and 85 %, respectively. The overall rate of improvement in signs and symptoms after Gamma Knife SRS, compared with the pretreated state, was 30 % (71 % versus 41 %; $p = 0.0001$). The Karnofsky Performance Scale scores improved significantly after Gamma Knife SRS, compared with the pretreated status (92 versus 80). Twenty patients (14.7 %) required resection. The findings of this study revealed that Gamma Knife SRS offers a high rate of tumor control, preservation of multiple nerve functions, and a good quality of life in patients with both new and recurrent meningiomas [43]. In 2014, Cohen-Inbar and colleagues published the long-term results of 135 cases treated with Gamma Knife SRS [44]. Patients with a World Health Organization grade I skull base meningioma who were treated with single-session Gamma Knife SRS and underwent a minimum of 60 months of follow-up were selected from a prospectively collected institutional review board-approved database. The cohort comprised 135 patients (73 men, 54.1 %). The median age was 54 years (range, 19–80 years). The median tumor volume was 4.7 cm (range, 0.5–23 cm). The median dose to the margin was 15 Gy (range, 7.5–36 Gy). The median follow-up duration was 102.5 months (range, 60.1–235.4 months). Patient and tumor characteristics were analyzed to determine predictors of neurological function and tumor progression. At the last follow-up, tumor volume control had been achieved in 88.1 % of the patients ($n = 119$). Post-SRS clinical improvement or stability was observed in 61.5 % of the patients. The 5-, 10-, and 15-year actuarial progression-free survival rates were 100 %, 95.4 %, and 68.8 %, respectively. Favorable outcomes (both tumor control and clinical preservation/improvement) were achieved by 60.8 % of the patients ($n = 79$). The pre-SRS Karnofsky Performance Scale score ($p = 0.001$) and post-SRS clinical improvement/preservation ($p = 0.003$) were found to influence tumor progression significantly. Again, the authors concluded that Gamma Knife SRS offers a highly consistent rate of tumor control for World Health Organization grade I skull base meningiomas, along with an acceptably low incidence of neurological deficits. In addition, the Karnofsky Performance Scale score at the time of radiosurgery serves as a reliable long-term predictor of the overall outcome [44].

In 2015, Navarria and colleagues reported the use of hypofractionated radiosurgery in 27 patients (f/m) with skull base meningiomas [45]. Patients (f/m) received a dose of 30 Gy in 5 fractions via volumetric modulated arc therapy. A total of 18 patients (f/m) were symptomatic before treatment. The study endpoints were local toxicity and symptom relief. Tumors were located in the anterior skull base in 4 of 26 cases, the middle skull base in 12 of 27 cases, and the posterior skull base in 11 of 27 cases. Radiosurgery was performed as the initial treatment in 17 (65 %) patients and subsequent to previous partial resection in 9 (35 %) patients. The median follow-up duration was 24.5 months (range, 5–57 months). The clinical remission of symptoms, either complete or partial, was achieved in the vast majority of patients after treatment. Of the 18 symptomatic patients, partial remission occurred in 9 patients (50 %) and complete remission in the other 9 patients (50 %). All asymptomatic patients retained their status after treatment. No severe (grades III–IV) neurologic toxicity events were recorded. No increase in recurrent meningioma at the treatment site was observed; 16 (62 %) patients had stable disease and

9 (38 %) exhibited a tumor reduction. The mean tumor volume after treatment was 10.8. The mean actuarial overall survival duration was 54.4 ± 2.8 months. The 1- and 2-year overall survival rate was 92.9. Again, hypofractionated radiosurgery was proven feasible for patients who were ineligible for full surgery or ablative radiation therapy. The achieved local control and durability of results suggest that this approach should be recommended for properly selected cases [45].

In 2015, Starke and colleagues published their data with a focus on large skull base meningiomas [17]. When symptomatic, patients with such tumors are often initially treated with resection. For tumors located in close proximity to eloquent structures or patients unwilling or unable to undergo resection surgery, SRS may be an acceptable therapeutic approach. In this study, the authors reviewed the SRS outcomes of skull base meningiomas with volumes >8 ccm, which corresponds to lesions with approximate diameters of 2.5 cm. The authors reviewed data from a prospectively compiled database that documented the outcomes of 469 patients with skull base meningiomas who were treated with single-session Gamma Knife SRS. Seventy-five patients had tumor volumes >8 ccm, which was defined as a large tumor. All patients were followed up for a minimum of 6 months, but were included if they experienced a complication at any time point. Thirty patients were initially treated with Gamma Knife SRS, and 45 were treated after microsurgery. The patient and tumor characteristics were assessed to determine the predictors of new or worsening neurological function and tumor progression after Gamma Knife SRS. After a mean follow-up duration of 6.5 years (range, 0.5–21 years), the tumor volume was unchanged in 37 patients (49 %), decreased in 26 patients (35 %), and increased in 12 patients (16 %). The actuarial rates of progression-free survival at 3, 5, and 10 years were 90.3 %, 88.6 %, and 77.2 %, respectively. Four patients developed new or worsened edema after Gamma Knife SRS, and preexisting edema was reduced in three patients. In a Cox multivariable analysis, the covariates associated with tumor progression were 1) presentation with any cranial nerve deficit from III to VI (hazard ratio [HR] = 3.78; 95 % CI, 1.91–7.45; p <0.001), history of radiotherapy (HR = 12.06; 95 % CI, 2.04–71.27; p = 0.006), and a tumor volume >14 ccm (HR = 6.86; 95 % CI, 0.88–53.36; p = 0.066). Among patients subjected to detailed clinical follow-up (n = 64), neurological function was unchanged in 37 patients (58 %), improved in 16 patients (25 %), and deteriorated in 11 patients (17 %). In a multivariate analysis, factors identified as predictive of new or worsening neurological dysfunction were a history of surgery (odds ratio [OR] = 3.00; 95 % CI, 1.13–7.95; p = 0.027), presentation with any cranial nerve deficit from III to VI (OR = 3.94; 95 % CI, 1.49–10.24; p = 0.007), and decreasing maximal dose (OR = 0.76; 95 % CI, 0.63–0.93; p = 0.007). Tumor progression was present in 64 % of patients with new or worsening neurological deficits. The authors concluded that Gamma Knife SRS affords a reasonable rate of tumor control in patients with large skull base meningiomas, with a low incidence of neurological deficits. Patients with a tumor volume <14 ccm and no cranial nerve deficits from III to VI were more likely to achieve effective tumor control [17].

Our group has extensively communicated its data [1]. We focused on one clinical study of skull base meningiomas [2]. The purpose of this study was to analyze the

feasibility, safety, and long-term efficacy of Linac-based fractionated radiosurgery for skull base meningiomas. We evaluated the long-term clinical outcomes of patients and identified prognostic factors after fractionated radiosurgery. We included 136 patients with a median age of 57 years who received fractionated radiosurgery for skull base meningioma. A total of 34 patients had a grade I meningioma; no histologic information was obtained for 102 cases (grade 0). Treatment was delivered as primary treatment for 57 patients and postoperatively for 79. Patients received a mean total dose of 56.95 Gy (range, 32.4–63 Gy). The median follow-up duration was 44.9 months. The overall progression-free survival rates were 96.9 % after 3 years, 93.8 % after 5 years, and 91.5 % after 10 years. Patients with unknown histology had progression-free survival rates of 100 %, 98.7 %, and 93.5 % at 3, 5, and 10 years, respectively, whereas those with biopsy-proven grade I meningioma had corresponding rates of 100 %, 91.7 %, and 85.9 %, respectively. Patients treated with adjuvant radiotherapy had a significantly worse progression-free survival rate compared with those who had been treated with primary radiotherapy ($p = 0.043$); notably, the progression-free survival rates were independent of lesion size. The most common acute grade I symptoms were headache, fatigue, and local alopecia. The most common chronic grade I symptoms were fatigue and headache. Through this large study, we were able to demonstrate, in concurrence with other authors, that fractionated radiosurgery is an effective and safe treatment modality that yields high progression-free survival rates among patients with intracranial meningioma. We identified "prior surgery" as a significant poor prognostic factor [2].

Sinus Cavernous Lesions

Meningiomas that originate in the cavernous sinus have been shown to respond well to SRS. Size is an important feature of these tumors; Kondziolka and colleagues [24] and Maruyama and colleagues [46] have suggested that cavernous sinus tumors with a maximal diameter of 3 cm are the most appropriate for SRS. This size typically allows the delivery of an effective dose while maintaining visual safety. In addition to considering tumor size, Maruyama and colleagues [46] devised a management algorithm whereby microsurgical resection—in most cases, planned subtotal resection—is recommended for lesions that pose a structural risk to the optic apparatus or if the diagnosis is unclear. In this suggested approach, the residual tumor is managed with SRS. The greatest challenge associated with SRS-based management of cavernous sinus meningiomas is attributed to difficulties in accurately differentiating the target volume from the surrounding structures for contouring purposes and in determining the safety dose limit tolerated by critical structures. Although convexity meningiomas are not as intricately associated with critical neural structures such as the cranial nerves and brainstem, resection of these tumors may still be high risk, given the association of these tumors with the venous sinuses, veins, and underlying cortex. Furthermore, resection may be inappropriate for elderly or frail patients (f/m) [24].

Although reasonable results have been achieved via SRS for convexity meningiomas, the control rates are lower and toxicities are higher than those observed at other

locations [47]. This discrepancy likely has a multifactorial cause. A greater proportion of these cases often represent failed resections or recurrences of high-grade meningiomas that were referred for SRS; in addition, a non-basal location and prior resection have been suggested as predictors of high-grade meningiomas [48]. Other groups have suggested that, by nature, convexity meningiomas tend to be of a higher grade than meningiomas in other locations, regardless of prior treatment [49, 50].

Given the higher tolerability of some cortical brain regions to the mass effect—in comparison with the brainstem, for example—it is also likely that patients with convexity meningiomas will present at a later stage and with larger lesions. The greater pial contact interface also increases the risk for edema following SRS [20]. This is particularly true if peritumoral edema is present before radiosurgery. Regardless, SRS plays a critical role in the management of convexity lesions, particularly when used as an adjunct in the management of high-grade meningiomas or recurrences.

Role of Lesion Size

Tumor size may be represented by volume or diameter. Regardless, tumor size affects progression in patients undergoing SRS for meningiomas [51–53].

Various cutoffs that correlate with local control rates and progression have been suggested. Lesion size affects the maximal safe deliverable SRS dose, which varies by location; the dose reduction necessary to avoid morbidity is the primary limiting factor affecting SRS outcomes for large meningiomas. Although size categories are a useful guide, predictors of tumor responses are multifactorial, and binary cutoffs should not be used in isolation [47, 54].

Role of Lesion Histology

Histology has played an eminent role in the prognosis of meningioma [20, 55, 56].

The histological grade of a meningioma has treatment implications; for example, grade I lesions are associated with the best outcomes [4].

Most authors have reported studies of patients with an average follow-up period of 2–5 years; few studies have obtained 10-year follow-up data. From a study of Linac-based treatment in 14 patients with World Health Organization grade II and 14 patients with grade III meningiomas (maximum diameter, 3 cm), El-Khatib and colleagues reported 5- and 10-year actuarial total control rates of 81 % (grade II) and 60 % (grade III) [57]. The mean follow-up duration was 5 years; only a few patients were followed for up to 10 years. All patients had undergone a previous microsurgical resection. This study was limited by its small sample size. Patients with high-grade meningiomas also have a low disease-specific survival rate: overall survival rates after SRS among grades II and III patients have been reported to vary from 59 % to 81 % 28–31, 33 and from 0 % to 59 %, respectively [57].

Other outcome data are presented in Table 7.1, 7.2, and 7.3.

Table 7.1 The role of histology WHO grade I for the clinical outcome

Study	Machine	Nr	Local control in %	Survival in %	Comment
Bledose (2010) [58]	GK	116	95.7	5-y OS: 98	23 % toxicity
Flannery (2010) [59]	GK	163	90	10-y OS: 81	8 % toxicity
Zada (2010) [60]	GK	116	94.1	10-y PFS: 84	8 % toxicity
Kondziolka (2009) [61]	GK	32	96.9	5-y OS: 96.9	9.6 % toxicity
Kondziolka (2008) [62]	GK	384	93	10-y OS: 96.2	7.7 % toxicity
Kreil (2005) [63]	GK	200	98	10-y PFS: 97.2	2.5 % toxicity
Di Biase (2004) [64]	GK	162	91.7	5-y OS: 91	8.3 % toxicity
Nicolato (2002) [65]	GK	122	97.5	5-y OS: 100	4 % toxicity
Eustacchio (2002) [66]	GK	121	98.3	–	1.7 % toxicity
Stafford (2001) [67]	GK	168	91	5-y OS: 100	

GK Gamma Knife, *CK* CyberKnife, *L* linear accelerator, *OS* overall survival, *PFS* progression-free survival

Table 7.2 The role of histology WHO grade II for the clinical outcome

Study	Machine	Nr	Local control in %	Survival in %	Comment
Kim (2012) [68]	GK	33	56.7	5-y OS: 65	6.7 % toxicity
EL Khatib (2011) [57]	L	8	85.7	10-y OS: 87.5	3.5 % toxicity
Kondziolka (2009) [61]	GK	15	50	5-y OS: 85.7	–
Kondziolka (2008) [62]	GK	54	50	10-y OS: 52	–
Harris (2003) [69]	GK	18	–	10-y OS: 59	3.3. toxicity
Stafford (2001) [67]	GK	13	–	5-y OS: 76	

GK Gamma Knife, *CK* CyberKnife, *L* linear accelerator, *OS* overall survival, *PFS* progression-free survival

Table 7.3 The role of histology WHO grade III for the clinical outcome

Study	Machine	Nr	Local control in %	Survival in %	Comment
Kim (2012) [68]	GK	10	21	–	6.7 % toxicity
EL Khatib (2011) [57]	L	8	57.1	10-y PFS: 43	3.5 % toxicity
Kondziolka (2009) [61]	GK	6	50	5-y OS: 33.3	–
Kondziolka (2008) [62]	GK	29	50	5-y OS: 20	–
Harris (2003) [69]	GK	12	–	5-y OS: 59	3.3 % toxicity
Stafford (2001) [67]	GK	9	–	5-y OS: 0	8 % toxicity
Ojemann (2000) [70]	GK	22	–	5-y OS: 40	

GK Gamma Knife, *CK* CyberKnife, *L* linear accelerator, *OS* overall survival, *PFS* progression-free survival

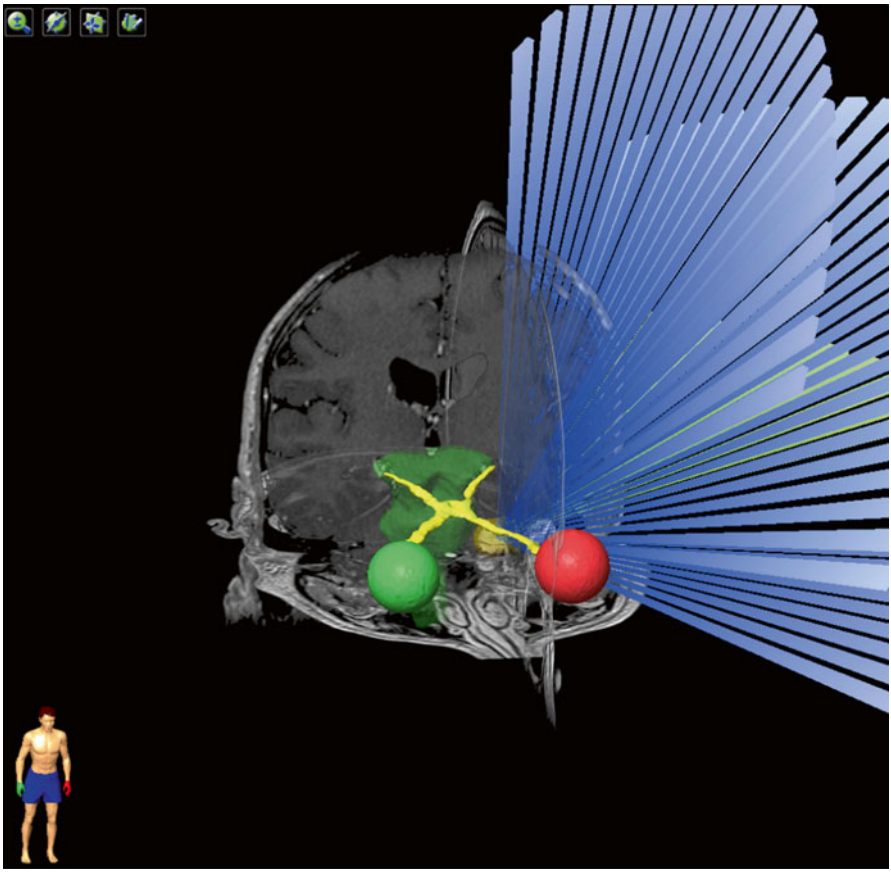
Summary

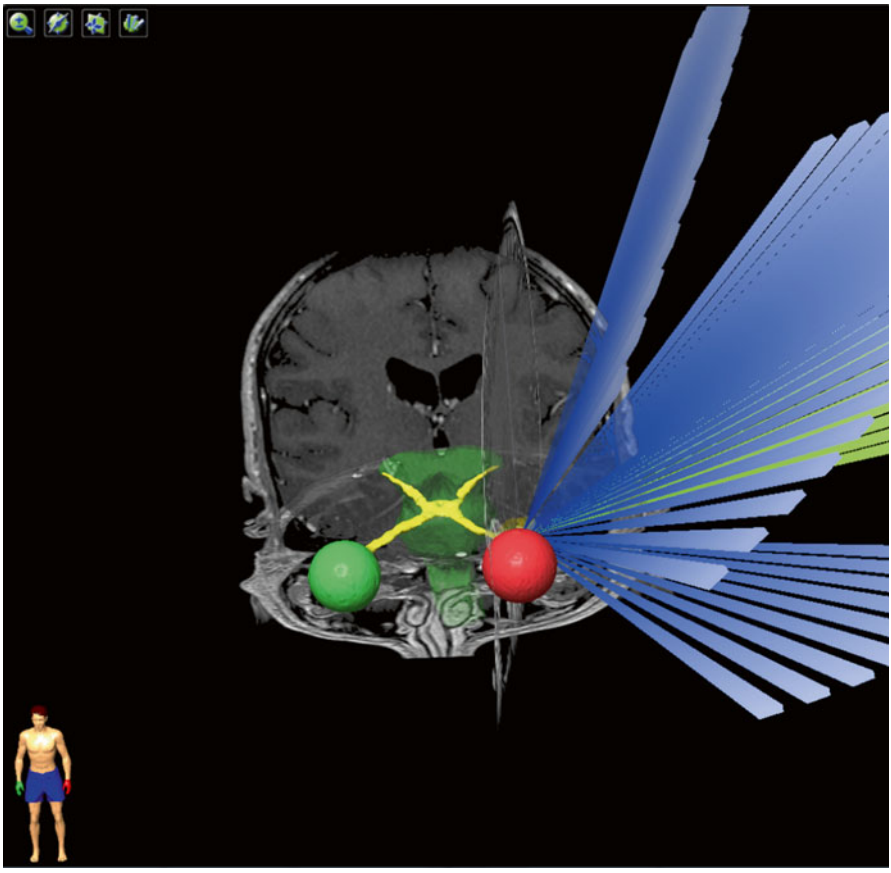
Stereotactic radiosurgery is a safe, effective treatment method for patients (f/m) with meningioma, independent of histology, location, and size. With special regard to the clinical outcome like local control in patients (f/m), this noninvasive method is a good alternative to any surgery. It is true for postoperative setting too.

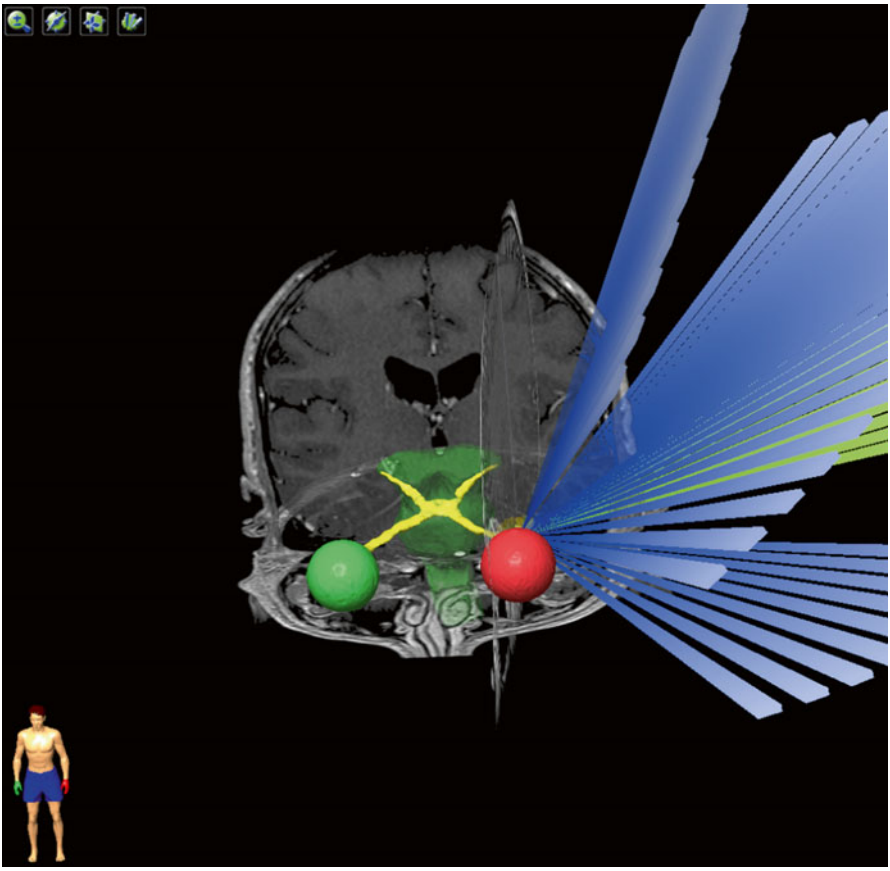
Stereotactic radiosurgery is indeed cost-efficient too.

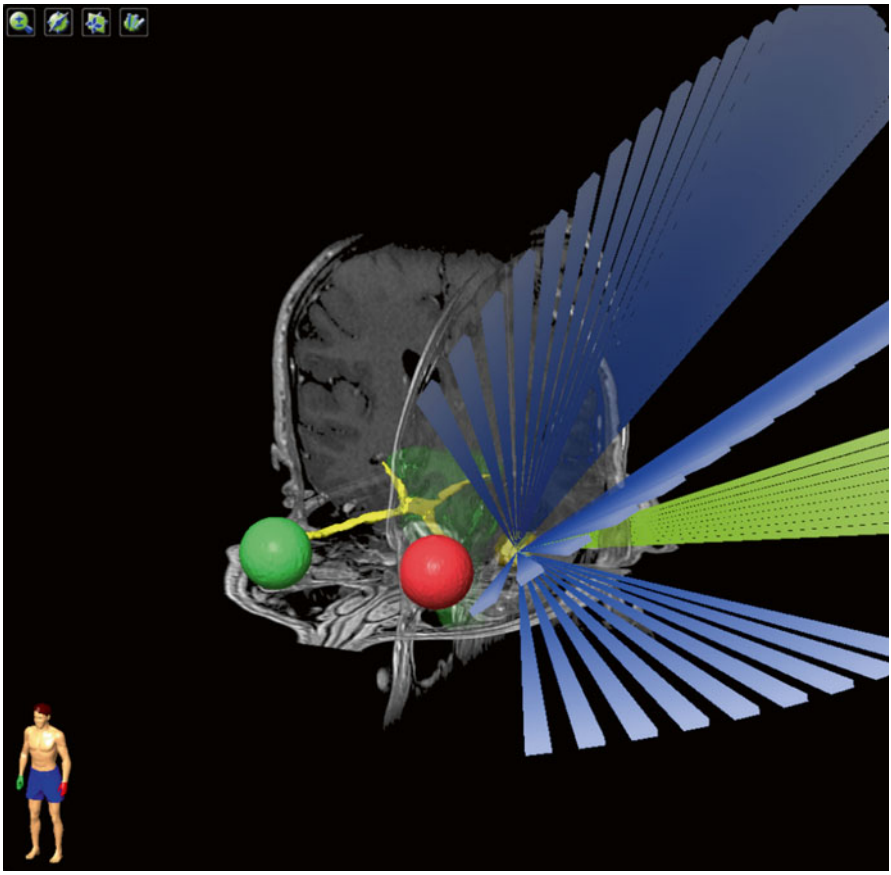
The nonarbitrary selection of the best available scientific evidence, in this case it was "level of evidence 2b," noninvasive image-guided stereotactic radiosurgery appears to be safe and effective, independent of the selected study type.

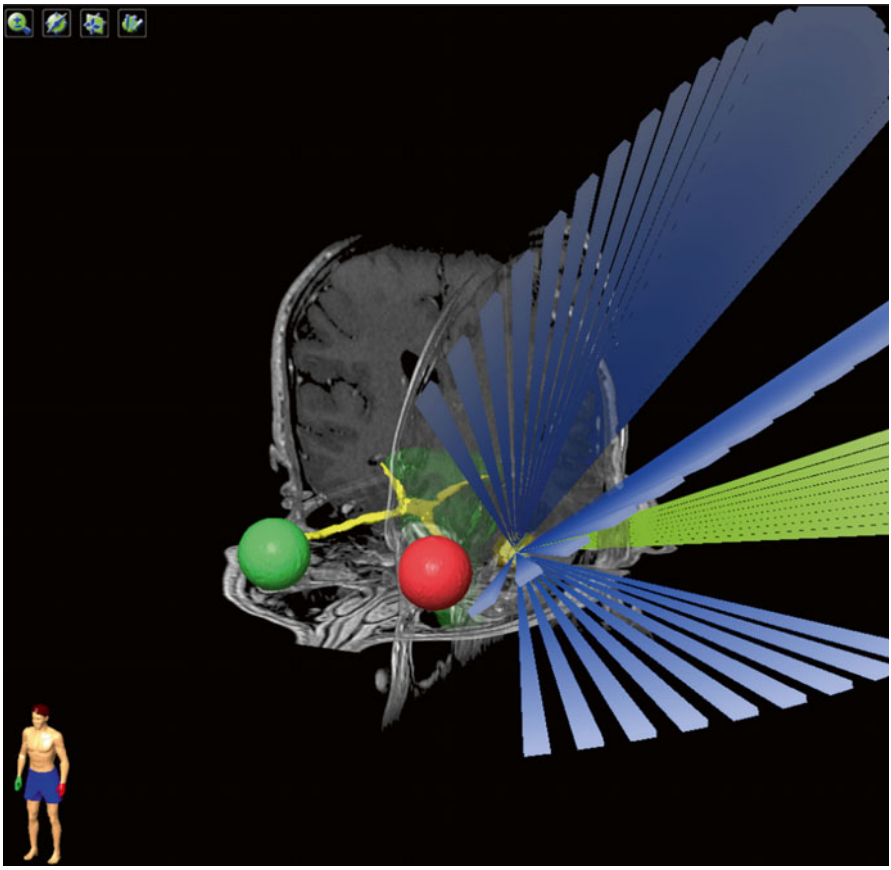
This was also true for the use of noninvasive image-guided fractionated stereotactic radiosurgery via dedicated accelerators such as Novalis, as we have demonstrated in large cohorts by our own experiences.

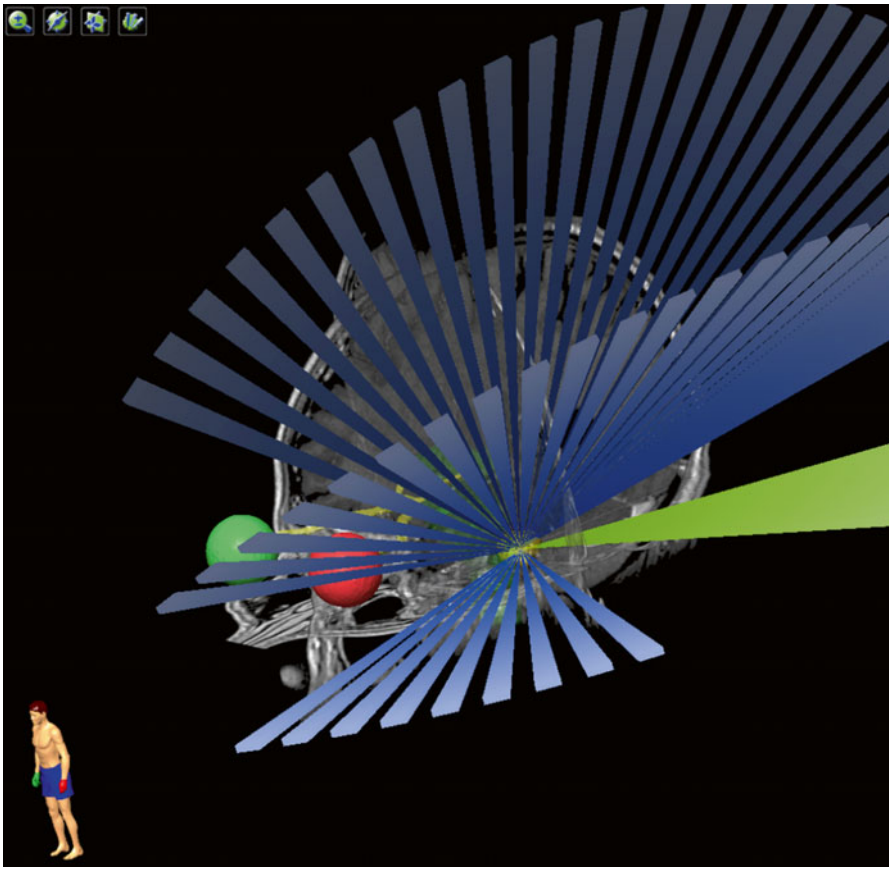


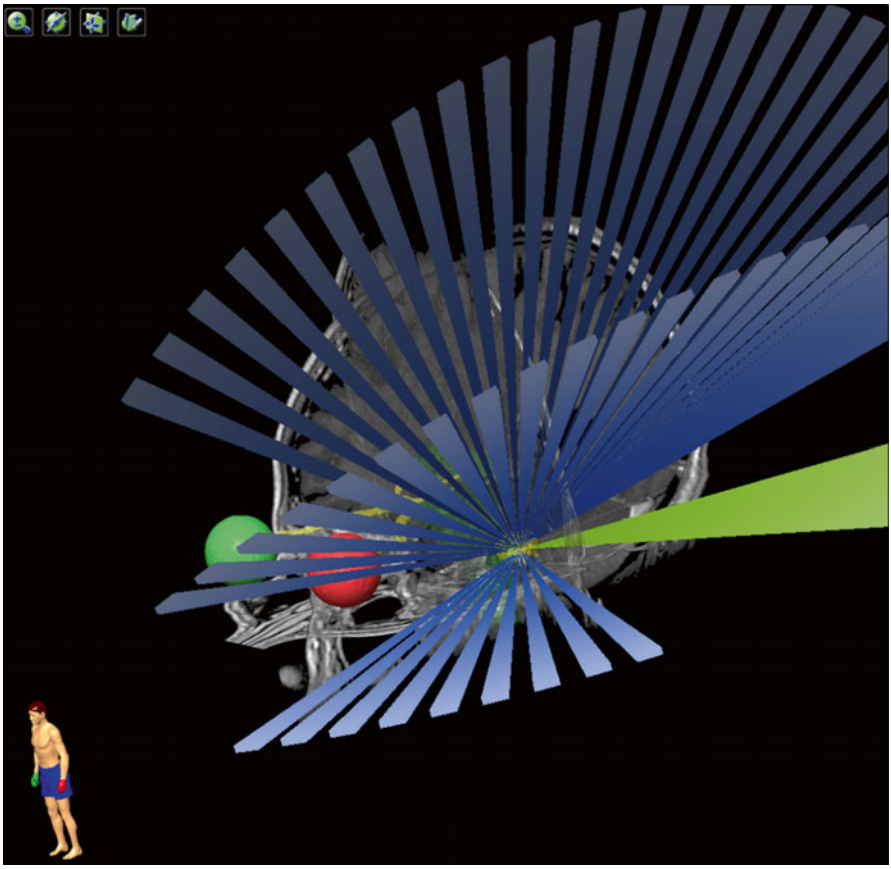


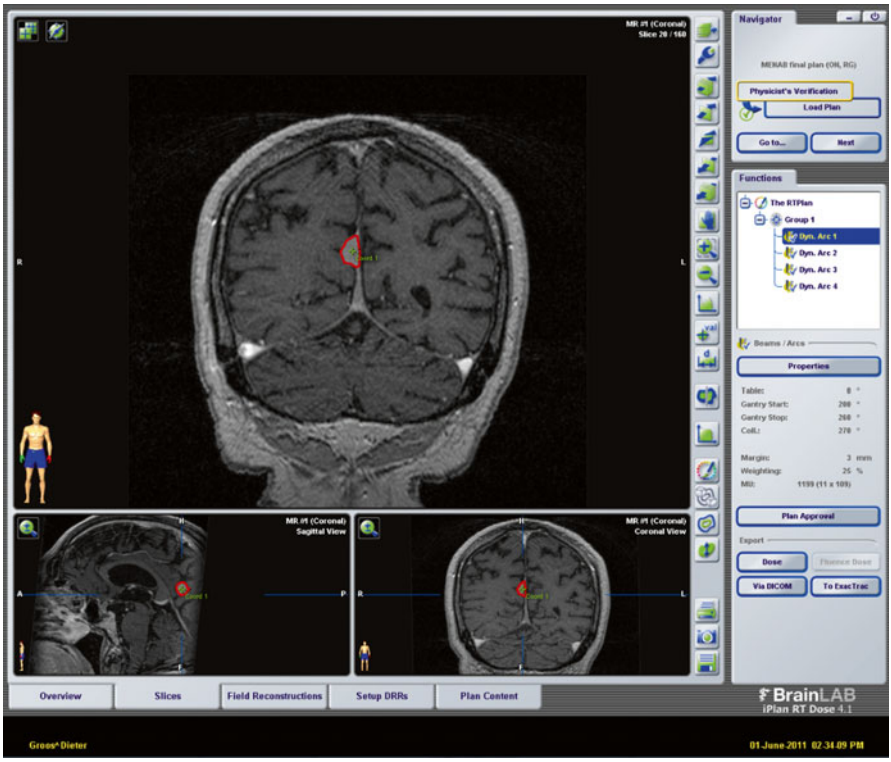








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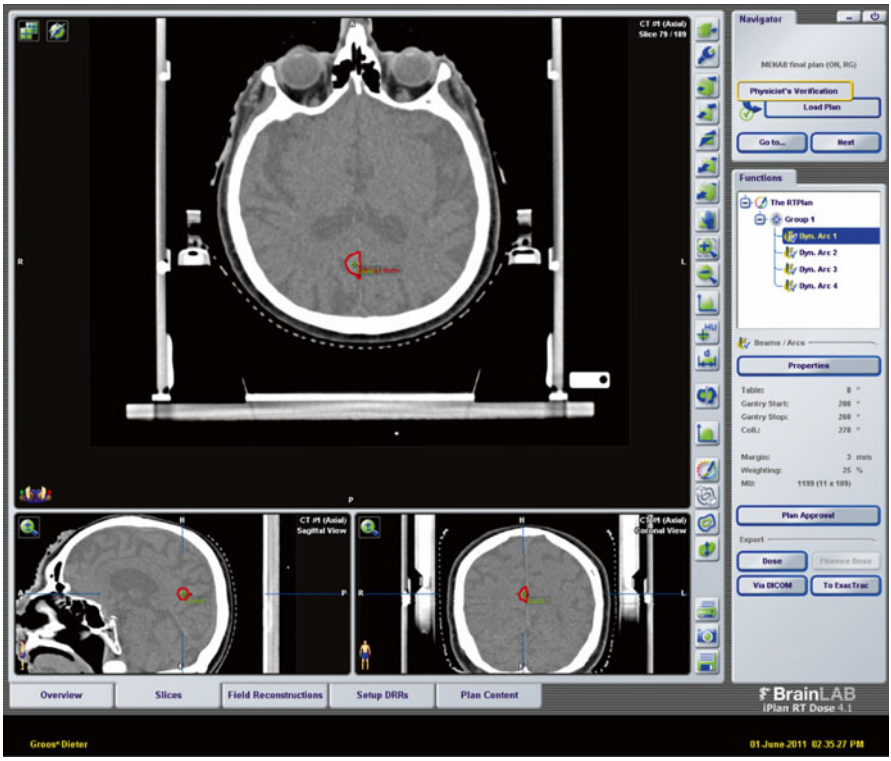
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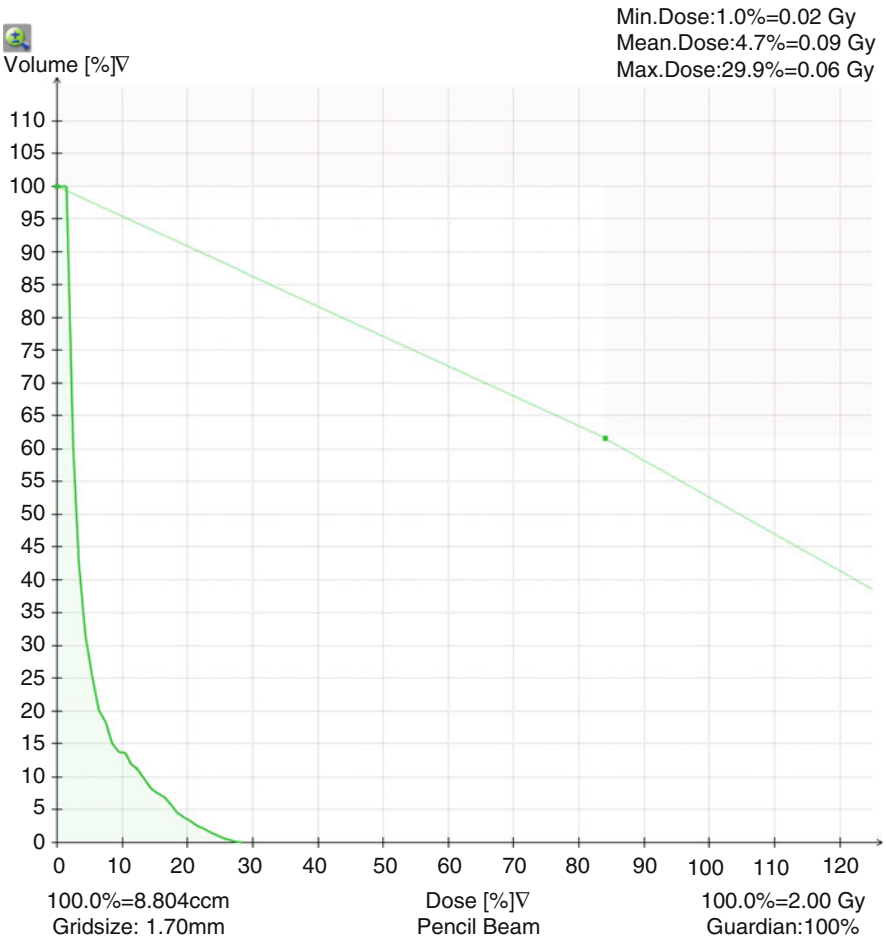
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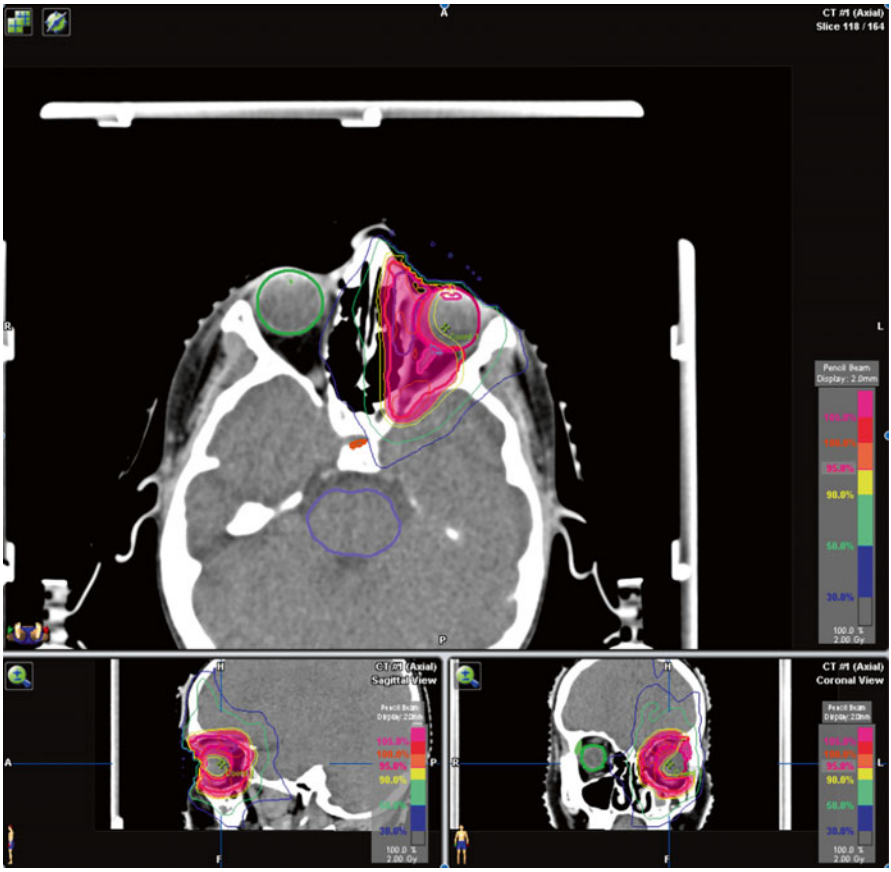
100.0%=2.00 Gy
Guardian:100%



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Arteriovenous Malformations of the Central Nervous System

8

Abstract

Arteriovenous malformations are abnormal lesions, a tangle (or nidus) of blood vessels connecting directly, which means without capillaries, veins, and arteries in the brain. The redirection of the arterial blood away from brain parenchyma and through the nidus is referred to as a shunt. High blood flow and shunting of high-pressure arterial blood cause the feeder arteries and veins to dilate the nidus and make it vulnerable to bleeding due to ruptures that might happen when these lesions remain untreated.

Invasive surgical procedures and radiologic interventions seem to be the method of choice. Image-guided stereotactic radiosurgery in its multiple technologic appearances as the Linac, Gamma Knife, or CyberKnife radiosurgery could affect in combined regimens the lesion and avoid bleeding, when performed in combination with radiologic interventions and surgery.

Consecutively, it demonstrates a noninvasive high-precision and safe technique in treating patients (f/m) with traceable improvement of quality of life. Image-guided stereotactic radiosurgery is cost-efficient.

Background

An arteriovenous malformation, or AVM, is an abnormal lesion, a tangle (or nidus) of blood vessels directly connecting veins and arteries in the brain. This tangle is characterized by the lack of capillaries that usually compose the transition zone between veins and arteries. These congenital vascular abnormalities are further represented by the redirection of the arterial blood away from the brain parenchyma and through the AVM; this is referred to as a shunt. These specific shunts determine, depending on the location and size, the onset of symptoms.

The pathophysiological basis is explained and determined by the high blood flow through the nidus of the AVM. Whether the flow is a cause or effect of the abnormal blood vessels is not yet clear. The arterial blood rushes through the nidus, instead of

H. Badakhshi, *Image-Guided Stereotactic Radiosurgery*,
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working through available capillary beds; this feeds the surrounding brain tissue, further increasing blood flow through the nidus.

Over time, the high blood flow and shunting of high-pressure arterial blood through the AVM cause dilation of the feeder arteries and veins of the AVM. This dilation weakens the veins, making them vulnerable to bleeding; feeder arteries, meanwhile, become susceptible to aneurysms.

The most frequently observed signs of the condition are headaches and seizures. Other symptoms include a pulsing noise in the patient's (f/m) head, fatigue, and numbness. Additionally, progressive deterioration in vision characterizes a worsening condition. Untreated AVMs can enlarge and rupture, causing cerebral hemorrhage or subarachnoid hemorrhage, resulting in permanent brain damage. Smaller AVMs present with hemorrhage more often than large ones. In addition, the size of the hematoma is larger from the small AVMs, compared with the medium or large AVMs. There appears to be no difference in the frequency of hemorrhage between large and medium AVMs.

The incidence of AVMs is estimated to be 1 in 100,000 (US data). The prevalence is estimated at 18 in 100,000. Approximately two-thirds of AVMs occur before the age of 40. Each hemorrhage poses a 20 % risk of death or stroke, 30 % neurological symptoms, and 10 % mortality.

When hemorrhage occurs, it tends to affect the following regions: cerebral (41 %), subarachnoid (24 %), ventricular (12 %), and various combinations (23 %). AVMs are the second most identifiable cause of subarachnoid hemorrhage after cerebral aneurysms, accounting for 10 % of all cases of subarachnoid hemorrhage. About 1 % of patients (f/m) will develop epileptic seizures for the first time.

AVMs are usually diagnosed by magnetic resonance imaging and angiography. These tests may need to be repeated to evaluate a change in size, recent bleeding, or the appearance of new lesions. AVM location is an important factor to consider when weighing the relative risks of surgical versus nonsurgical treatment. Preventing the rupture or re-rupture of vascular malformations is one of the major reasons why early neurosurgical treatment is recommended for AVMs. A commonly used grading scale to predict the risk of surgical morbidity and mortality with brain AVMs is the Spetzler–Martin grading (SMG) scale that is shown in Table 8.1.

The principal goal of causal therapy is to prevent [1] new or potential hemorrhage of the lesion into the brain tissues [2]. Seizure control and stabilization of progressive neurological deficits are occasional treatment goals, as well. Interventional treatment of ruptured brain AVMs is generally advisable, considering that they are associated with a higher subsequent hemorrhage risk (4.5–34 %) than previously unruptured ones (0.9–8 %) [3, 4].

The clinical care of AVMs (ruptured or unruptured) includes observation or an array of interventions, such as microsurgery, endovascular embolization, and stereotactic radiosurgery (SRS), applied either as a sole modality or combined in a defined sequence. The treatment strategy employed depends on the degree of associated morbidity and mortality. A treatment plan is devised to offer the lowest risk, yet the highest chance of obliterating the lesion.

Table 8.1 Spetzler–Martin grade scale for brain arteriovenous malformations (AVMs)

	Points
Nidus size	1
<3 cm	2
3–6 cm	3
>6 cm	
Eloquence of adjacent brain	
Brainstem	1
Thalamus or hypothalamus	1
Cerebellar peduncles	1
Sensorimotor, language, or primary visual cortex	1
Deep venous drainage	
Any or all drainage is through deep veins (internal cerebral veins, basal veins, precentral cerebellar veins)	1

Although microsurgical treatment affords the opportunity for immediate removal of the lesion, some patients may be best dealt with multimodality treatment. In some patients, the lesion is monitored on a regular basis, with the understanding that there may be some risk of hemorrhage or other neurological symptoms. In the most recent study (ARUBA) on 223 patients with unruptured brain AVMs, the risk of death or stroke was significantly lower in the medical management group (patients were symptomatically treated) than in the interventional therapy group, after a mean follow-up of 33 months [5, 6].

Microsurgery is frequently performed, usually on an elective basis, except in cases of large, life-threatening hematomas. In such cases, only superficial AVMs that are readily controllable are removed along with the hematoma. When the hematoma is caused by a complicated AVM, the blood clot can be removed. Microsurgery may be part of a multimodality treatment involving a preliminary endovascular intervention to reduce nidus volume and size and mitigating subsequent additional vascular anomalies, such as aneurysms. The standard is microsurgery whenever safely doable, which has a control rate of 94–100 % of cases with low morbidity rates (from 1 to 10 %) for small (nidus < 3 cm) AVMs in experienced hands. A meta-analysis on the microsurgical management of AVMs reported permanent neurological deficits or death in a mean of 7.4 % (range, 0–40 %) patients after microsurgery; successful brain AVM obliteration was achieved in 96 % (range, 0–100 %) of patients [7].

Embolization includes interventions to obliterate the small malformations or to make the nidus smaller in a presurgical setting, allowing safer resection, size reduction prior to radiosurgery, or elimination of certain associated vascular anomalies. Endovascular embolization uses specially designed microcatheters, which are image guided directly into the nidus. Materials used include fast-drying biologically inert glues, polyvinyl alcohol particles, and fibered titanium coils. Neuroendovascular therapy can make subsequent surgical removal of an AVM safer or can reduce the size of an AVM to a size that may inevitably improve the outcome of stereotactic

radiosurgery. This procedure is also associated with substantial risk, since the path taken by such embolic materials can be difficult to predict, and blockage of normal vessels or of the outflow of the AVM may occur. The former may result in stroke and the latter in bleeding from the AVM. These procedures are therefore used judiciously and with ample clinical judgment.

Stereotactic radiosurgery (SRS) has been proven to be a safe and effective therapeutic modality in the care of patients (f/m) with AVMs. Its application has resulted in lowering the morbidity and mortality associated with the treatment of deep AVMs. SRS has been used as a primary mode of therapy, as well as in conjunction with embolization and microsurgery, in the management of AVMs. The obliteration rate after SRS has been reported to range from 35 to 92 %. Smaller AVMs receiving higher marginal doses have obliteration rates of 70 % and more. The median follow-up reported in most series is approximately 36–40 months. The median time to obliteration has been reported to be approximately 24–36 months in most series. Toxicity is reported in less than 10 % of patients, with a 1.5–6 % risk of developing a new permanent neurological deficit. The bleeding rate during the latency to obliteration has been reported to be approximately 5 %. This review describes the experience reported in literature with respect to the indications, dosage, factors affecting obliteration rate of AVMs, and complications after SRS [8–10].

Availability and Quality of Scientific Evidence

Clinical data from different studies on validity, plausibility, and quality are available. Merely putting the last year in focus, we found a sufficient number of studies [1, 8–34].

Below are the degrees of validity and quality of available data with regard to usage of SRS, formulated as questions.

Do we have plausible and valid data on "level of evidence 1A," with special regard to usage of SRS in patients (f/m) with AVMs?
No, there are no meta-analyses of controlled randomized trials (CRTs) with prospective designs available.

Do we have plausible and valid data on "level of evidence 1B," with special regard to usage of SRS in patients (f/m) with AVMs?
No, controlled randomized trials (CRTs) with prospective designs that explicitly investigate SRS effects in patients (f/m) with AVMs have been performed to date.

However, there is one multicenter (39 cites), non-blinded, randomized trial published in 2014 by Mohr and colleagues, called the ARUBA trial: A Randomized Trial of Unruptured Brain Arteriovenous Malformations. The aim of the study was to compare the risk of death and symptomatic stroke in patients (f/m) who were allocated to either medical management alone or medical management with interventional therapy. The primary outcome is time to the composite endpoint of death or symptomatic stroke; the primary analysis is by intention to treat. At this point,

outcome data were available for 223 patients (mean follow-up 33.3 months [SD 19.7]), 114 assigned to interventional therapy and 109 to medical management. The primary endpoint had been reached by 11 (10.1 %) patients in the medical management group, compared with 35 (30.7 %) in the interventional therapy group. The risk of death or stroke was significantly lower in the medical management group than in the interventional therapy group (hazard ratio, 0.27; 95 % CI, 0.14–0.54). A higher number of strokes (45 vs. 12, $p<0.0001$) and neurological deficits unrelated to stroke (14 vs. 1, $p=0.0008$) were noted in patients allocated to interventional therapy, compared to those allocated to medical management. The authors concluded that medical management alone is superior to medical management with interventional therapy for the prevention of death or stroke in patients followed up for 33 months [5].

It is clear that the overall quality of available data is not sufficient for robust conclusions and firm recommendations. The ARUBA trial, however, was able to enumerate the risks of interventions beyond symptomatic medical management.

Do we have plausible and valid data on "level of evidence 2A," with special regard to usage of SRS in patients (f/m) with AVMs?

There have been five recent publications systematically reviewing retrospective cohort studies and analyzing pooled data by different methods.

Mau and colleagues examined data retrieved from cohort studies, including hemorrhage intensity and risk in patients (f/m) with high-grade Pollock–Flickinger AVMs. They reported that the annual AVM hemorrhage rate after radiosurgery for all patients ($n=673$) was 3.22 % (99.3 hemorrhages, 3080.5 follow-up years, 95 % confidence interval [95 % CI] 2.64–3.89 %). Mortality rate from hemorrhage was 40.08 % (95 % CI, 31.21–49.90 %). A total of 203 patients presented with hemorrhage and 395 did not. In patients with first-time hemorrhage, the annual hemorrhage rate was 3.53 % (95 % CI, 2.66–4.77 %). The annual hemorrhage rate of those with hemorrhagic presentation was 6.10 % (95 % CI, 4.65–8.07 %). The odds ratio comparing re-hemorrhage rate versus first-time hemorrhage is 1.768 (95 % CI, 1.1571–2.7014, $p=0.0084$). Complete obliteration of all AVMs was 33.27 % (95 % CI, 29.25–37.54 %). Considering that the mortality rate from hemorrhage is at 40.08 % (95 % CI, 35.54–44.62 %), the authors concluded that the consequences of SRS for large AVMs are significantly worse than the reported 10–30 % fatality rate from hemorrhage of an untreated AVM. Additionally, the overall mortality rate was 6.24 %; however, the percentage of mortalities from hemorrhage was 97.62 % [9].

Another meta-analysis of cohort studies aimed to assess case fatality rates, long-term risk of hemorrhage, complications, and successful obliteration of brain AVMs after interventional treatment and to evaluate the determinants and associations of these outcomes using Poisson regression analysis. A total of 142 cohorts were included, totaling 13,698 patients and 46,314 patient-years of follow-up. Case fatality was 0.68 (95 % CI, 0.61–0.76) per 100 person-years overall, 1.1 (95 % CI, 0.87–1.3; $n=2549$) after microsurgery, 0.50 (95 % CI, 0.43–0.58; $n=9436$) after SRS, and 0.96 (95 % CI, 0.67–1.4; $n=1019$) after embolization. Intracranial hemorrhage rates were 1.4 (95 % CI, 1.3–1.5) per 100 person-years overall, 0.18

(95 % CI, 0.10–0.30) after microsurgery, 1.7 (95 % CI, 1.5–1.8) after SRS, and 1.7 (95 % CI, 1.3–2.3) after embolization. More recent studies were associated with lower case fatality rates (rate ratio [RR], 0.972; 95 % CI, 0.955–0.989) but with higher rates of hemorrhage (RR, 1.02; 95 % CI, 1.00–1.03). Male sex (RR, 0.964; 95 % CI, 0.945–0.984), small brain AVMs (RR, 0.988; 95 % CI, 0.981–0.995), and AVMs with strictly deep venous drainage (RR, 0.975; 95 % CI, 0.960–0.990) were associated with lower case fatality. Lower hemorrhage rates were associated with male sex (RR, 0.976, 95 % CI, 0.964–0.988), small brain AVMs (RR, 0.988, 95 % CI, 0.980–0.996), and brain AVMs with deep venous drainage (0.982, 95 % CI, 0.969–0.996). Complications leading to permanent neurological deficits or death occurred in a median 7.4 % (range, 0–40 %) of patients after microsurgery, 5.1 % (range, 0–21 %) after SRS, and 6.6 % (range, 0–28 %) after embolization. Successful brain AVM obliteration was achieved in 96 % (range, 0–100 %) of patients after microsurgery, 38 % (range, 0–75 %) after SRS, and 13 % (range, 0–94 %) after embolization. They concluded that case fatality after treatment has decreased over time and that treatment of brain AVMs remains associated with considerable risks and incomplete efficacy [7].

Another recent review and analysis of available cohort studies was published in 2014 by Xu and colleagues. The aim of this analysis was to assess current "evidence" regarding the efficiency and safety of SRS for AVM patients with and without prior embolization.

Ten studies were identified, which included 1,988 patients (f/m) from whom 593 had undergone embolization followed by SRS and 1,395 had undergone SRS alone. The AVM obliteration rate was significantly lower in patients who had undergone embolization followed by SRS than in those who had undergone SRS alone (41.0 % vs. 59 %, OR 0.46, 95 % CI, 0.37–0.56, $p < 0.00001$). However, the rates of hemorrhage (7.3 % vs. 5.6 %, OR 1.17, 95 % CI, 0.74–1.83, $p = 0.50$) and permanent neurological deficits related to radiation-induced changes (3.3 % vs. 3.4 %, OR 1.41, 95 % CI, 0.64–3.11, $p = 0.39$) were not significantly different between the two groups. The conclusion of the authors was that pre-SRS embolization significantly decreases the AVM obliteration rate. However, there is no significant difference in the risk of hemorrhage and permanent neurological deficits after SRS alone and following embolization. Further validation by well-designed prospective or randomized cohort studies is still needed [35].

Another study by Baranoski and colleagues aimed to determine if the modality selected (SRS; microsurgery or MS; and endovascular embolization or EVE) to treat AVMs affects the rate of seizure occurrence. They identified 24 studies with a total of 1,157 patients (f/m). The surgery group had the best seizure control ($p < 0.01$), with the relative predicted rates of seizure outcome as follows: MS 78.3 % (95 % CI, 70.1–85.8 %), SRS 62.8 % (95 % CI, 55.0–70.0 %), and EVE 49.3 % (95 % CI, 32.1–66.6 %). Patients in the SRS group who had complete obliteration of their AVMs achieved the highest rate of seizure control [85.2 % (95 % CI, 79.1–91.2 %); $p < 0.01$]. The development of new-onset seizures occurred more frequently in patients undergoing EVE [39.4 % (95 % CI, 8.1–67.8 %)] compared with MS [9.1 % (95 % CI, 5.0–13.1 %)] and SRS [5.4 % (95 % CI, 3.0–7.8 %)]

($p<0.3$ and $p<0.01$, respectively). The conclusion was that surgery resulted in the highest proportion of seizure control. However, if SRS resulted in successful obliteration of the AVM, then this modality is the most effective in achieving seizure control [36].

The question of whether an AVM has to be treated as soon as possible or if watchful waiting is a viable option is of high importance. The understanding of the natural history of these lesions is significant for making decisions at the right time and under the right conditions. Gross and colleagues performed a "meta-narration" rather than a meta-analysis, with focus on this critical question. Nine natural history studies with 3,923 patients and 18,423 patient-years of follow-up were identified for analysis. The overall annual hemorrhage rate was 3.0 % (95 % CI, 2.7–3.4 %). The rate of hemorrhage was 2.2 % (95 % CI, 1.7–2.7 %) for unruptured AVMs and 4.5 % (95 % CI, 3.7–5.5 %) for ruptured AVMs. Prior hemorrhage (HR 3.2, 95 % CI, 2.1–4.3), deep AVM location (HR 2.4, 95 % CI, 1.4–3.4), exclusively deep venous drainage (HR 2.4, 95 % CI, 1.1–3.8), and associated aneurysms (HR 1.8, 95 % CI, 1.6–2.0) were statistically significant risk factors for hemorrhage. Any deep venous drainage (HR 1.3, 95 % CI, 0.9–1.75) and female sex (HR 1.4, 95 % CI, 0.6–2.1) demonstrated a trend toward an increased risk of hemorrhage that was not statistically significant. Small AVM size and older patient age were not significant risk factors for hemorrhage. The conclusion of the authors was that AVMs with prior hemorrhage, deep location, exclusively deep venous drainage, and associated aneurysms have greater annual hemorrhage rates than their counterparts, influencing surgical decision-making and the selection of radiosurgery for these lesions [37].

The neurosurgery team of Virginia University, led by JP Sheehan, has published a series of valuable articles that coherently and comprehensively review the effectiveness of SRS alone or in a multimodality context [12, 13], although these provide only a "level of evidence 2 and 3." The aim of one review was to analyze the outcomes of SRS in patients (f/m) with AVMs of the basal ganglia and the thalamus. The management of these deep-seated lesions continues to challenge experts because basal ganglia and thalamic AVMs show a higher rate of hemorrhage and are associated with devastating morbidity and mortality. Recent evidence from A Randomized Trial of Unruptured Brain AVM (ARUBA) further deters aggressive approaches that carry a significant risk of treatment-related adverse events. SRS is an effective therapeutic option for AVMs of the thalamus and basal ganglia that are deemed high risk for resection. SRS offers acceptable obliteration rates, with generally lower risks of hemorrhage occurring during the latency period compared to the natural history of an AVM. Considering that incompletely obliterated lesions still harbor the potential for rupture, additional treatments, such as repeat SRS and microsurgical resection, should be considered when complete obliteration is not achieved by an initial SRS procedure [12].

The other part of the series from this experienced team investigated the effects of SRS in the brainstem. SRS offers acceptable obliteration rates with lower risks of hemorrhage occurring during the latency period. Complex nidal architecture requires a multidisciplinary treatment approach. Nidi partly involving the subpial/epipial regions of the dorsal midbrain or cerebellopontine angle should be

considered for a combination of endovascular embolization, microsurgical resection, and SRS. Considering the fact that incompletely obliterated lesions (even when reduced in size) could still cause lethal hemorrhages, additional treatment, including repeat SRS and surgical resection, should be considered when complete obliteration is not achieved by first SRS [13].

To close the chapter on systematic reviews of evidence of retrospective cohort studies, it should be stated that there is a clear defined role for SRS in the treatment of patients (f/m) with AVMs in different clinical settings. It is safe and it is effective.

Do we have plausible and valid data on "level of evidence 2B," with special regard to usage of SRS in patients (f/m) with AVMs?

Yes.

In this context, as we have done in other chapters, we select representative studies conducted over the last 5 years. The selection criteria we use may be found in the chapter "Levels of Evidence."

Effects of treatment in regard to the size of AVM lesion

Seymour and colleagues published a report on large AVMs in 2016 [10]. The lesion size was, in context in this study, defined as being larger than 10 ccm in volume. In the second part of the study, the researchers prospectively decreased the AVM treatment volume, increased the SRS dose per stage, and shortened the interval between stages. A total of 69 patients (f/m) with a median age of 34 years (range 9–68 years) were included in the study. The authors stratified the cohort according to a modified radiosurgery-based AVM score (mRBAS), total AVM volume, and volume per stage. In the two distinctive study periods (1992–2004 and 2004–2008) the mRBAS, total AVM volume, and volume per stage were 3.6 versus 2.7, 27.3 ml versus 18.9 ml, and 15.0 ml versus 6.8 ml, respectively. The median radiation dose per stage was 15.5 Gy in first study period and 17.0 Gy in second study period, and the median clinical follow-up period in living patients was 8.6 years in first study period and 4.8 years in second study period. Near or complete obliteration was more common in second study period (log-rank test, $p = 0.0003$), with 3- and 5-year probabilities of 5 and 21 %, respectively, in first study period compared with 24 and 68 % in second study period. Dose, AVM volume per stage, total AVM volume, era, compact nidus, Spetzler–Martin grade, and mRBAS were significantly associated with near or complete obliteration on univariate analysis. Dose was a strong predictor of response (Cox proportional hazards, $p < 0.001$, HR 6.99), with 3- and 5-year probabilities of near or complete obliteration of 5 and 16 %, respectively, at a dose less than 17 Gy versus 23 % and 74 % at a dose more than 17 Gy. Dose per stage, compact nidus, and total AVM volume remained significant predictors of near or complete obliteration on multivariate analysis. Seventeen patients (25 %) had salvage surgery, SRS, and/or embolization. Allowing for salvage therapy, the probability of cure was more common in second study period (log-rank test, $p = 0.0007$) with 5-year probabilities of 0 % in first study period versus 41 % in second study period. The strong trend toward improved cure in second study period persisted on

multivariate analysis even when considering mRBAS (Cox proportional hazards, $p = 0.055$, HR 4.01, 95 % CI 0.97–16.59). The complication rate was 29 % in first study period compared with 13 % in second study period (Cox proportional hazards, not significant). To the authors, SRS is seen as an option to obliterate or downsize large AVMs. "Decreasing the AVM treatment volume per stage to less than 8 ccm with this technique allowed a higher dose per fraction and decreased time to response, as well as improved rates of near obliteration and cure without increasing complications. Reducing the volume of these very large lesions can facilitate a surgical approach for cure"—so the conclusion of the authors [10].

In special regard to the large-sized AVMs, Lindvall and colleagues reported their experiences in 2015 [18].

The analysis concluded the interpretation of obliteration and complications in 24 patients with medium- to large-sized cerebral AVMs (mean volume, 18.5 ± 8.9 ccm; range, 10–42). AVMs are congenital lesions associated with a high morbidity and mortality. Radiosurgery is one option for treatment. However, in larger AVMs with volumes exceeding 10 ccm, obliteration rates are less favorable and radiation-induced complications more frequent. For larger AVMs, volume-staged radiosurgery is one option, while another option may be the use of fractionated regimen. Patients (f/m) were treated with 6-7Gy in five fractions to a total dose of 30–35 Gy (mean total dose, 32.9 ± 1.6 Gy [standard error of the mean]). Sixteen patients (f/m) (69.6 %) showed obliteration after a mean time of 35.2 ± 14.8 months (range, 24–60). Only one patient (4.2 %) experienced symptomatic radionecrosis. The authors concluded that the "treatment with fractionated radiosurgery seems safe and efficient for treatment of medium- to large-sized AVMs. Treatment results seem to be in line with volume-staged radiosurgery and may be an alternative for AVMs not suitable for single fraction radiosurgery" [18].

Hanakita and colleagues communicated a paper with an adaptive radiosurgery approach in 2015 [24].

In this study, we evaluated the efficacy and safety of volume-staged SRS in patients with AVM more than 20 ccm with more than 3 years of follow-up. The study included 18 patients with AVMs more than 20 ccm treated by volume-staged SRS. The median target volume was 38 ccm (interquartile range, IQR, 31–53 ccm). Treatment was 2–3 stages with a median 6 months of interval. Results revealed after a median follow-up of 53 months a complete nidus obliteration in six patients (33 %). The obliteration rate at 5 years after initial SRS was 35 % by the Kaplan–Meier method. The annual hemorrhage rate after last SRS treatment was 3.9 % (95 % confidence interval, 0.8–11.5 %). Two patients experienced radiation-induced adverse effects. The authors interpreted their experiences as follows: "there is still a high risk for hemorrhage (approximately 4 %/year) after radiosurgery, which seemed to be higher than the rate observed in common post-treatment course of single-session SRS for AVM with average size. If this challenging treatment method could be regularly considered, based on its efficacy and risks, including comparison with the natural history of large AVMs" [24].

Ding and colleagues published recent outcome data on patients (f/m) with partially resected AVMs [11]. By analyzing data from a prospective database of AVM

patients (f/m) treated with radiosurgery, the authors matched cases from 15 years. The matching process yielded 88 patients (f/m) in each of the previously resected and unresected AVM cohorts. In the resected AVM cohort, the actuarial AVM obliteration rates at 3 and 5 years were 47 and 75 %, respectively; the rates of radiologic and symptomatic radiation-induced changes were 10 and 3 %, respectively; and the annual hemorrhage risk after radiosurgery was 1.1 %. The lack of prior AVM resection ($p < 0.001$) and superficial AVM location ($p = 0.009$) were independent predictors of radiologic radiation-induced changes. The actuarial rates of obliteration ($p = 0.849$) and hemorrhage ($p = 0.548$) after treatment were not significantly different between the resected and unresected AVM cohorts. The authors concluded that radiosurgery may afford "a reasonable risk-to-benefit profile for incompletely resected AVMs. For those with a small-volume residual nidus after resection, radiosurgery should be considered an effective alternative to repeat resection" [11].

Effects of treatment in regard to the age of patients (f/m)

Another recent paper was published by Zeiler and colleagues in 2015 [14]. The report contains a total of 19 cases. The treatment was executed by a Gamma Knife machine. The mean age was 14.2 years (range, 7–18 years), with 10 being males (52.6 %). The mean AVM diameter and volume were 2.68 cm and 3.10 ccm, respectively. The mean Spetzler–Martin (SM) and Pollock grades of the treated AVMs were 2.4 and 0.99, respectively. The mean follow-up was 62 months. All AVMs treated demonstrated a response on follow-up imaging. Nine of 15 (60.0 %) patients displayed obliteration of their AVMs. Nine of 11 patients with a minimum of 3 years follow-up (81.8 %) displayed obliteration, with SM and Pollock grades correlating to the chance of obliteration in this group. Two patients developed post-radiosurgery edema requiring short-course dexamethasone therapy. No major complications occurred. No permanent complications occurred. The authors closed with the statement that radiosurgery for patients (f/m) with AVMs "offers a safe and effective treatment option, with low permanent complication rates during early follow-up" [14].

Another series on 45 young patients (f/m) was reported by Galvan De la Cruz and colleagues also in 2015 [26]. They examined the role of several indexes to classify AVMs, which are supposed to predict the outcome for each specific treatment. The indices differ in the variables considered, but they are all based in adult populations. The minimum follow-up of the study was 10 months and the maximum 112 months. One major finding was that the technique of radiation may influence the obliteration occurrence ($p = 0.057$). The data suggests that circular arcs are a more efficient treatment technique than dynamic arcs. However, no relationship of dose or volume with treatment technique could be found. Obliteration was also dependent on follow-up time, and after 3 years of follow-up, the obliteration probability decreases ($p = 0.024$). According to Kaplan–Meier analysis, the nidus obliteration time was related with the location according to the Spetzler–Martin index. If the nidus was located in a non-eloquent region, there was a tendency of a shorter obliteration time ($p = 0.071$). The summary of this study, though small by number, was that to date none of the previously proposed indices are predictive for children and teenagers because they have been derived in adult. They conclude that "treatment

technique, eloquence, and follow-up time were the only variables that showed influence in obliteration. Since the highest probability of obliteration occurs during the first 3 years, if the nidus has not been obliterated after this time, then another treatment option could be considered" [26].

Age was the focus in this study, which was published by Ding and colleagues in 2015. The group of Dr. Ding, which is highly active in communication on AVMs, reported hereby on young patients (f/m) in 2015 [27]. The study population was younger than 18 years. Because this population was excluded from the "A Randomized Trial of Unruptured AVMs (ARUBA)," the effects of noninvasive image-guided stereotactic radiosurgery are poorly understood. The goal of this study was to determine the outcomes and define the predictors of obliteration following SRS for unruptured AVMs in pediatric patients. A total of 51 patients (f/m) with unruptured AVM were included for the analysis. The median age was 13 years, and the most common presentation was seizure in 53 %. The median nidus volume and radiosurgical margin dose were 3.2 cm [3] and 21.5 Gy, respectively. The median radiologic follow-up was 45 months. The actuarial AVM obliteration rates at 3, 5, and 10 years were 29 %, 54 %, and 72 %, respectively. In the multivariate Cox proportional hazards regression analysis, higher margin dose ($p = 0.002$), fewer draining veins ($p = 0.038$), and lower Virginia Radiosurgery AVM Scale ($p = 0.003$) were independent predictors of obliteration. Obliteration rates were significantly higher with a margin dose of at least 22 Gy ($p = 0.003$) and for nidi with two or fewer draining veins ($p = 0.001$). The incidences of radiologically evident, symptomatic, and permanent radiation-induced changes were 55 %, 16 %, and 2 %, respectively. The annual post-radiosurgery hemorrhage rate was 1.3 %, and the incidence of post-radiosurgery cyst formation was 2 %. The authors concluded that this method "affords a favorable risk-to-benefit profile for unruptured pediatric AVMs. Pediatric patients with unruptured AVMs merit further study to define an optimal management approach" [27].

Age was in the following report also the focus, but they studied effect of noninvasive image-guided stereotactic radiosurgery in elderly [28]. The study population was older than 60 years. The hypothesis was that radiosurgery outcomes are not adversely affected by increased age, different than in surgical series published to date. The goals of this case–control study are to analyze the radiosurgery outcomes for elderly patients with AVMs and determine the effect of elderly age on AVM radiosurgery outcomes. The radiologic follow-up of more than 2 years or nidus obliteration was selected for analysis. The study population was matched, in a 1:1 fashion and blinded to outcome, to adult nonelderly patients with AVM (age, <60 years). A total of 132 patients (f/m) were included in each of the elderly and nonelderly AVM cohorts. In the elderly AVM cohort, the actuarial AVM obliteration rates at 3, 5, and 10 years were 37 %, 65 %, and 77 %, respectively; the rates of radiologically evident, symptomatic, and permanent radiation-induced changes were 36 %, 11 %, and 0 %, respectively; the annual hemorrhage risk after radiosurgery was 1.1 %, and the AVM-related mortality rate was 1.5 %. Elderly age was not significantly associated with AVM obliteration, radiation-induced changes, or hemorrhage after radiosurgery. The authors concluded that "age does not appear to

confer appreciably worse AVM radiosurgery outcomes, unlike its negative effect on AVM surgical outcomes. Thus, when an AVM warrants treatment, radiosurgery may be the preferred treatment for elderly patients" [28].

Summary

Noninvasive image-guided stereotactic radiosurgery has proven to be an effective and safe strategy in the management of patients (f/m) with intracranial arteriovenous malformations in children and adults.

Its application has resulted in lowering the morbidity and mortality associated with treatment of deep-seated AVMs. Radiosurgery has been used as a primary modality of treatment as well as in addition with embolization and microsurgery in the management of AVMs. The obliteration rate after noninvasive image-guided stereotactic radiosurgery has been reported to range from 35 to 92 %. Smaller AVMs receiving higher marginal doses have obliteration rates of 70 % and more. The median follow-up reported in most series is approximately 36–40 months. The median time to obliteration has been reported to be approximately 24–36 months in most series. Radiation-induced neurological complications have been reported in less than 10 % of patients, with a 1.5–6 % risk of developing a new permanent neurological deficit. The bleeding rate during the latency to obliteration has been reported to be approximately 5 %. This review describes the experience reported in literature with respect to the indications, dosage, factors affecting obliteration rate of AVMs, and complications after SRS.

Stereotactic radiosurgery is indeed cost-efficient too.

The nonarbitrary selection of the best available scientific evidence, in this case, was "level of evidence 2b"; noninvasive image-guided stereotactic radiosurgery appears to be safe and effective, independent of the selected study type.

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Pituitary Adenoma

9

Abstract

Pituitary adenomas are benign lesions located in the pituitary gland. They might present in multiple forms; besides the heterogeneous histologic types, it is important whether a lesion is hormonally active or not. Pituitary adenomas grow in eloquent bony structures in the base of the skull and induce different symptoms. All hormonal function related to the pituitary gland could be affected, and additionally, the rising volume effect leads to headaches and other neurologic affections.

Invasive surgical procedures seem to be the one method of treatment. Image-guided stereotactic radiosurgery in its multiple technologic appearances as the Linac, Gamma Knife, or CyberKnife radiosurgery could affect hormonal dysfunctions by impacting the growth, when applied alone or after invasive surgical arsenal with incomplete resection.

Consecutively, it demonstrates a noninvasive high-precision and safe technique in treating patients (f/m) with traceable improvement of quality of life. Image-guided stereotactic radiosurgery could be performed in outpatient setting and is cost-efficient.

Background

Pituitary adenomas (PAs) are benign lesions located in the pituitary gland. All glandular functioning might therefore be influenced by these lesions.

PAs account for more than 70 % of all pituitary lesions, but only 15 % of intracranial neoplasms [1]. Other pathological forms include invasive adenomas and carcinomas. PAs arise from one of five cell types that are present in the anterior pituitary.

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These lesions are true neoplasms with a monoclonal cell origin. Although a globally accepted, definitive pathological classification is lacking, some indications have originated with respect to pathologic morphology or clinical presentation. The estimated prevalence of PAs is 77.6 per 100,000 persons [1]. Although autopsy and imaging data suggest that the prevalence might be as high as 20 %, a large number of these lesions are asymptomatic and thus clinically insignificant [2]. However, it remains challenging to predict the clinical course of an adenoma. Gomez-Hernandez and colleagues emphasize that an "accurate subtyping of pituitary adenomas offers valuable prognostic information that together with other clinical and radiological information serves as a platform for tailored treatment." They further assume that silent subtype III PAs, silent corticotroph adenomas, acidophil stem cell adenomas, Crooke cell adenomas, and sparsely granulated somatotroph adenomas "show more invasive growth" [2].

Clinically, PAs manifest in three ways: first, the presence or absence of hormonal secretion; second, neurologic symptoms consequent to a volume increase; and, third, an incidental finding during imaging studies performed for other purposes [1]. The diagnostic approach taken for a suspicious finding in the pituitary gland depends on the symptoms and available imaging technology. Patients who present with hormonal symptoms must undergo an array of tests to determine the true nature of a lesion that might have been revealed via imaging (magnetic resonance imaging [MRI] is the method of choice). An endocrine panel is suggested as the primary laboratory work-up. This panel evaluates insulin-like factor 1, luteinizing hormone, follicle-stimulating hormone, serum prolactin, thyroid-stimulating hormone (TSH), thyroxin (T4), estradiol (female), and testosterone (male) and initially includes highly accurate 24-h urinary free cortisol, late night salivary cortisol, and overnight dexamethasone suppression tests [3]. Thus, hypersecretory syndrome and any deficiencies might be clarified.

Therapeutic options also depend on the primary setting in which the patient presents himself or herself. The primary goal should be to reduce hormonal hypersecretion and the corresponding clinical syndrome, followed by attempt to reduce the lesion volume and consequent mass effect and to correct or restore the endocrine deficiency.

Generally, so-called functioning lesions, which should be called "endocrine active lesions," must be differentiated from inactive lesions. Prolactinomas and growth hormone (GH) or adrenocorticotropic hormone (ACTH)-secreting lesions are active. The former can be treated using dopamine agonists if the indication is strong. Treatment of the latter might be referred to as multidisciplinary team (MDT) comprising neurosurgeons, radiation oncologists, and endocrinologists.

Non-active lesions, which may be either microadenoma or macroadenoma, should be addressed using an individual and risk-adapted approach.

Patients with microadenoma might undergo a follow-up MRI and laboratory work-up after 12 months to evaluate the situation. If no change is observed, another follow-up MRI might be conducted after 2 or 3 years. The patient should be treated if the lesion volume is observed to have changed, when the lesion abuts the optic chiasm and/or the lesion is larger than 1 cm.

Patients with macroadenomas should be referred for visual field testing; if a deficit or other neurologic symptoms are present, the patient should undergo the same procedure used to treat GH-/ACTH-secreting lesions [1], which involves a MDT of neurosurgeons, radiation oncologists, and endocrinologists.

The decision-making process begins once the case of a patient with a lesion requiring definitive treatment is presented to the MDT. This process represents the crux of the matter. To date (January 2016), the US-based National Cancer Institute recommends a differential and risk-adapted approach. For endocrine active lesions, the NCI recommends the following procedures: prolactinomas might be subjected to drug therapy, surgery, fractionated stereotactic radiotherapy (FSRT), or stereotactic radiosurgery (SRS). One option would be a hybrid approach that includes microsurgery and SRS. Identical recommendations have been made for ACTH-producing lesions. GH- and TSH-secreting lesions should be treated with surgery with or without SRS and drug therapy to block hormone production. Patients with recurrent disease should be subjected to either microsurgery or radiosurgery.

Stereotactic Radiosurgery for the Treatment of Patients with PA

A sufficient number of publications have described the use of using SRS in patients with PA. These publications support a fair, patient-centered, and objectively differential approach in terms of recommending and discussing with patients innovative treatment options that are safe, noninvasive, and effective but lie beyond the traditional microsurgical method. This does not suggest that the clinician should influence the patient's preferences, but should instead promote informed consent based on the best available recent data.

Availability and Quality of Scientific Evidence

An evaluation of the degrees of validity and quality of the available data regarding initial and postoperative or hybrid SRS usage is presented below in question/answer format.

Do we have plausible and valid data at the "level of evidence 1a" with particular regard to the initial usage of SRS?
No, not in the context of a meta-analysis of prospectively designed, controlled randomized trials (CRT).

Do we have plausible and valid data at the "level of evidence 1b" with particular regard to the initial usage of SRS?
No, as yet no prospectively designed CRTs on this issue are available.

In summary, it has become clear that the overall quality of the available data is not sufficient to allow robust conclusions and firm recommendations.

Do we have plausible data at the "level of evidence 2a" with particular regard to the postoperative or hybrid usage of SRS?

One publication systematically reviewed retrospective cohort studies and analyzed pooled data using a random effect model.

Abu Dabrh and colleagues reviewed 30 eligible publications, with a total of 2,464 patients. That review aimed to compare conventional radiotherapy (RT) with SRS. The available data failed to reveal a statistically significant difference between the two abovementioned methods. However, an increase in the remission rate at the most recent follow-up (52 % vs. 36 %; $p = 0.14$) was found to favor SRS, as was a significantly lower IGF-I level at follow-up. SRS was associated with a lower incidence of hypopituitarism relative to RT; however, this difference was not significant (32 % vs. 51 %, respectively; $p = 0.05$) [4]. The authors concluded that SRS might be associated with a better biochemical remission and had a lower risk of hypopituitarism with at least one deficient axis when compared with conventional RT.

Do we have plausible data at the "level of evidence 2b" with particular regard to the initial and hybrid usage of SRS?

Yes, there are data indicating the effectiveness of noninvasive image-guided stereotactic radiosurgery in patients (f/m) with AP.

Since 2010, more than 30 retrospective cohort studies have been published [1, 5–38].

The validity, plausibility, and quality of the above-quoted references are highly heterogeneous, as might be expected. These studies have incorporated different SRS modalities, including standard and dedicated accelerators, Gamma Knife, and CyberKnife.

The focus of this book, as mentioned previously, is the principles of SRS and its safety and effectiveness for the local control of PAs in patients (f/m).

In the following sections, we will not clearly distinguish between device types, even if we are aware of significant technological differences, but instead intend to focus on the clinical outcome as the main determinant with the highest importance for our patients (f/m).

Herein, we will discuss some recent representative and clinically significant studies that have involved different devices, encompassing relevant information, and have included sufficient numbers of patients (f/m).

Puataweepong and colleagues recently reported the treatment of 115 cases using an adapted conventional accelerator. The patients were classified to receive either SRS or FSRT. With a median follow-up time of 62 months, the overall 6-year progression-free survival rate was 95 % (93 % for SRS and 95 % for FSRT). The endocrine renormalization rates at 3 and 5 years were 20 % and 30 %, respectively, with average times to renormalization of approximately 16 months for SRS and 20 months for FSRT. The incidence of new hypopituitarism was 10 % in the SRS group and 9 % in the FSRT group. Four patients (5 %) developed optic neuropathy (one in the SRS group and three in the FSRT group). The selection criteria for this study comprised a

simple treatment setting with regard to device type and availability [5]. Minniti and colleagues reported the treatment of 85 patients with PA who underwent FSRT using an identical adapted but conventional accelerator. At a median follow-up of 75 months (range, 12–120 months), the 5- and 10-year actuarial local control rates were 97 % and 91 %, respectively, with corresponding overall survival rates of 97 % and 93 %, respectively. Forty-nine patients experienced tumor reduction, 16 remained stable, and 3 exhibited disease progression. The relative tumor volume reduction rate was 47 %. This treatment was well tolerated, with minimal acute toxicity. The actuarial incidence of new anterior pituitary deficits was 40 % at 5 years and 72 % at 10 years. No other radiation-induced complications occurred [6].

Xu and colleagues reported a study of 104 patients (f/m) that aimed to investigate the safety and effectiveness of SRS in patients with a silent corticotroph adenoma (SCA) relative to those with other subtypes of non-ACTH-staining nonfunctioning pituitary adenoma (NFA). The median follow-up after SRS was 56 months (range, 6–200 months). No patients with an SCA developed Cushing disease during follow-up. Tumor control was achieved in 21 of 34 patients (62 %) in the SCA group, compared with 65 of 70 patients (93 %) in the NFA group. The median progression-free survival (PFS) duration was 58 months in the SCA group. The actuarial PFS rates at 3, 5, and 8 years were 73 %, 46 %, and 31 %, respectively, in the SCA group and 94 %, 87 %, and 87 %, respectively, in the NFA group. SCAs treated with a dose of ≥17 Gy had an improved PFS. New-onset loss of pituitary function developed in 10 patients (29 %) in the SCA group and in 18 patients (26 %) in the NFA group. Eight patients (24 %) in the SCA group experienced exacerbation of a visual field deficit or visual acuity that was attributed to tumor progression, as did 6 patients (9 %) in the NFA group [13].

This study reached an identical conclusion; namely, high local control rates could be achieved even with mid-scale technology.

In a multicenter study based on Gamma Knife technology, Sheehan and colleagues addressed different questions and issues.

Under the auspices of the North American Gamma Knife Consortium, nine Gamma Knife-equipped SRS centers retrospectively combined their outcome data from 512 patients with NFAs. Prior resection had been performed in 479 patients (93.6 %), and prior fractionated external beam radiotherapy had been performed in 34 patients (6.6 %). Patients had received a median dose of 16 Gy to the tumor margin. The median follow-up duration was 36 months (range, 1–223 months). In that study, overall tumor control was achieved in 93.4 % of patients at the last follow-up, and the actuarial tumor control rates at 3, 5, 8, and 10 years post-SRS were 98 %, 95 %, 91 %, and 85 %, respectively. A smaller adenoma volume (odds ratio [OR] = 1.08 [95 % confidence interval (CI), 1.02–1.13], $p = 0.006$) and absence of suprasellar extension (OR = 2.10 [95 % CI, 0.96–4.61], $p = 0.064$) were associated with progression-free tumor survival. New or exacerbated hypopituitarism after treatment was reported in 21 % of cases. New or progressive cranial nerve deficits were noted in 9 % of patients; 6.6 % exhibited worsened or new-onset optic nerve dysfunction. In the multivariate analysis, a younger age, larger lesion volume,

history of prior SRS, and history of prior endocrine deficiency were predictive of new or worsening cranial nerve dysfunction. No patient died as a result of tumor progression. Favorable tumor control and neurological preservation outcomes were reflected by a 4-point SRS pituitary score [23].

Hasegawa and colleagues reported results from a cohort that had undergone initial Gamma Knife SRS. The median clinical follow-up period was 98 months. The last follow-up images demonstrated tumor regression in 15 patients (f/m). No patient developed a cranial nerve injury or radiation-induced neoplasm [10].

Bir and colleagues also reported results from a cohort that had undergone initial Gamma Knife SRS. The median follow-up period was 45.57 months. Significant variations in tumor growth control were observed, including a decreased tumor size in 32 patients (56.1 %), arrested growth in 21 patients (36.1 %), and an increased tumor size in 4 patients (7 %). The progression-free survival rates at 3, 7, and 10 years were 100 %, 98 %, and 90 %, respectively. The neurologic signs and symptoms were significantly improved after treatment when compared with the pretreatment signs and symptoms (14 % vs. 107 %; $p < 0.0001$) [11]. In summary, Gamma Knife SRS is a safe, effective, and well-tolerated treatment.

Data are also available for specific accelerators (e.g., Novalis, BrainLab). In 2015, Barber and colleagues published a report of the outcomes of 75 patients (f/m). The radiographic progression-free survival rate was 100 % over a mean radiographic follow-up period of 47.8 months (range, 12.0–131.2 months). Endocrine renormalization was observed in 69.2 % of patients with functional adenomas after FSRT, whereas 30.8 % achieved partial hormonal control. Mild, grade I acute adverse effects were observed in 36 patients (48 %) during radiotherapy treatment, and an objective, persistent decrease in vision occurred in a single patient (1.5 %). New hormonal deficits were observed in 28.0 % of patients (f/m) [12]. In this technological setting (Novalis, BrainLab), Liao and colleagues analyzed the feasibility of SRS in 34 cases. The mean tumor volume before treatment was 5.06 ± 3.08 ccm. After a mean follow-up of 36.8 ± 15.7 months (range, 16–72 months), the tumor size was reduced in 7 (20.6 %) patients and remained stable in the remaining 27 (79.4 %) patients. Vision was improved in one patient and remained stable in the remainder. Only one patient developed transient posttreatment diplopia.

A prospectively initiated two-center study of risk-adapted single-fraction SRS or fractionated radiotherapy (FSRT) in 73 patients (f/m) with inactive (nonsecretory) PA was reported by Bostrom and colleagues. The treatment protocol allocated cases to SRS (planning target volume [PTV] <4 ccm, distance >2 mm to optic pathways = low risk) or FSRT (PTV >4 ccm, distance <2 mm to optic pathways) at two Novalis® centers. The mean tumor volume was 7.02 ccm (range, 0.58–57.29 ccm). The median follow-up duration was 5 years, with a 5-year overall survival rate of 90.4 % (95 % CI, 80.2–95 %) and 5-year local control and progression-free survival rates of 100 % (95 % CI, 93.3–100 %) and 90.4 % (95 % CI, 80.2–95 %), respectively. New post-SRS/FSRT visual disorders occurred in two patients (2.7 %), new-onset oculomotor nerve palsy occurred in one pre-irradiated patient, and preexisting visual disorders

improved in three patients (4.1 %). Complete hypopituitarism occurred as a new-onset disorder in four patients (13.8 %) and in three patients (25 %) with preexisting partial hypopituitarism. The pituitary function remained normal in 26 % of patients. Patients with tumor shrinkage (65.75 %) had a significantly longer follow-up ($p = 0.0093$). A multivariate analysis confirmed the correlation of new-onset hypopituitarism with the duration of follow-up ($p = 0.008$), as well as a correlation of new-onset hypopituitarism with tumor volume ($p = 0.023$) [39].

This study and a number of other studies suggest that SRS using a dedicated accelerator is safe for the treatment of PAs near the optic apparatus [15].

The endocrine status of the pituitary gland might be a critical point. Grant and colleagues reported 31 cases treated with single-fraction SRS with doses to the margin ranging from 20 to 24 Gy. Patients with secretory active PAs (ACTH, $n = 15$; GH, $n = 13$; prolactin, $n = 2$; TSH, $n = 1$) were treated with 35 Gy to the 50 % isodose line and followed up for a mean duration of 40.2 months (range, 12–96 months). All patients were evaluated after SRS to determine the time to hormonal normalization, time to relapse, and the incidence rates and time courses of radiation-induced hypopituitarism and cranial neuropathies. Initial normalization of hypersecretion was achieved in 22 patients (70 %), with a median time to remission of 17.7 months. After the initial hormonal remission, seven patients (32 %) experienced an endocrine relapse, with a mean time to relapse of 21 months. New-onset endocrine deficiencies within any of the five major hormonal axes occurred in ten patients (32 %). One patient (3 %) developed new-onset unilateral optic nerve pallor within the temporal field after 3 years [19]. In a clinical setting, another research group recently evaluated the long-term outcomes after fractionated RT for 116 cases of gross residual PA. GH, ACTH, prolactin, or TSH hypersecretion was documented in 30 patients (26 %). The RT dose administered to most (78 %) patients was 45 Gy in 1.8-Gy fractions. The major outcome endpoint was clinical and biochemical control, defined as a lack of growth on follow-up scans and normalization of pre-RT hypersecretion, if present. An outstanding long-term (10-year) tumor control rate of 96 % was achieved for inactive lesions. However, a significantly lower 10-year clinical and biochemical control rate of 62 % was achieved for active lesions ($p < 0.0001$ vs. 96 % for inactive lesions). A multivariate analysis confirmed that secretory status was the only independent prognostic factor [40].

By far, the most common complication after radiosurgery is delayed hypopituitarism, followed by cranial neuropathies. The effect of suppressive medication use on radiosurgery outcomes remains controversial. Given the rare but well-documented incidence of late recurrence after endocrine remission, a rigorous long-term clinical and radiographic follow-up is necessary for all patients with PA who are treated with radiosurgery [20, 23].

To summarize the above statements and quotations, SRS is safe and effective when used in an initial or postoperative setting [4, 40–44].

If available, this technology should be considered and recommended to patients (f/m).

Summary

Despite advances in surgical techniques and medical therapies, a significant proportion of pituitary adenomas remain endocrinologically active, demonstrate persistent radiographic disease, or recur when followed for long periods of time.

While surgery remains the first-line therapy, noninvasive image-guided stereotactic radiosurgery presents a good alternative, and it is indeed increasingly recognized as a viable treatment option for these often challenging tumors.

The literature clearly supports the use of noninvasive image-guided stereotactic radiosurgery, with endocrinologic remission rates and time to remission varying by tumor type, be it prolactinoma, 20–30 %; growth hormone-secreting adenomas, ~50 %; adrenocorticotrophic hormone-secreting adenomas, 40–65 %; and radiographic control rates almost universally greater than 90 % with long-term follow-up.

It is true even after stratifying the outcomes by tumor type, review the importance of prognostic factors (particularly, pretreatment endocrinologic function and tumor size), and discuss the complications of treatment.

In total, data support the use of noninvasive image-guided stereotactic radiosurgery for patients (f/m) with primary and for those with surgery-refractory pituitary adenomas, providing the patient with a noninvasive, safe, and effective treatment option for an otherwise resistant tumor.

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Part III

Radiosurgery for Cancer and Its Metastases

Brain Metastases

10

Abstract

Brain metastases represent a serious problem of medicine because they cause substantially cancer mortality. Independent of the organotropism of common tumors like breast cancer, lung cancer, or melanomas, any solid malignant tumor could disseminate tumor cells to the brain where they produce severe problems and lead to the death of patients (f/m).

Image-guided stereotactic radiosurgery in its multiple technologic appearances as the Linac, Gamma Knife, or CyberKnife radiosurgery could affect brain metastases, limited by volume, number, and occurrence site, by impacting the growth, when applied alone or after invasive surgical procedures with removal of some large or cystic metastases. The aim would be to prolong the time free of neurologic symptoms and, therefore, of a better quality of life for our patients (f/m).

Consecutively, it demonstrates a noninvasive high-precision and safe technique in treating patients (f/m) with traceable improvement of daily life with no or less symptoms. Image-guided stereotactic radiosurgery could be performed in outpatient setting and is cost-efficient.

Background

Brain metastases (BMs) represent a significant challenge to global healthcare [1–3].

BMs of solid tumors comprise a large proportion of all intracranial lesions in adults, and it is estimated that at least 40 % of cancer patients (f/m) will develop BMs during the trajectory of their illness [4–9]. In addition, BMs are among the most feared consequences of cancer. Progressive brain disease may cause severe headaches, nausea, and vomiting. In addition, this condition causes devastating neurological deficits, cognitive impairment, irreversible emotional decline, delirium,

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and, frequently, death. I, like all who are involved in the care of patients (f/m) with BMs, have experienced these tragic scenarios.

BMs are among the leading causes of death in patients (f/m) with cancer [1, 10–16]. In other words, cancer mortality is largely due to BMs.

This presents a significant challenge for the entire medical field with regard to both strategic and technological perspectives, the ethical duties of society, and, last but not least, the patient's quality of life during their remaining lifespan [17, 18].

The body of knowledge regarding the prognosis, transformation, and dynamics of BMs remained limited until the end of the 1970s. In 1980, Houten and Reilley published one of the largest autopsy-based studies (including 4728 patients) (f/m), in the field of cancer research [18]. Despite the observational study design, these authors found powerful evidence of a link between failure of the central nervous system and intracranial bleeding and infarction as an important cause of death in cancer patients (f/m). However, the study does not appear to have had the expected impact in terms of demonstrating the severity of the situation faced by the affected patients.

Although Chao and colleagues began to investigate issues related to BMs in the early 1950s and published data demonstrating a high success rate of short-term palliation with whole-brain irradiation in patients (f/m) with BMs in 1954 [19], this issue was not evaluated through well-designed (according to the available criteria) clinical trials until the late 1970s [14].

Given the persistent lack of effectiveness of chemotherapy, the Radiation Therapy Oncology Group (RTOG) executed the first two pivotal clinical trials in which various radiation therapy dosage regimens (30 Gy in 10 fractions and 37.5 Gy in 15 fractions) were evaluated, as reported by Borgelt and colleagues [20]. In the second half of the twentieth century, whole-brain radiotherapy (WBRT) remained the only, albeit largely palliative, effective treatment modality [14].

Whole-Brain Radiotherapy

By the end of the last century, whole-brain radiotherapy (WBRT) had become an accepted therapeutic and palliative disease control option for solid tumors that had metastasized to the brain [4, 8, 9, 13, 14, 17].

Given the limitations associated with blood–brain permeability and consequent limited degree of immune isolation, the brain remains an important sanctuary for many malignancies, including those associated with the highest mortality rates, such as lung cancer, breast cancer, melanoma, and renal cell carcinoma [21–27].

WBRT is used to achieve two main goals: local control of existing lesions discovered using imaging modalities such as magnetic resonance imaging (MRI) and control of assumed areas of microscopic seeding, which occur frequently, depending on the primary tumor biology and organotropism. Such seeding is estimated to occur in more than 60 % of cases [13, 14, 17].

Together with focal therapies, WBRT reduces the rates of local failure and leptomeningeal dissemination and dramatically reduces subsequent compartmental

regional failure in the brain. Although focal therapies yield very high local control rates, these occasionally confound existing level 1 data that demonstrate a further enhancement of local control with WBRT [17].

The application of WBRT, which is currently the standard of care, has evoked three issues: first, the decline of the cognitive capacities of patients (f/m) undergoing WBRT remains a highly significant and yet unresolved problem; second, the impact of WBRT on regional disease control is questionable; and, third, the influence of WBRT on overall survival should be determined, as a patient (f/m) may either undergo or omit WBRT.

Neurocognitive Dysfunction Induced by WBRT

Data are available regarding "the elephant in the room" [14] or neurocognitive issues related to WBRT. Diffuse radiographic periventricular changes in white matter after cranial radiation have been well described and occur at a far higher frequency with WBRT than with stereotactic radiosurgery (SRS) [28]. Neurocognitive dysfunction after cranial radiation is multifactorial and is typically mild to moderate; however, it remains one of the most distressing side effects of WBRT and often is the rationale given against its use (Tables 10.1 and 10.2).

Chang and colleagues executed a phase III study of patients (f/m) with 1–3 BMs and compared approaches involving a combination of SRS and WBRT versus SRS alone [29]. The primary endpoint of this study was neurocognitive function, measured using the Hopkins Verbal Learning Test-Revised (HVLT-R). However, this trial was

Table 10.1 Characteristics of patients ($n = 346$) included in prospective studies comparing stereotactic radiosurgery alone versus whole-brain radiotherapy and radiosurgery

Variables	Total no. of cases	SRS alone	SRS and WBRT
Number of metastases			
1	217	111	106
2	88	44	44
3	47	24	23
4	12	7	5
Extracranial metastases	202	100	102
Cancer			
Lung	214	109	105
Breast	43	22	21
Kidney	24	11	13
Local failure (in %)	20	27	12
Salvage treatment (in %)	63	73	38
Distant brain failure (in %)	43	53	34
Death (in %)	86	84	88
Neurologic death (in %)	27	30	25

RPA Z recursive partitioning analysis

Table 10.2 Outcome of patients ($n=346$) included in prospective studies comparing stereotactic radiosurgery alone versus whole-brain radiotherapy and radiosurgery according the age, an analysis of hazard ratios (95 % confidence interval)

Age in years	Overall survival	Distant brain failure
35	0.46 (0.24–0.9)	0.90 (0.42–1.94)
40	0.52 (0.29–0.92)	1.05 (0.56–1.98)
45	0.58 (0.35–0.95)	1.23 (0.73–2.05)
50	0.64 (0.42–0.99)	1.43 (0.95–2.15)
55	0.72 (0.49–1.05)	1.67 (1.19–2.35)
60	0.80 (0.56–1.14)	1.95 (1.40–2.71)
65	0.90 (0.62–1.29)	2.27 (1.55–3.33)
70	1.0 (0.67–1.49)	2.65 (1.64–4.27)
75	1.12 (0.71–1.76)	3.09 (1.70–5.61)
80	1.24 (0.73–2.11)	3.60 (1.75–7.44)

References [57–59]

terminated early after accruing 58 patients because of a high probability that SRS plus WBRT would induce significant declines in learning and memory function (total recall) at 4 months, compared with SRS alone. As described in two previous studies, more frequent CNS recurrence was observed in the group treated with SRS alone; 73 % of patients in the SRS and WBRT group remained free from CNS recurrence at a 1-year follow-up, compared with 27 % of patients who received SRS alone [29].

Aoyama and colleagues [30] reported that progressive disease has a greater impact than WBRT in terms of cognitive decline, such that patients who received SRS alone exhibited a more rapid decline in mini-mental state examination scores.

The North Central Cancer Treatment Group (NCCTG) recently completed patient accrual for a phase III trial (N0574) in which SRS alone was compared with SRS followed by WBRT in patients with 1–3 BMs; early cognitive change has been included as an endpoint. The results of this trial are pending.

Mitigation of cognitive dysfunction, therefore, has become an important topic of research. The RTOG conducted two studies in an attempt to modulate this side effect. In the RTOG 0614 trial, patients were randomly assigned to receive memantine, an NMDA receptor agonist, versus placebo [31]. Patients (f/m) in the memantine arm required a significantly longer time before manifesting a cognitive decline (p 0.02). The median decrease in the HVLT-R scale score was 0 in the memantine arm, compared with −2 in the placebo arm (p 0.059). In addition, fewer patients treated with memantine exhibited decreased Controlled Oral Word Association Test scores at 16 weeks (p 0.004) or Trail Making Test Part A scores at 24 weeks (p 0.014).

Hippocampal neural stem cell injury caused by irradiation during WBRT might play a primary role in memory decline by shifting the stem cell maturation cycle from neurogenesis to gliogenesis, a phenomenon that has been well established in preclinical models [32, 33].

In a prospective clinical study, a strong association between an increasing hippocampal radiation dose and neurocognitive dysfunction was demonstrated [34].

Regarding the use of intensity-modulated radiotherapy for the prevention of hippocampal damage, Gondi and colleagues conducted a single-arm phase II study of hippocampal avoidance (HA)-WBRT for BMs, using a prespecified comparison

with a historic control arm of patients treated with WBRT without hippocampal avoidance (RTOG 0933). The primary endpoint was the change in HVLT-delayed recall (DR) at 4 months. The historic control (without hippocampal avoidance) resulted in a 30 % mean relative loss in the HVLT-DR from baseline to 4 months. The actual observed mean relative decline in the HVLT-DR from baseline to 4 months was, in fact, only 7.0 %, which was significantly lower than the historic control of 30 % (p 0.0003). No decline in the quality of life scores was observed over a period of up to 6 months [35].

Influence of WBRT on Regional Disease Control in the Brain

The above-discussed randomized studies demonstrate clear improvement in intracranial BMs with postoperative WBRT [9, 13, 14, 17].

Impact of WBRT on Overall Survival

Although the above-discussed randomized studies demonstrate that postoperative WBRT clearly improves the intracranial control of BMs, they also demonstrate that this benefit has not categorically translated into an overall survival benefit [14, 17].

More importantly, emerging data presented by Sahgal and colleagues demonstrate an overall survival advantage of SRS alone vs. WBRT (10 vs. 8.2 months) in patients aged 50 years or younger with 1–4 BMs, according to a meta-analysis of three phase III studies [15]. This pooled data analysis was conducted by merging the EORTC 22952–26001, JROSG99-1, and MDACC NCT00460395 data sets. Collectively, these three trials included patients with 1–4 BMs who had been treated with SRS in the presence or absence of WBRT; however, the entry criteria varied among the trials, and considerable variability was reported in terms of systemic therapies, enrollment eras, SRS doses, follow-up imaging schedules, and retreatment considerations. Furthermore, the EORTC trial also included patients who underwent resection at the physician's discretion. The collated dataset included a total of 364 patients, of whom 51 % (185 patients) were treated with SRS alone and only 19 % (69 patients) were younger than 50 years. The results demonstrate a curious range of outcomes; the overall survival was superior in the SRS-alone arm (10 vs. 8.2 months) of a post hoc defined subset of patients younger than 50 years, whereas the time to distant brain failure was shorter for patients older than 55 years who were treated with SRS alone (4.5 vs. 6.5 months). The time to local failure was superior with WBRT (7.4 vs. 6.6 months). It is important to emphasize that the recommendation regarding survival benefits in the category of younger patients treated with SRS alone was based on an enrollment of approximately 35 patients per arm and a post hoc analysis of a cohort in which pre-enrollment balance regarding the extent of systemic disease could not be assured, as structured pre-SRS staging—a necessary element for assessing overall survival as an endpoint while avoiding systemic burden as a confounder—was not performed. Therefore, it is reasonable to

hypothesize that the survival benefit from WBRT is limited primarily to patients who do not experience extracranial disease progression.

The data that most strongly call into question the meta-analysis by Sahgal and colleagues, however, were obtained from one of the key sources used in that analysis, JROSG 99–1. At the JASTRO 2014 annual meeting, Dr. Aoyama presented a reanalysis of this study based on the now widely accepted disease-specific Graded Prognostic Assessment (DS-GPA), a prognostic stratification tool [36]. The DS-GPA relies on molecular variables to stratify patients with breast cancer; as this information was not collected during the JROSG 99–1 trial, these patients could not be adequately categorized and were excluded. Furthermore, 88 of 132 enrolled patients with non-small cell lung cancer were grouped into the favorable (DS-GPA of 2.5–4; 47 patients) and unfavorable (DS-GPA of 0.5–2; 41 patients) categories. The median survival times in the favorable group were 16.7 and 10.6 months for the WBRT arm and SRS alone arm, respectively (p 0.03), whereas a similar survival improvement was not observed in the unfavorable group (personal communication with Mehta, March 2015, quoted with permission) [14]. Mehta stated in a recent review that "this lends credence to the hypothesis that in patients with a high ds-GPA category, improved brain control translates to a survival advantage because these patients do not die as rapidly from extracranial progression. Therefore, the beneficial effects of improved brain control from WBRT actually affect overall survival. This is quite contrary to the current wisdom of reserving WBRT only for the prognostically least-favorable group of patients. This issue, therefore, remains unresolved" [14].

The Emergence of a "Standard" of Care: SRS Without WBRT in Patients with One to Four BMs

In the mid-1990s, the persistent lack of chemotherapeutic effectiveness led to several new treatment options. Technological advancements enabled neuro-oncologists in the fields of radiation oncology and neurosurgery to redefine the roles of surgery and radiotherapy in the care of patients (f/m) with BMs. New microsurgical approaches had shifted the operating range of neurosurgical techniques, particularly with regard to single "resectable" BMs and large cystic metastatic lesions that were contraindicated for radiotherapy. In this context, in 1990, Patchell and colleagues published the first randomized trial of a surgical approach for single "resectable" BMs [37]. The aim of that study was to assess the efficacy of surgical resection of BMs from extracranial primary cancers. Patients with a single BM were assigned randomly to undergo either surgical removal of the brain tumor followed by radiotherapy or needle biopsy and WBRT. Forty-eight patients (25 in the surgical group and 23 in the radiation group) formed the study group; six other patients (11 %) were excluded from the study after biopsy analysis proved their lesions to be either second primary tumors or related inflammatory or infectious processes. Recurrence at the site of the original metastasis was less frequent in the surgical group than in the radiation group (5/25 [20 %] vs. 12/23 [52 %]; $p < 0.02$). The median overall survival duration was significantly longer in the surgical group (40 weeks vs. 15

weeks in the radiation group; $p<0.01$), and patients in the surgical group remained functionally independent for a longer period (median, 38 weeks vs. 8 weeks in the radiation group; $p<0.005$). This study established the Western standard of care in this specific scenario for at least another decade [14, 37].

At the end of the previous century (1998), Patchell and colleagues published another pivotal randomized study [38]. In the next stage of refinement, the authors attempted to determine whether post-surgery radiotherapy would result in improved neurologic control of disease and increased survival. In this multicenter, randomized, parallel group trial, 95 patients (f/m) with single BMs that had been treated with complete surgical resection (tested by MRI) were included. Patients were randomly assigned either to post-surgery WBRT ($n=49$) or no further treatment ($n=46$). During respective median follow-up periods of 48 and 43 weeks, the incidence of tumor recurrence anywhere in the brain was less frequent in the radiotherapy group than in the observation group (9/49 [18 %] vs. 32/46 [70 %]; $p<0.001$). Postoperative radiotherapy prevented brain tumor recurrence both at the site of the original metastasis (5/49 [10 %] vs. 21/46 [46 %]; $p<0.001$) and at other sites in the brain (7/49 [14 %] vs. 17/46 [37 %]; $p<0.01$). Patients in the radiotherapy group were less likely to die of neurologic causes than were those in the observation group (6/43 [14 %] vs. 17/39 [44 %]; $p=0.003$). There was no significant difference between the two groups in terms of the overall survival duration or the duration of continued functional independence [38]. For many years, this pivotal study has set a new standard of care for patients with a single resectable metastasis, and this approach remains standard in some medical centers in Europe and the USA.

In a recent review [14] of the long trajectory of BM treatment, Mehta and Ahluwalia stated that the following navigational thrusts emerged as a consequence of the Patchell study:

> First, in several quarters, WBRT became a routine and accepted standard of care after resection to dramatically and convincingly lower intracranial relapse; second, SRS became widespread as a modality for the local control of at-first limited number of brain metastatic lesions but more recently of multiple lesions; third, the role of WBRT in terms of enhancing local control came under intense scrutiny because of concerns regarding its potential for neurotoxicity and a perceived lack of a survival benefit. The bidirectional evolutionary ramifications of the latter trend were to better understand the mechanisms underlying some of these neurotoxicities and efforts to modulate these through the conduct of innovative clinical trials, as well as to become more selective regarding the application of WBRT primarily for patients who had multiple (with a flexible definition of this concept) BMs. This selection often has been in the context of a combined approach with systemic therapeutics, a direction that recently has experienced an upsurge because of the emergence of blood–brain barrier–penetrating agents, primarily in malignancies with driver mutations [14].

Personal Comments on the Mehta Review from 2015

To my knowledge and understanding, SRS was not merely an indirect consequence of the pivotal Patchell study that provided formative momentum toward an understanding of the biological dynamics of BMs, although that was certainly inductive

and cogent; the emergence of SRS was also attributable to formative changes in the industry that occurred independently of medical academia.

This was likely a fortuitous coincidence that was initiated not by medical professionals, but rather by industrial pioneers who anticipated future developments.

We extensively cite the Mehta and Ahluwalia review for two reasons. First, the authors' research has had a real and well-recognized impact on the standards of care for patients (f/m) with BMs on a global scale. Second, the valuable and appreciated experience of these authors has allowed them to have a very special regard to the history of clinical oncology and, specifically, the field of neuro-oncology. We defer to the authors.

Furthermore, Mehta and Ahluwalia stated that "SRS now has become the most widely used focal treatment modality for patients who have brain metastasis. The efficacy of SRS for BMs was first reported in multiple retrospective studies." In the next evolutionary step in this narrow field, in 2001, Sanghavi and colleagues demonstrated [39] in a retrospective, multi-institutional analysis of 502 patients who were stratified according to recursive partitioning analysis (RPA) classes I, II, and III that patients treated with WBRT and SRS exhibited a significant increase in the median survival duration, compared to those treated with WBRT alone. The survival durations of patients in classes I, II, and III were 16.1 versus 7.1 months, 10.3 versus 4.3 months, and 8.7 versus 2.1 months when treated with combination therapy versus WBRT alone, respectively (p 0.05). In 2004, the RTOG 9508 trial was published by Andrews and colleagues; this trial included 333 patients (f/m) with "one to three BMs and a Karnofsky performance score (KPS) of 70 or greater who were treated with WBRT and SRS or WBRT alone" [40]. In patient (f/m) with a single brain metastasis, the treatment with WBRT and SRS compared with only WBRT resulted in a decreased rate of local recurrence at 1 year (18 % vs. 29 %; p 0.01) and superior median survival times (6.5 vs. 4.9 months; p 0.039). In patients (f/m) with 2–3 BMs, local control was significantly improved in the combination arm, but there was no difference in survival time between the two groups. There was an additional benefit in outcomes (maintenance or improvement of KPS and corticosteroid use) in patients who received SRS and WBRT compared with WBRT alone [40]. Herein, the review provides a legitimate narrative of a breakthrough in the standards of care.

Another step was taken shortly after the crucial RTOG9508 trial; in 2006, Aoyama and colleagues reported a Japanese trial (JROSG 00–1) in which 132 patients with a KPS score of at least 70 and fewer than 4 BMs were randomly assigned to undergo SRS with or without WBRT. Although the results did not demonstrate a survival difference (8.0 months for SRS vs. 7.5 months for SRS with WBRT; p 0.42), a trend in longer-term survival was observed to favor the WBRT arm (1-year survival rates, 38.5 % in the group treated with WBRT plus SRS vs. 28.4 % for SRS alone) [30]. A recent update to the Japanese trial revealed new insights regarding complex issues of regional control [10]. After a median follow-up time of 8.05 months, 47 patients with a favorable prognosis and DS-GPA scores of 2.5–4.0 (26 SRS alone and 21 WBRT + SRS [DS-GPA 2.5–4.0 group]) and 41

with an unfavorable prognosis and DS-GPA scores of 0.5–2.0 (19 SRS alone and 22 WBRT + SRS [DS-GPA 0.5–2.0 group]) were examined. In the DS-GPA 2.5–4.0 group, significantly better overall survival was observed with WBRT + SRS versus SRS alone, with median survival times of 16.7 (95 % confidence interval [CI], 7.5–72.9) months versus 10.6 (95 % CI, 7.7–15.5) months (hazard ratio [HR], 1.92; 95 % CI, 1.01–3.78; $p = 0.04$). However, no such difference was observed in the DS-GPA 0.5–2.0 group (HR, 1.05; 95 % CI, 0.55–1.99; $p = 0.86$). This benefit could be attributed to a difference in BTR rates, such that prevention against BTR with WBRT had a more significant impact in the DS-GPA 2.5–4.0 group (HR, 8.31; 95 % CI, 3.05–29.13; $p < 0.001$) than in the DS-GPA 0.5–2.0 group (HR, 3.57; 95 % CI, 1.02–16.49; $p = 0.04$). The authors concluded that despite the current trend toward the use of SRS alone, WBRT should be considered to have an important role in the treatment [10].

Two other trials provided additional information. The EORTC 22952–26001 study [41] randomly assigned 359 patients with 1–3 BMs to either receive 30 Gy of WBRT or observation following surgery or SRS. WBRT after either surgery or SRS was associated with improved local and distant brain control (p 0.001). More robust intracranial control led to a reduced use of salvage therapies and slightly longer progression-free survival, but had no impact on overall survival or survival with functional independence [41].

To date, these have been the most decisive trials conducted in the first decade of the new century. All have added to the body of knowledge regarding the dynamics of survival and mortality in patients with BMs.

Therefore, a new global standard of care was set; specifically, patients (f/m) with solid tumors and a maximum of 4 BMs might receive SRS with or without WBRT, if SRS technology is available [9, 13, 42, 43].

Amplification of the "Standard" of Care: SRS Without WBRT in Patients with Five to Ten BMs

The next question arises automatically: under the control of progressive caregivers, what is the fate of patients (f/m) who are in good physiologic condition, remain active in daily life, have a controlled primary tumor, and develop a greater but still limited number of BMs (e.g., 5–10) with relatively small volumes and no severe neurologic symptoms?

Given the realistic nature of this clinical scenario, it would be legitimate to ask such a question when advocating for an individual patient (f/m).

According to the intrinsic logic of progressive investigations, the next trial was published in 2012, shortly after the standard of care had been established. Mohammadi and colleagues at the Cleveland Clinic addressed the above-asked question in a retrospective study of 170 patients (f/m) with ≥5 BMs and demonstrated a median overall survival duration of 7.5 months after treatment with SRS [44]. That duration exceeded all expectations derived from the earlier literature. The device used in that study was a Gamma Knife. Astonishingly, the absolute number

of BMs was not a significant predictor of survival; rather, a higher intracranial tumor burden, and thus greater volume, was predictive of a poorer outcome.

This study marks the starting point of the amplification of so-called standard care.

In a highly disputed, prospective, observational study of patients (f/m) with 1–10 BMs conducted at 23 Japanese SRS centers, no difference in overall survival was observed between patients with 2–4 BMs and those with ≥5 BMs following treatment with SRS alone. A 2014 publication by Yamamoto and colleagues in Lancet Oncology [45] attempted to exceed the borders of technical feasibility and, simultaneously, the threshold of the community's compliance with such experimental settings. The disputes that were initiated after this publication are ongoing [46]. The median overall survival after SRS was 13.9 months in patients with a single BM, 10.8 months in patients with 2–4 BMs, and 10.8 months in patients with 5–10 BMs [45]. This suggests that SRS may be a reasonable approach for selected patients with up to 10 BMs, thus broadening the scope for the use of SRS in these patients (f/m) [13, 17]. The recent Mehta review stated that "this also supports the hypothesis that the volume, and not the number, of metastases may be the driver in determining the outcomes in brain metastases" [14].

Again, progressive neuro-oncologists continue their attempts to exceed the borders of feasibility.

An ongoing prospective trial, NAGKC 12–01, is comparing neurocognitive outcomes and survival in patients with ≥5 BMs who were treated with either SRS or WBRT (NCT01731704) and is expected to further define the role of SRS in this patient population.

Amplification of the "Standard" of Care: SRS Without WBRT After Resection in Patients with Less Than Four BMs

The next question also arises automatically: under the control of progressive caregivers, what is the fate of patients (f/m) who maintain a good physiologic condition, are active in daily life, have a controlled primary tumor, and develop fewer than four lesions of which at least one is resectable?

The hybrid usage of SRS rather than WBRT for the prevention of local recurrence after resection is of interest. Given the realistic nature of this clinical scenario, it would be legitimate to ask such a question when advocating for an individual patient (f/m). It must be noted, however, that clinical resection bed SRS targeting is more complex because of uncertainties regarding the interpretation of postoperative MRI [14].

The first clinically consistent study was published by Soltys and colleagues in 2008 [47].

Seventy-two patients with 76 cavities who were treated from 1998 to 2006 met the inclusion criteria. SRS was delivered at a median marginal dose of 18.6 Gy (range, 15–30 Gy) to an average tumor volume of 9.8 ccm (range, 0.1–66.8 ccm). During a median follow-up of 8.1 months (range, 0.1–80.5 months), follow-up

imaging data that were assessable for control analyses were obtained for 65 patients. The actuarial local control rates at 6 and 12 months were 88 % and 79 %, respectively. Local control was 100 % for the least conformal quartile compared with 63 % for the remaining quartiles. The target volume, dose, and number of sessions were not statistically significant parameters [47]. In 2012, Choi and colleagues reflected on their experiences [48] with a relatively large group of 112 patients (f/m). With death as a competing risk, the 12-month cumulative incidence rates of LF and DF were 9.5 % and 54 %, respectively. In a univariate analysis, expansion of the cavity with a 2-mm margin was associated with a decreased incidence of LF; the 12-month cumulative incidence rates of LF with and without this margin were 3 % and 16 %, respectively ($p = 0.042$). The 12-month toxicity rates with and without this margin were 3 % and 8 %, respectively ($p = 0.27$). In a multivariate analysis, histological findings of melanoma ($p = 0.038$) and number of BMs ($p = 0.0097$) were associated with a higher incidence of DF. The median OS time was 17 months (range, 2–114 months), with a 12-month OS rate of 62 %. Overall, WBRT was avoided in 72 % of the patients (f/m) [48].

We reported on our group's first experience with 52 patients. Fractionated radiosurgery was not delayed in any case. The onset of acute toxicity was observed in 40 cases (76.9 %); however, no grade 3 or higher events were observed. The local recurrence-free survival duration was 32.6 months, and the local control rates at 6, 12, 18, and 24 months were 85 %, 77.9 %, 65.9 %, and 65.9 %, respectively. Overall, local failure occurred in 34.1 % of the patients. The overall survival rates at 6, 12, 18, and 24 months were 90.3 %, 63.9 %, 47.7 %, and 31.6 %, respectively. The median survival duration was 18.3 months (range, 13.8–22.8 months), and 17.3 % of the total patient population remained alive at the time of the final analysis. The distant control rates at 6, 12, 18, and 24 months were 49.4 %, 38.2 %, 25.5 %, and 22.3 %, respectively. A median distant recurrence-free survival of 6 months (range, 0–12.0 months) was observed, with overall distant failure in 77.7 % of the cases (our paper is available at http://www.hoajonline.com/journals/pdf/2054-1945-2-3.pdf).

Concerns related to this approach include the possibility of leptomeningeal spread secondary to resection, especially in patients with breast cancer and those with posterior fossa disease [49]. The NCCTG study N107C is an ongoing intergroup study that is comparing WBRT versus SRS after resection in patients with 1–4 BMs (NCT01372774).

One therapeutic option that is used to prevent leptomeningeal spread is the performance of preoperative SRS with an aim to sterilize tumor cells before surgical resection. Asher and colleagues reported an evaluation of 47 patients who underwent preoperative SRS with a median dose of 14 Gy (range, 11.8–18 Gy) [50]. Surgical resection after SRS resulted in a control rate of 86 % at 1 year, and only 15 % of the patients eventually required WBRT. Significantly, no leptomeningeal failures were observed in that study [50].

Currently, no evidence level 1a/b or 2 data are available to support the use of SRS instead of microsurgery.

Retrospective cohorts of patients with a single BM who underwent SRS or microsurgery have been examined extensively [51–53]. However, these and

similarly designed publications have not achieved the level quality required to direct clinical decisions and provide foundations for guidelines.

"The issue, therefore, remains unresolved" [14].

Future Perspectives

The emergence of biological agents that target specific molecules represents a significant field with considerable promise for the care of patients with BMs in the near future. Unfortunately, the initial hope that such agents would yield dramatic intracranial responses and disease control has been tempered by the generally very low true response rates. Furthermore, although some reports have included optimistic survival data, the only large prospective randomized trial that included a combination of targeted agents with WBRT—the RTOG 0320 trial—actually demonstrated inferior survival with this combination in a patient cohort that was not specifically selected for target expression [54].

That study was closed because of accrual limitations after enrolling 126 patients. The median survival times with WBRT + SRS, WBRT + SRS + temozolomide, and WBRT + SRS + ETN were qualitatively different (13.4, 6.3, and 6.1 months, respectively), although these differences were not statistically significant. The time to central nervous system progression and performance status at 6 months were better in the WBRT + SRS arm. The frequencies of grade 3–5 toxicity events were 11 %, 41 %, and 49 % in arms 1, 2, and 3, respectively ($p < 0.001$). The conclusion was that the addition of TMZ or ETN to WBRT + SRS in patients with non-small cell lung cancer and 1–3 BMs did not improve survival and possibly had a deleterious effect. Because this analysis was underpowered, these data suggest but do not prove that increased toxicity was the cause of inferior survival in the arms with drug combinations [54].

Other combined studies, such as the RTOG 1119 trial, are currently underway. The effective control of micrometastatic disease with targeted agents, together with the treatment of macroscopic disease using aggressive focal approaches such as SRS, is considered the "new standard" of treatment for BMs. The LANDSCAPE trial, which involved patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer and BMs, demonstrated a high response rate of 66 % with a combination of lapatinib and capecitabine, prompting an in-house trial at our institution of the combination of these agents with SRS in patients with up to 10 BMs [55].

Reports of the efficacy of up-front systemic therapy or targeted agents for primary intracranial therapy or radiosensitization have been mixed.

Immune checkpoint inhibitors, especially when used in combination with radiotherapy, represent a rational exploratory strategy; although some preliminary data have supported this approach as an investigational method in other disease types, no major efforts to evaluate this approach for BMs have yet been undertaken.

The idea of SRS as a possible "radiogenic vaccine" [17] also merits a prospective evaluation. The hypothesis underlying this use of SRS is that a single large ablative radiation fraction might induce robust cell death, thus unleashing a wave of antigens that were previously relatively "masked" in the immunoprivileged environment of the brain, and that this "antigenic flood" would elicit an effective antitumor T-cell response. The avoidance of WBRT would protect these T cells from the lymphocidal effects of radiation and, in combination with an immune checkpoint inhibitor, would negate the host- and tumor-mediated immune silencing associated with cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 (PD-1). Furthermore, this process would also lead to an abscopal, systemic effect and is thus clearly ripe for clinical testing and is currently under development by NRG Oncology [56].

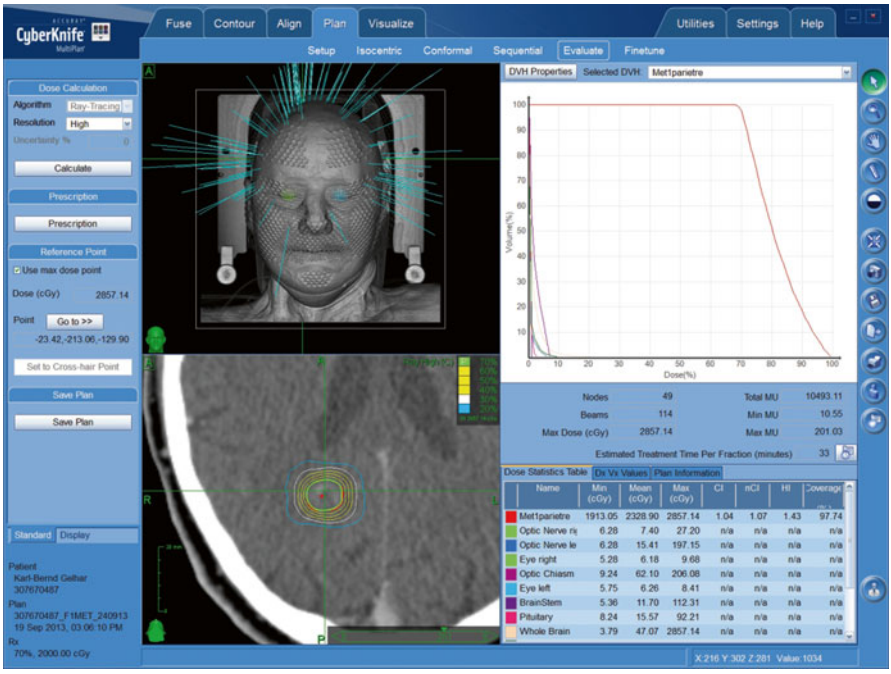
Potential detriments of the use of systemic therapy to treat intracranial disease might include disease progression within the brain, leading to worsened neurologic symptoms or a potentially worse prognosis if additional small tumor deposits progress into more clinically significant lesions. When considering an initial therapy for limited intracranial disease, a radiation oncologist should be consulted initially in the context of close multidisciplinary observation to ensure timely access to radiotherapy.

Summary

Over the last five decades, the clinical care of brain metastases has evolved from mere palliation with WBRT to an era of investigations that could redefine groups of patients (f/m) who do not urgently require WBRT. However, the current data do not permit definitive decisions regarding the extent to which WBRT could be omitted.

Based on a meta-analysis of three underpowered trials [15], it has been widely concluded that the omission of WBRT does not decrease overall survival. However, other factors that contribute to the lack of a difference in survival include the effectiveness of salvage therapies and the fact that systemic progression is a significant competing cause of mortality. Moreover, although it might be true that the omission of WBRT does not decrease overall survival, a diligent review of the available data suggests caution against jumping to such a conclusion, as the supporting data are relatively weak and contradictory data have recently emerged.

However, local therapies such as WBRT and SRS are important modalities in the management of BMs. Areas of active investigation include radiotherapeutic techniques for the preservation of neurocognitive function. The optimal management strategy for patients with BMs involves a multidisciplinary approach that accounts for the individual characteristics of both the patient and the tumor.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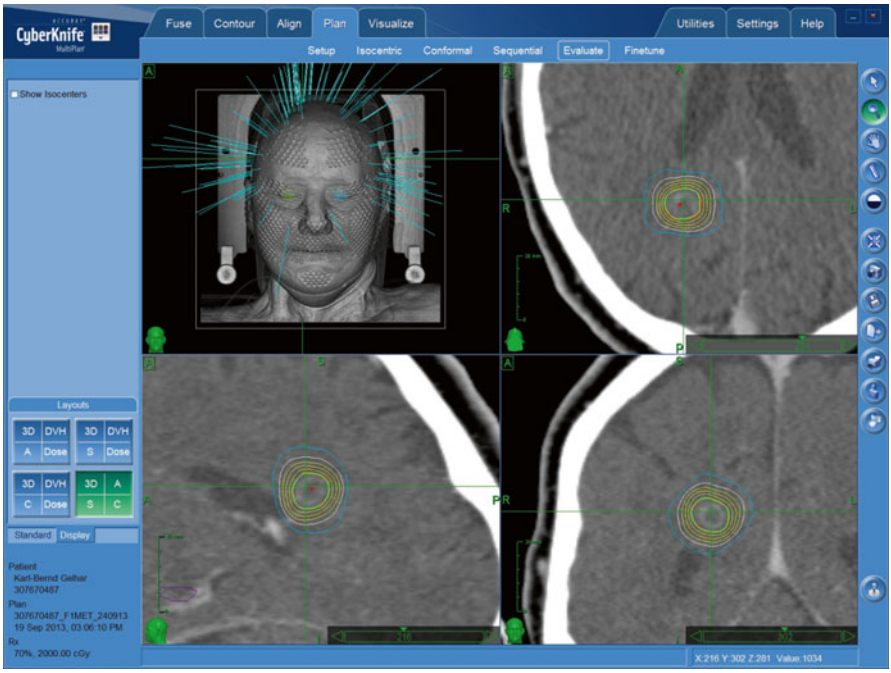
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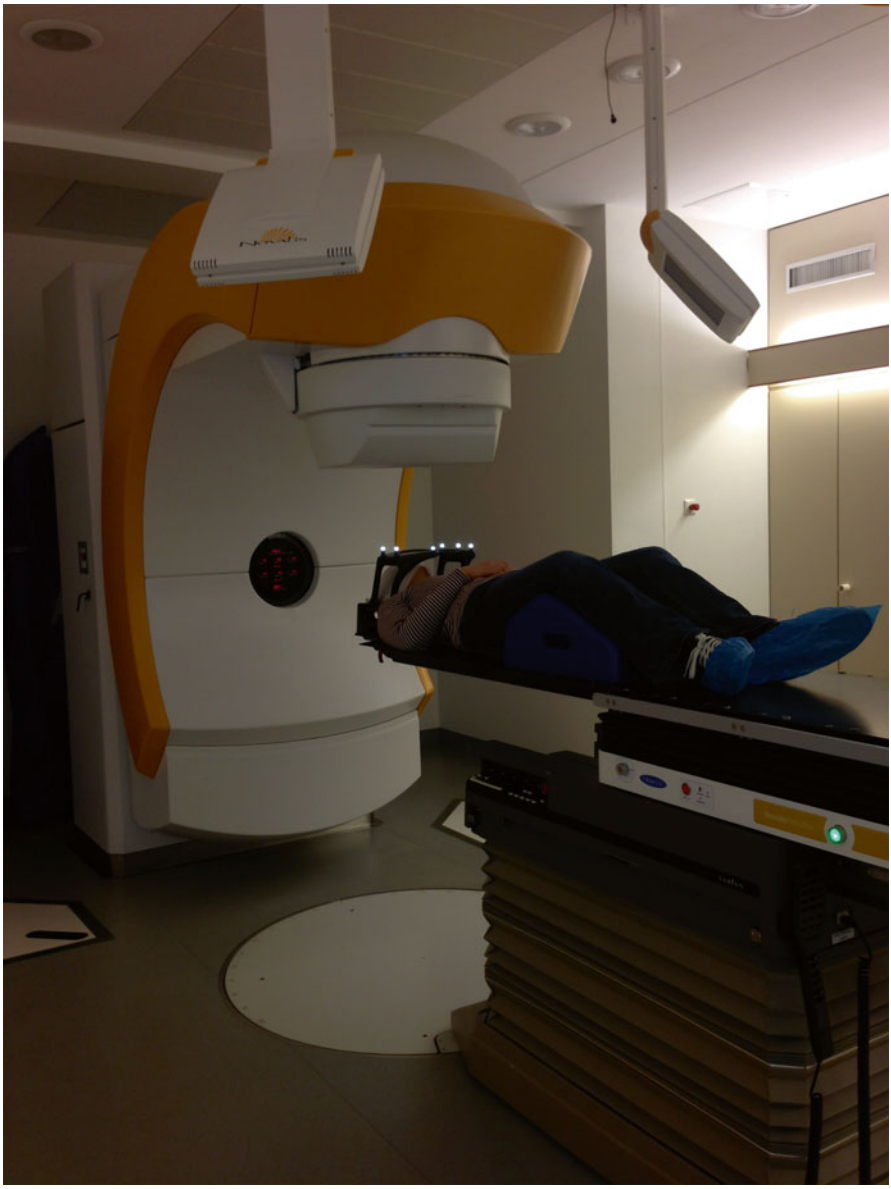

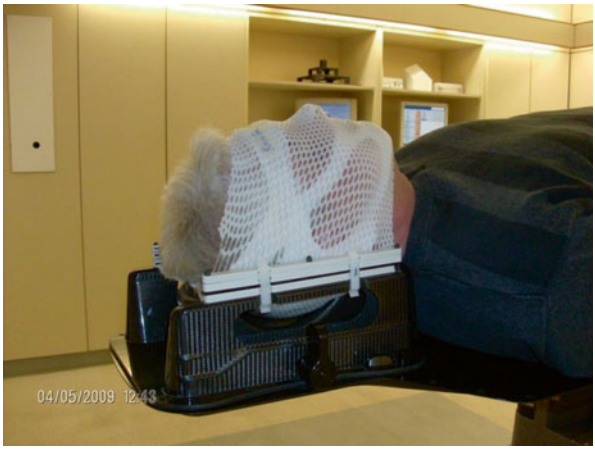
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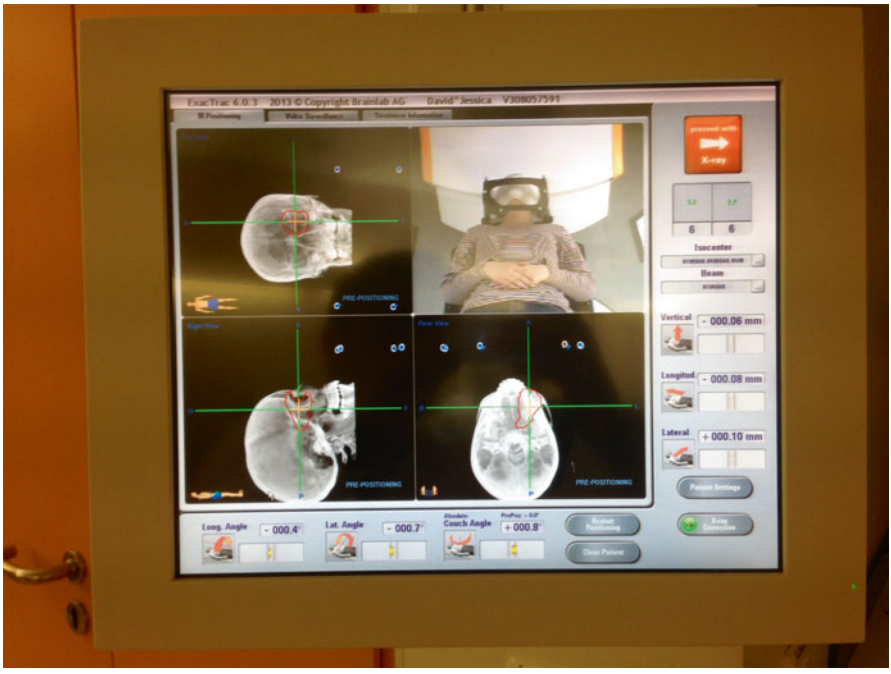
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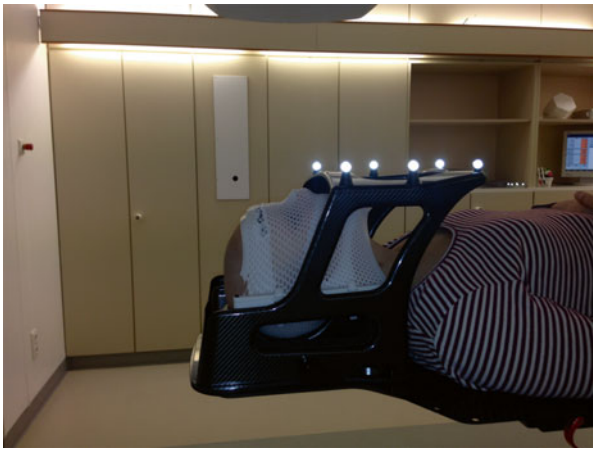

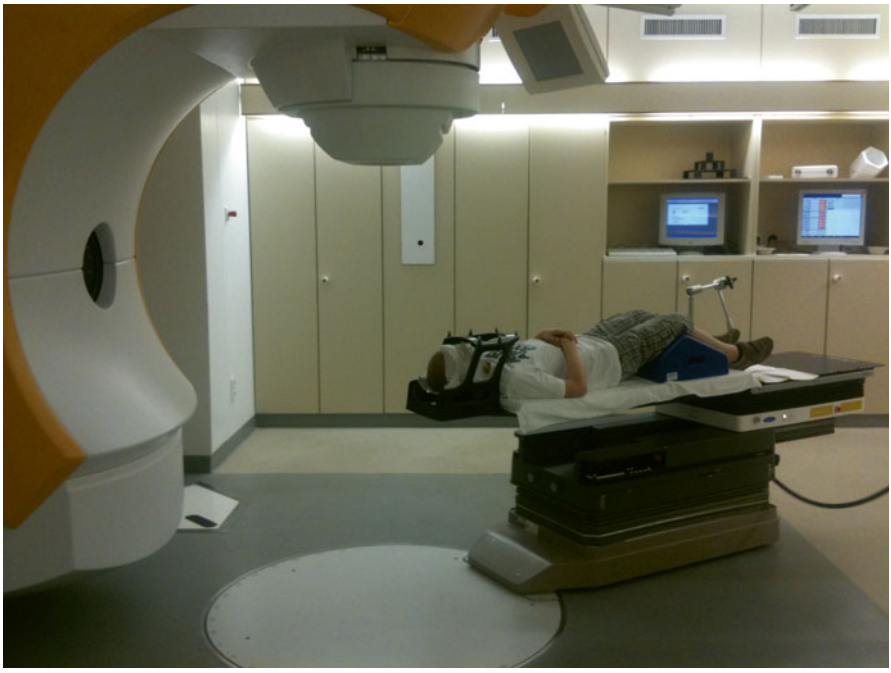

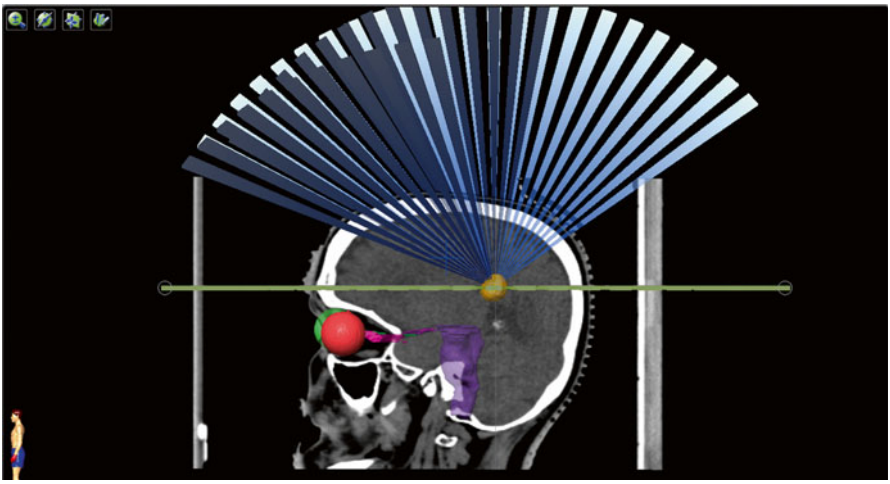

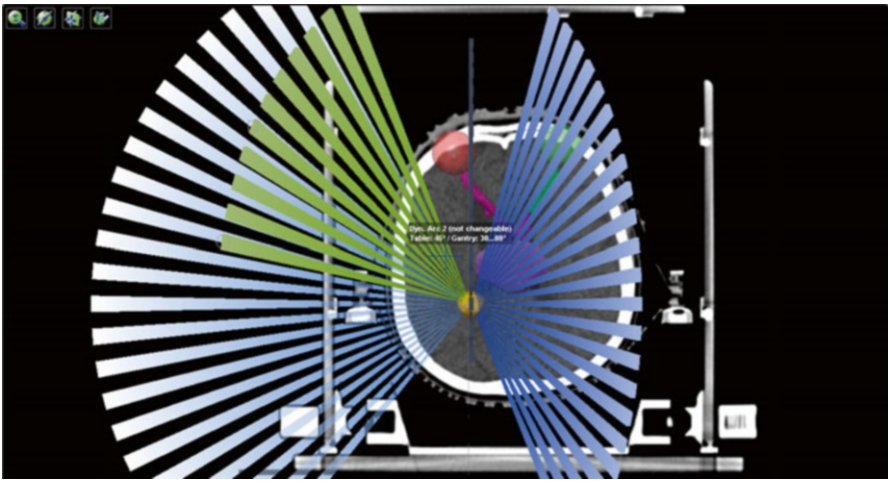

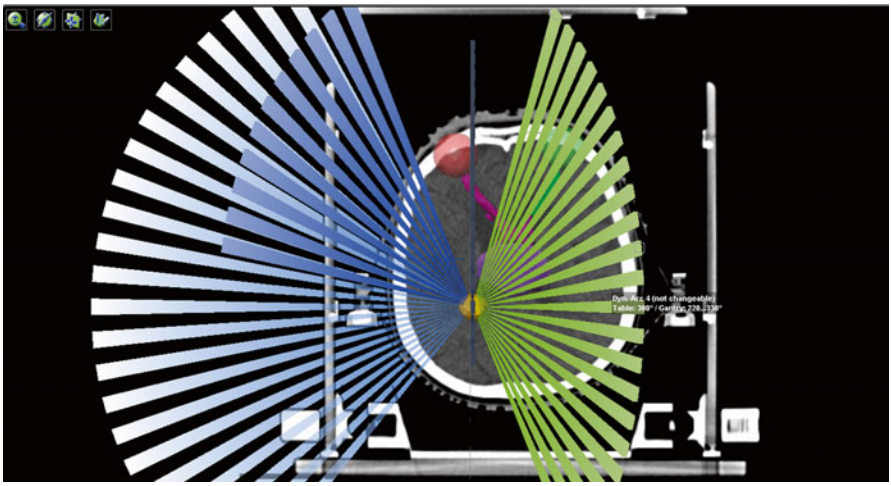

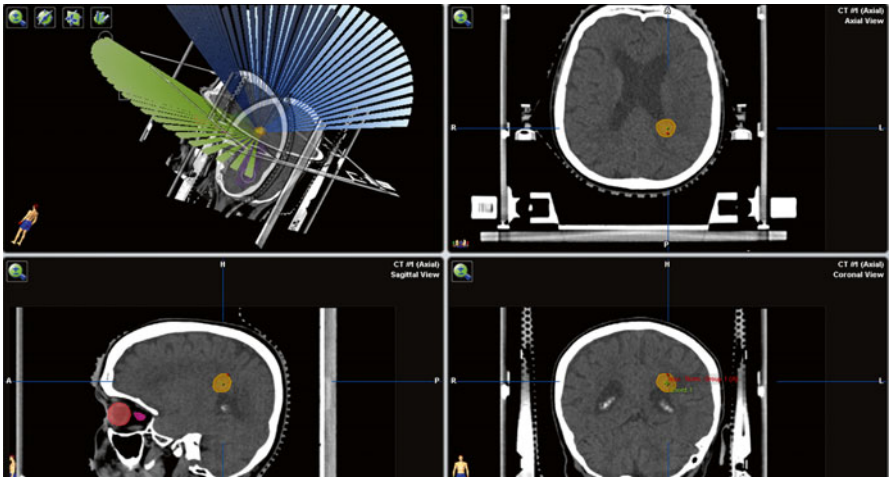
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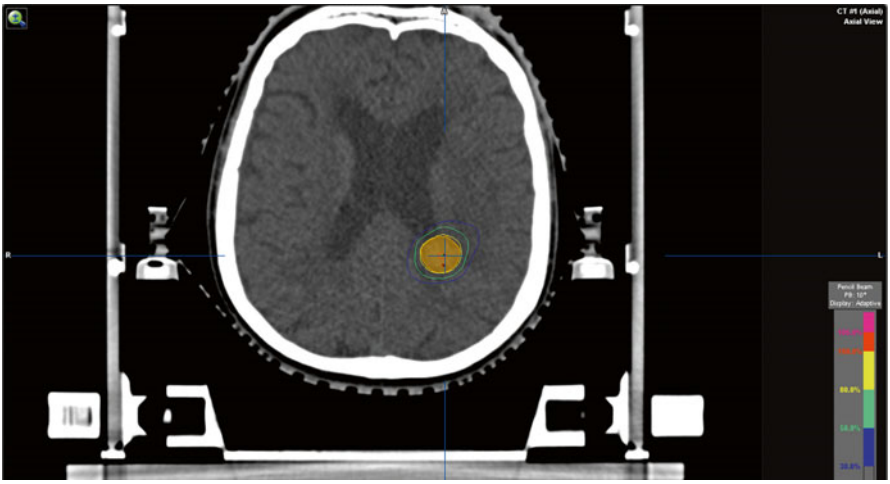
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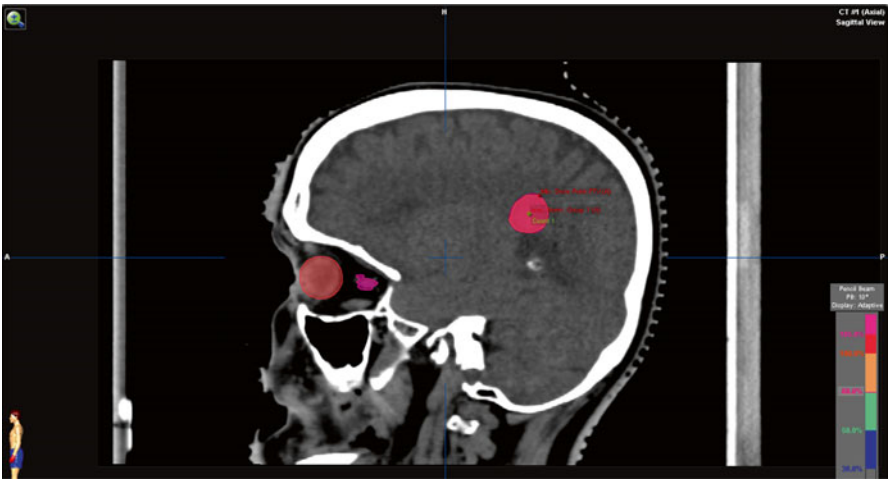
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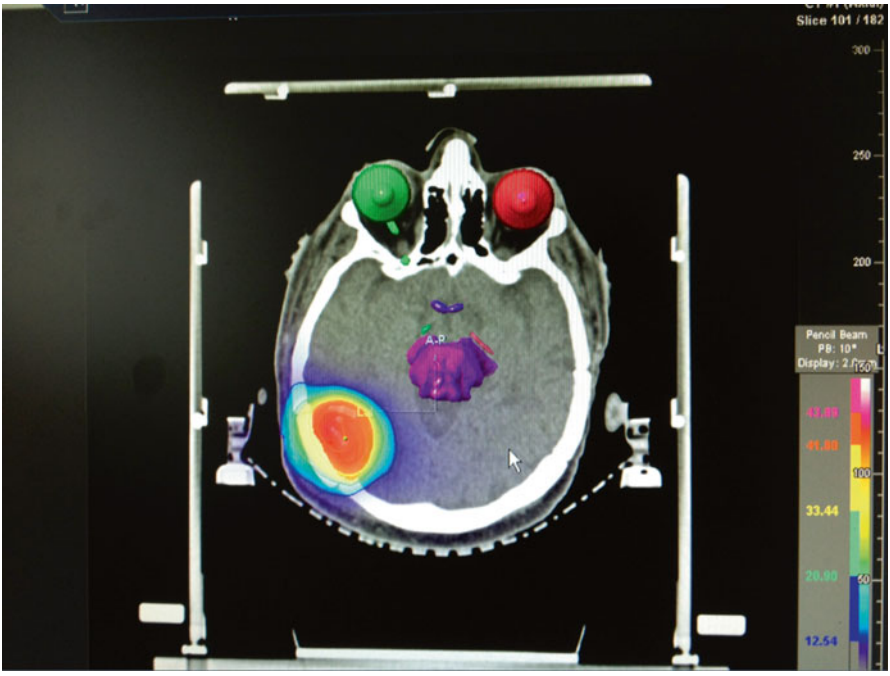
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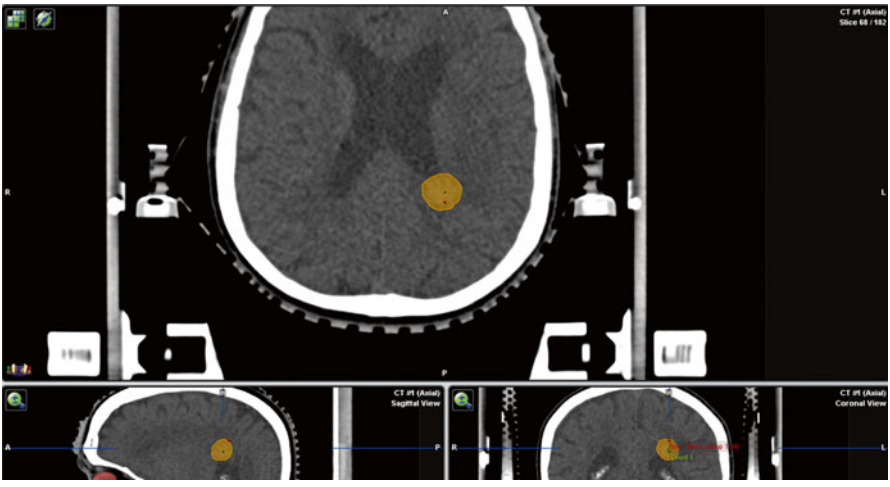
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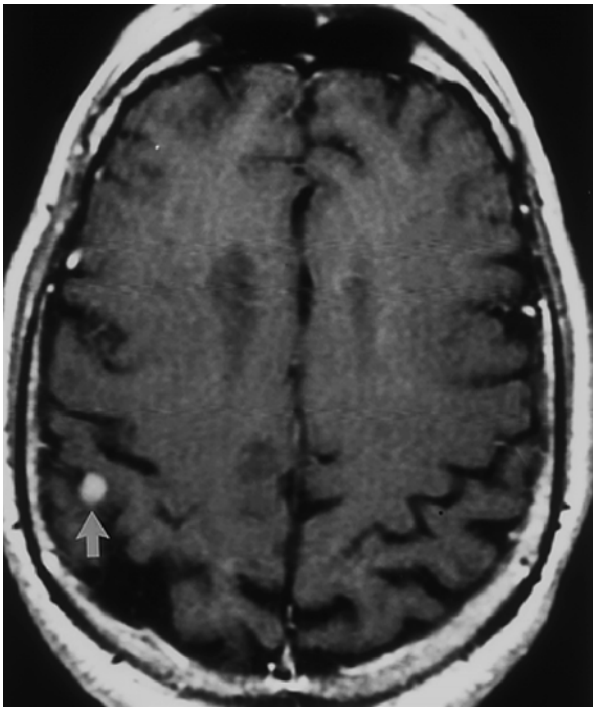

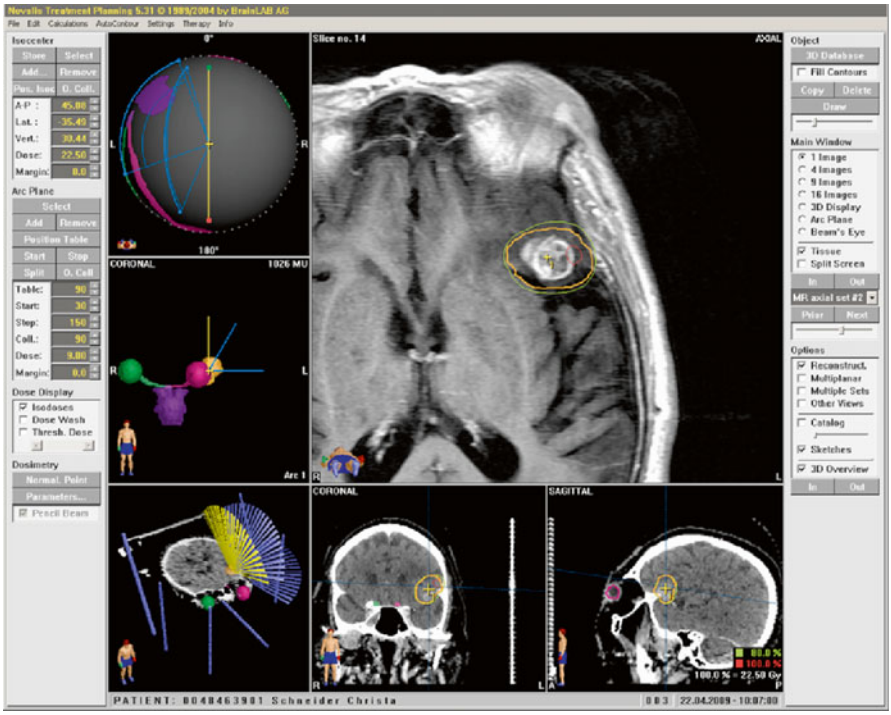
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Stereotactic Radiosurgery for Lung Lesions

11

Abstract

Early-stage non-small cell lung cancer represents still an important problem in thoracic oncology because it causes cancer mortality despite the early-stage status. Oligometastases of solid tumors to the lung might lead to severe functional affections and, and in some cases, to fatal organ failure in patients (f/m) with lung lesions.

Invasive surgical procedures like lobectomy performed openly or minimally invasive seem to be the historic "standard." Any "standard" has to prove its superiority in terms of safety and effectiveness for patients (f/m), and it is true in the frame of cost efficiency too.

Image-guided stereotactic radiosurgery with its multiple labels like stereotactic ablative radiotherapy (SABR) or stereotactic body radiotherapy (SBRT) could affect lung lesions by deactivating tumor cells. Early-stage non-small cell lung cancer is responsive to high-dose radiotherapy. Metastases, limited by volume, number, and occurrence site, react to radiation by stopping their growth. The aim would be the deactivation of lesions or, at least, to prolong the time free of pulmonary symptoms and, therefore, to have a better quality of life.

Consecutively, it demonstrates a noninvasive high-precision and safe technique in treating patients (f/m).

Background

The issue of local therapy for lung lesions has long been at stake in the field of clinical thoracic oncology [1–10].

Since the 1980s, a large number of research groups have achieved improvements in the clinical outcomes of patients (f/m).

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Historical presupposition suggests that the initial valuable efforts, which were undertaken between 1980 and 2000, were characterized by more experimental investigations with pragmatic methods of execution. Later, the idea of a systematic approach to the issue of the care of patients with lung-metastasized cancer very slowly influenced and overcame the investigators. This transformation in scientific thinking was accompanied by fundamental changes in the features and widespread availability of imaging technologies. For example, computed tomography (CT) first became available outside of large university medical centers in the mid-1990s. The rapid dynamics of imaging technologies led to decisions regarding profound and practical problems associated with conventional surgery, minimally invasive surgery, and radiosurgery, along with related technological and conceptual implications.

"Standard" Surgery or "Alternative" Radiosurgery for Early-Stage Lung Cancer

The "Standard": Surgery

Alternative treatment options for early-stage lung cancer were rarely investigated, while invasive surgical procedures remained the "standard" of treatment. Due to the "curative doctrine" of surgery, which led to the hegemony of surgery alone for the treatment of pulmonary lesions, early-stage lung cancers and metastases of other solid tumors to the lung were treated explicitly by thoracic surgeons [11]. Surgeons at large, such as Theodor Billroth (1829–1894) and Johann von Mikulicz (1850–1905), conducted pioneering technical and physiological work that led to the emergence of thoracic surgery. However, experimental surgery of the thorax became the field of thoracic surgery as a result of work conducted by Ferdinand Sauerbruch (1875–1951). His 1918 textbook, *Die Chirurgie der Brustorgane*, is considered the first book on thoracic surgery [11]. Notably, Sauerbruch principally dedicated the initial phase of thoracic surgery to all diseases and not implicitly to lung cancer. Other pioneers include the Sauerbruch admirer Willy Meyer (1858–1922); Samuel Metzler (1851–1921) of the USA; Tudor Edwards (1890–1946) of the UK; Theodore Tuffier (1857–1929) of France, who performed the first lung resection in 1891; and, of course, Alexis Carrel (1873–1945), who won a Nobel Prize [11].

The first pneumonectomy for lung cancer was performed in 1933 by Evarts Graham (1183–1957) [11]. However, by that time, the New York-based surgeon Harold Neuhof had already published a paper on the surgical treatment of lung cancer [12]. Additional relevant clinical and experimental work was conducted by Alfred Blalock (1899–1964) of Johns Hopkins University in Baltimore, USA.

A systematic approach to the study of lung cancer was later realized with the founding of the International Association for the Study of Lung Cancer (IASLC) in 1972 and the introduction of the TNM lung staging classification by Cliff Mountain at the MD Anderson Cancer Center in the USA [12]. Since the publication of a pivotal paper by Churchill and colleagues in 1950, lobectomy has been considered the "standard" of surgical care for lung cancer [13]. This great work influenced

several generations of physicians in the field of lung cancer over a period exceeding 50 years. However, a shift occurred with the emergence of video-assisted thoracic surgery (VATS) in the last decade of the twentieth century. One of the first clinicians to report a large series of lobectomies using VATS for early-stage lung cancer was Dr. Ralph Lewis in 1992 [14]; this marked the beginning of a new era of minimally invasive thoracic surgery.

In the first decade, however, neither the "standard" conventional lobectomy nor video-assisted lobectomy was compared with other invasive, less-invasive, or noninvasive procedures in prospectively designed studies. However, at the turn of the century, hundreds of articles regarding video-assisted lobectomy had been published in indexed journals.

A somewhat systematic review, published in 2013, summarized the outcome data of comparative studies conducted during the first decade after 2000 [15]. In this review, Zhang and colleagues reported on studies that had been published between 1990 and 2011. From among 1099 studies, the authors filtered 21 studies that fit their criteria. However, only two randomized controlled trials (RCTs) had been published at the time of the meta-analysis. All others were retrospective case reports or cohort studies. Both RCTs had been conducted during the first decade of video-assisted lobectomy. The first RCT was reported by Kirby and colleagues in 1995 [16].

This randomized study was conducted to define the advantages of video-assisted lobectomy versus muscle-sparing thoracotomy and lobectomy. Sixty-one patients with presumed clinical stage I non-small cell lung cancer were enrolled in the study. The thoracotomy group included 30 patients, and the video-assisted group included 25 patients (f/m). No oncologic outcomes were reported [16].

The other study, which was published by Sugi and colleagues in 2000 [17], included 20 cases for which cytokine dynamics was measured and did not report any oncologic endpoints.

As neither study reported an oncologic endpoint, none of the results are useful or valid with respect to oncology.

To summarize this systematic review, no valid outcome data were reported from a prospective (randomized or non-randomized) study, and therefore the value of these analyses with regard to oncologic endpoints could not be evaluated [15].

A second meta-analysis was published by Cai and colleagues in the same year [18]. The results of this study were identical to those reported in the first meta-analysis. Similarly, it was not helpful to discriminate the presumed value of video-assisted lobectomy versus conventional "standard" surgery.

Interestingly, in the year 2013, four systematic reviews or meta-analyses were published, despite the lack of new perspectives or insights [15, 18–20].

To date, not one existing prospective RCT of a sufficient number of patients (f/m) with early-stage lung cancer has been able to demonstrate a real difference between conventional open and video-assisted lobectomy.

In the last decade, robotic thoracic surgery emerged as a new option for minimally invasive, video-assisted procedures.

Both benefits and disadvantages are associated with the use of robotic-assisted technology when performing lobectomies in patients with early-stage lung cancer.

Investigations have shown that robotic-assisted lobectomies are feasible and safe for patients with stage 1A or 1B lung cancer; however, there is a steep learning curve, and long-term randomized studies of robotic-assisted lobectomy with conventional posterolateral thoracotomy or video-assisted thoracic lobectomy are needed [21–25]. A recent meta-analysis of retrospective cohorts, published by Ye and colleagues in 2015, included eight studies with 3379 patients (f/m) [26].

Overall, the pooled analysis indicated similar rates of perioperative morbidity and mortality with robotic and video-assisted lobectomy (morbidity-risk ratio [RR], 1.02; 95 % confidence interval [CI], 0.94–1.10; $p = 0.605$; mortality-RR, 0.28; 95 % CI, 0.06–1.25; $p = 0.095$). No evidence of publication bias was observed [26].

One more recent and emerging trend is the use of uniportal VATS. This technology was introduced extensively in 2004 by Dr. Gaetano Rocco and colleagues in the UK [27–31] and underwent further development and refinement [32–37]. Other teams, especially that of Gonzalez-Rivas and colleagues in Spain, also followed the trend of uniportal VATS and communicated their results [38–43]. My colleague Dr. Mahmoud Ismail, of Charité at Berlin University, is working jointly with Dr. Gonzalez-Rivas to conduct excellent research in this field [44]. Uniportal VATS might truly become a good alternative to classic VATS [37].

The value of surgery as a "standard" treatment for early-stage lung cancer remains indisputable. Despite the lack of valid, well-designed prospective studies that have compared surgery with less- or noninvasive procedures, surgery appears to be an unavoidable component of thoracic oncology. However, the value of conventional versus video-assisted lobectomy is not currently quantifiable.

For more than two decades, maximally invasive or minimally invasive surgery has been the new "standard" by which the safety and effectiveness of all new treatment methods should be measured.

The "Alternative": Radiosurgery

Compared with tumors in other anatomic regions (e.g., pelvis), historically, less- or noninvasive treatment options for early-stage lung cancer have been suggested to few systematic and/or comparative investigations. This is attributable to various causes: first, the emergence of thoracic surgery in Europe in the 1920s and 1930s, and subsequently in the USA, was accompanied by tremendous disciplinary self-confidence and astonishing dialectics of intradisciplinary belief and disbelief in peculiar individual practices. Second, the epistemic dynamics of the accumulation of knowledge and skills occurred in a very narrow and simultaneously irreducible field of activity and was thus constitutive for thoracic surgery.

Procedural options other than invasive surgery for cancers (e.g., for skin or pelvic tumors) had been available in the early modern period of scientific medicine (i.e., 1900–1920). The first application of such an option was reported in 1907 by Krönig for endometrial cancer. Additional reports in other fields were published in the early twentieth century [45–48].

In the second half of the twentieth century, the option of radiotherapy was investigated for almost any anatomical site or tumor entity. This led to the clinical establishment of a wide range of indications for cancer radiotherapy [49–53]. The scientific endeavors and processes identified during the search for alternatives were not limited to a particular geographic region [54–61] or topographic site [62–64].

In contrast, lung cancer was never evaluated in such a systematic and scientific manner.

Accordingly, historical research must determine why the approach to lung cancer differed.

Throughout the technological development of radiation technology, conventional radiotherapy had always been used as a solely palliative procedure for lung cancer. Therefore, thoracic surgeons affixed the seal of "palliative doctrine" onto radiotherapy, in a dialectic opposition to the imagined "curative doctrine" of surgery for early-stage lung cancer.

The shift toward a "curative intended good practice" [65] of radiotherapy for early-stage lung cancer occurred near the end of the last century [66]. This resulted from the high rate of mortality associated with chemotherapy, which was used to treat the vast majorities of cases of lung cancer, thus promoting a search for real alternatives [67–71].

Different terms have been implemented for the principles of radiosurgery for non-cranial lesions or so-called body stereotactic procedures.

Initially, such procedures were described as "extracranial radiosurgery" [72]. The sole purpose was to introduce a novel use at new anatomical sites, rather than a new technology or new strategy.

After several years, the label "stereotactic body radiation therapy" (SBRT) emerged [73]. This was neither a truly innovative idea nor a good strategic move because some might wish to embed the principle of "stereotactic radiosurgery" (SRS) within other valid and useful oncologic therapeutic strategies. The intrinsic logic of this name or label selection remains obscure. It suggests that the "body" is essentially different than the "head" (synonyms: brain, cranium, cranial), as if the head is not part of the body, and as if the body is outside of the head. This confusing name seems to contribute to the maintenance of our professional and epistemic distance from the fields of humanities, including philosophy and linguistics, as well as social and, particularly, cultural studies.

Again, the name "SBRT" was intended as an internal clarification for the community of radiation oncologists; it was not meant for a patient-centered communication or an attempt to be understood by other oncology-related disciplines. SBRT does not entail the urgently required collaborations among oncologists of all involved disciplines. To date, however, the term "SBRT" prevails in publications focused on SRS.

The next step in the trajectory of naming and labeling of this simultaneous technological principle and therapeutic strategy was the introduction of "stereotactic ablative radiotherapy" (SABR).

This was a recent move by the radiation oncology community that has increased the difficulty of the existing situation. The adjective "ablative" should indicate the

cell killing effects of SRS, of which we have been aware for many decades. The inherent problem with this new name could have been forecasted by the fact that it distracts from the mode of conduct of SRS; in other words, SRS was essentially devised as a highly precise image-guided procedure.

The latter two descriptive notions are used in an equivalent manner in the current language of publications and conferences.

Nevertheless, we will use the term SRS hereafter. This decision is necessary not only for reasons of consistency in the language used throughout this book but also provides a useful requisite for interdisciplinary communication in order to avoid additional misunderstandings and confusion.

Availability and Quality of Scientific Evidence

A sufficient number of available publications have discussed the use of SRS in patients with early-stage lung cancer. These publications could be used to promote a fair, patient-centered, and objectively differential approach that involves the recommendation and discussion of innovative treatment options that are safe, noninvasive, and effective and extend beyond the traditional method of microsurgery. This does not suggest that the patient's preferences should be influenced, but rather that patients should be able to provide informed consent based on the best available recent data.

For more than two decades, maximally invasive or minimally invasive surgery has been the new "standard" against which the safety and effectiveness of any new treatment method should be measured.

Below, the validity and quality of the available data with respect to the initial, postoperative, and hybrid usage of SRS are presented in question and answer format.

Are plausible and valid data available at the "level of evidence 1a" with particular regard to the use of SRS for early-stage lung cancer?
Yes, such data are available from a meta-analysis of prospectively designed RCTs. One publication meets this level of validity [74].

This "yes" must be contextualized as a weak yes because the 2015 publication by Chang and colleagues in Lancet Oncology included two randomized controlled trials that were closed too early and thus included only a very small number of cases in both trials. Therefore, this study has already been criticized and neglected [75].

The title of this 2015 report from Lancet Oncology was "Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomized trials" [74]; this report was initially discussed with much excitement, which has subsequently abated.

The authors introduced the text with the following statements: "Standard therapy for operable, clinical stage I, non-small-cell lung cancer (NSCLC) is lobectomy with sampling or dissection of mediastinal lymph nodes. During the past decade, stereotactic ablative radiotherapy (SABR; also called stereotactic body

radiotherapy) has resulted in local control in excess of 90 % of tumors with medically inoperable and operable clinical stage I NSCLC," which they proceeded to support with 14 references.

Personal Comments

To my understanding, this is inadequate. Surgery for early-stage lung cancer is not standard that is supported by valid, high-quality, comparative, and thus scientific evidence. Rather, it is a legitimate, practical, and useful method when performed by skilled hands that has been passed to recent clinicians. Again, the problem of language seems to extend to Lancet Oncology. This text could have instead been used as an opportunity to designate a new and correct label as a new standard of terminology for SRS.

Furthermore, the authors explained the principle of radiosurgery to the Lancet Oncology readership as follows: "SABR delivers ablative doses of radiation (biologically effective dose [BED] >100 Gy) to tumours in 1–10 fractions. Several radiation fields (or arcs) are delivered from various angles to converge on a target, and the dose distribution is further adjusted so that the dose is sharply reduced within a few mm beyond the target, sparing nearby, crucial, normal structures from radiation-induced damage."

Personal Comments

There are no high-quality, valid, and thus scientific clinical evidence to support the so-called ablative doses of radiation. Data have shown that a biologically effective dose of ≥100 Gy could be considered a clinically effective dose for local tumor control. All of these data were collected either in non-randomized cohorts or from constellations of in vitro laboratory experiments. The descriptive label "ablative" is used in this context to suggest the existence of a true cutoff dose that ensures the local effectiveness of radiation for early-stage lung cancer. This is, unfortunately, not true.

To date, three prospective RCTs have been initiated to compare radiosurgery with conventional surgery in patients (f/m) with early-stage lung cancer: the STARS trial, the ROSEL trial, and the ACOSOG trial. All three trials were closed earlier than planned "because of slow accrual," according to the authors of the pooled analysis [74]. Because the entry criteria for the STARS and ROSEL trials were similar, the subsequent publication aimed to combine and analyze data from these two trials to assess overall survival, failure patterns, and toxic effects.

Personal Comments

Finally, it might be possible to obtain clinically necessary high-quality, valid, and thus scientific evidence to elucidate a highly significant problem faced by cancer researchers and general healthcare. In the simplified, plausible language of clinicians, "slow accrual" means that some trialists had the intention but not the motivation to acquire sufficient numbers of patients (f/m) for their trials, despite design and discussion processes that extended beyond 1 year. The author of this text witnessed a period of endless but useful discussions of these issues and decided not to participate in the anticipation that the trials would not succeed. In fact, they did not succeed.

Histological confirmation of early-stage non-small cell lung cancer via biopsy or cytological evaluation was required in the STARS trial, but was not mandatory in the

ROSEL protocol. In the ROSEL trial, which included only Dutch patients, those with no available pathological confirmation of diagnosis were eligible if they had a new or growing pulmonary lesion with radiological features consistent with malignant disease and tracer avidity on positron emission tomography (PET)-CT scans. All patients were required to undergo appropriate staging studies, including chest CT and PET/CT, that classified them as having operable stage T1–2a (<4 cm), N0, M0 disease according to the 7th edition of the American Joint Committee on Cancer–International Association for the Study of Lung Cancer staging classifications.

For the STARS trial, 28 sites in the USA, China, and France were approved for patient enrollment, from which seven patients were enrolled; for the ROSEL trial, ten centers in the Netherlands were approved, and four patients were enrolled.

The outcome data of 58 patients (f/m) were included in this pooled analysis (SABR, 31 and surgery, 27). No differences in age, sex, performance status, histology, T stage, or tumor location were noted between the two treatment groups or the two trials. The median follow-up duration for all patients (f/m) was 40.2 months (interquartile range [IQR], 23.0–47.3 months) in the SABR group and 35.4 months (IQR, 18.9–40.7 months) in the surgery group. All patients had stage I non-small cell lung cancer (<4 cm) and were considered medically operable for lobectomy, with performance statuses of 0–2. Of the 27 patients who underwent surgery, 19 underwent open lobectomy, five underwent video-assisted lobectomies, one underwent video-assisted thoracotomy biopsy, one underwent open wedge resection, and one had an aborted resection during surgery because of disease progression. In the STARS trial, 16 patients had peripherally located lesions and received 54 Gy of radiotherapy in 3 fractions, whereas 4 had central lesions and received 50 Gy in 4 fractions. In the ROSEL trial, 6 patients received 54 Gy in three 18-Gy fractions over 5–8 days, and 5 received 60 Gy in five 12-Gy fractions over 10–14 days, as a result of variability in the centers' protocols.

The pooled estimated overall survival rates at 1 and 3 years were 100 % (95 % CI, 100–100 %) and 95 % (95 % CI, 85–100 %) in the SABR group, respectively, and 88 % (95 % CI, 77–100 %) and 79 % (95 % CI, 64–97 %) in the surgical group, respectively. The difference in overall survival between the two groups was statistically significant (log-rank $p = 0.037$; HR = 0.14 [95 % CI, 0.017–1.190]). The difference in overall survival between two groups was significant only in the STARS cohort (log-rank $p = 0.0067$) but not in the ROSEL cohort (log-rank $p = 0.78$). Seven patients died during study follow-up, including six in the surgery group (two from cancer progression, one from secondary primary lung cancer, one from a surgical adverse event, and two from comorbidities) and one in the SABR group (cancer progression). Median overall survival was not reached for either treatment group.

They did not observe any significant differences in the frequencies of local, regional, or distant metastasis or recurrence-free survival between the treatment groups. After 3 years, 96 % (95 % CI, 89–100 %) of patients in the SABR group remained free of local recurrence compared with 100 % (95 % CI, 100–100 %) in the surgery group (log-rank $p = 0.44$). Four patients in the SABR group developed regional nodal recurrences, whereas 90 % [95 % CI, 80–100 %] remained free of regional recurrences at 3 years compared with one patient in the surgery group (96 %

[95 % CI, 89–100 %] at 3 years; HR = 2.89 [95 % CI, 0.32–26.1]; log-rank $p = 0.32$). One patient in the SABR group developed distant metastases and 97 % [95 % CI, 90–100 %] remained free from distant metastasis at 3 years compared with two patients in the surgery group (91 % [95 % CI, 80–100 %] at 3 years; HR = 0.38 [95 % CI, 0.035–4.23]; log-rank $p = 0.42$). The recurrence-free survival rate at 3 years was 86 % (95 % CI, 74–100 %) in the SABR group (five events) compared with 80 % (95 % CI, 65–97 %) in the surgery group (HR = 0.69 [95 % CI, 0.21–2.29]; six events; log-rank $p = 0.54$). The small number of events resulted in a low level of statistical power to detect significant differences in the frequencies of local, regional, and distant failure between the two groups. The reported relapse frequencies and recurrence-free survival outcomes were preliminary because of the short follow-up.

A single local recurrence in the SABR group was salvaged via lobectomy. Three patients in the SABR group that developed recurrences in isolated regional lymph nodes were treated with concurrent radiochemotherapy, and two remained free of disease. Two patients (one each from the SABR and surgery groups) developed both regional and distant metastases and were treated with chemotherapy and palliative radiotherapy. Two patients from the surgery group had secondary primary lung cancers and were treated with SABR or concurrent radiochemotherapy (one patient each). One patient from the SABR group developed a secondary primary lung cancer and was retreated with SABR. In the SABR group, three (10 %) patients experienced treatment-related grade 3 adverse events: two (6 %) patients developed grade 3 dyspnea or cough, three (10 %) developed grade 3 chest wall pain, and one (3 %) experienced grade 3 fatigue and a rib fracture. No patients in the SABR group experienced treatment-related grade 4 toxic effects or treatment-related deaths. In the surgery group, one (4 %) patient died of surgical complications, and 12 (44 %) patients had grades 3–4 treatment-related adverse events. One (4 %) patient in the surgery group developed grade 4 dyspnea, four (15 %) developed grade 3 dyspnea, two (7 %) developed grade 3 lung infections, and four (15 %) experienced grade 3 chest pain. Other treatment-related grade 3 toxic effects reported in the surgery group included bleeding, fistula, hernia, anemia, fatigue, nausea, weight loss, and cardiac arrhythmia (one case each).

The authors concluded that SABR was better tolerated in this cohort of patients (f/m). Specifically, "These findings justify a larger randomized clinical trial to investigate the superiority of SABR for such patients. Physicians should interpret these findings as confirmation of at least clinical equipoise between SABR and surgical options and should consider SABR as an option for treatment of operable stage I" non-small cell lung cancer [74].

Personal Comments

Physicians will consider the following situation to be a failure: a highly qualified professional group discussed the issue at hand for years prior to initiating these projects; after an astonishing approval of 28 sites in the USA, China, and France for the STARS trial and ten centers in the Netherlands for the ROSEL trial, only seven and four patients (f/m) were enrolled, respectively.

This desired large-scale randomized clinical trial may or may not eventually occur.

Are plausible and valid data available at the "level of evidence 1b" with particular regard to the use of SRS for early-stage lung cancer?

No. No full publications describing prospectively designed RCTs on this issue are currently available.

The pooled analysis reported by Dr. Chang from the MD Anderson Cancer Institute in Houston, USA, Dr. Senan from the Free University Amsterdam in the Netherlands, and their respective colleagues [74] is merely a pooled analysis without fully and separately published trials.

In summary, it is becoming clear that the overall quality of the available data is not sufficient to draw robust conclusions and firm recommendations.

Are plausible data available at the "level of evidence 2a" with particular regard to the use of SRS for early-stage lung cancer?

A few publications have systematically reviewed retrospective cohort studies and analyzed pooled data.

A "systematic review" of cohorts was published in 2010 by Chi and colleagues [76].

This review aimed to analyze the failure patterns, toxicity profiles, and factors influencing the efficacy of SRS (designated SBRT) for early-stage non-small cell lung cancer. Local control rates ranged from 80 to 100 % in most studies that provided an adequate isocentric or peripheral biologically effective dose. Recurrence was associated with an increased tumor size. The main failure pattern after SBRT was distant metastasis. Grades 3–5 toxicity events mainly occurred with centrally located tumors, and adjuvant chemotherapy was found to potentially reduce the incidence of all recurrences and thus might translate to a survival benefit for patients with large or centrally located tumors that cannot be safely treated with a high biologically effective dose. The authors concluded that SRS is an excellent treatment option for early-stage as well as mostly functionally inoperable early-stage, non-small cell lung cancers. Administration of a biologically effective dose to both the isocenter and tumor periphery is very important for optimal tumor control, and higher doses are required for large (T2) lesions. The authors further concluded that SRS "for centrally located tumors can be feasible with a much less aggressive dose regimen than 60–66 Gy at 3 fractions and adjacent critical structures excluded from the target volume; chemotherapy may optimize the clinical outcome in large or centrally located lesions" [76].

Are plausible data available at the "level of evidence 2b" with particular regard to the use of SRS for early-stage lung cancer?

In 2003, Timmerman and colleagues published the first admissible written communication in this highly interesting field of scientific inquiry [72]. Since then, the same group has published more than a decade's worth of sophisticated outcome data with respect to the quality and validity of their reports [77, 78]. In the initial report, Timmerman and colleagues addressed the question of noninvasive treatment options

for functionally inoperable early-stage lung cancers in the setting of a phase I study. Patients (f/m) with clinically staged pT1 or pT2 (<7 cm) cN0cM0 biopsy-confirmed early-stage non-small cell lung cancers, median age of 75 years, and median Karnofsky Performance Scale score of 80 were included. In other words, the research team was evaluating a group of patients (f/m) at risk for overall mortality. SRS was administered in three separate fractions over 2 weeks. Three to five patients were treated within each dose cohort, with a starting dose of 8 Gy per fraction (total, 24 Gy), followed by successive dose escalations of 2 Gy per fraction (total increase per cohort, 60 Gy). Dose cohorts were separated by time intervals to observe toxicity. Patients with T1 versus T2 tumors underwent separate independent dose escalations. Thirty-seven patients were enrolled. One patient experienced grade 3 pneumonitis, and another patient developed grade 3 hypoxia. Overall, there was no appreciable decline in cardiopulmonary function as determined using symptoms, physical examination, the need for oxygen supplementation, pulmonary function testing, arterial blood gas determination, or regular chest imaging. Both T stage groups ultimately reached and tolerated a dose of 20 Gy per fraction for 3 fractions (total, 60 Gy). After a median follow-up period of 15.2 months, 87 % of patients (f/m) responded to treatment (complete response, 27 %). Six patients experienced local failure, all of whom had received doses of <18 Gy per fraction. The authors concluded that a "high radiation dose were tolerated." [72].

The second compatible paper was published a year later by Onishi and colleagues [79]. A total of 35 patients with early-stage non-small cell lung cancer (IA, 15 and IB, 15), including 20 adenocarcinomas, 13 squamous cell carcinomas, and two others, were treated. Patients ranged in age from 65 to 92 years (median, 78 years). Twenty-three (66 %) patients had medically inoperable tumors because of mainly chronic pulmonary disease or an old age. Again, this research team was working with a group of patients (f/m) at risk for overall mortality. The total dose of 60 Gy was delivered in 10 fractions (over 5–8 days) via 6-MV X-ray to the minimum dose point in the planning target volume (PTV). After adjusting the isocenter of the PTV to the planned position with a unit comprising CT and linear accelerator, irradiation was performed under patient-controlled breath-holding and radiation beam switching. All patients completed the treatment course without complaint. The complete response and partial response rates were 8/35 (23 %) and 25/35 (71 %), respectively. The National Cancer Institute–Common Toxicity Criteria grade >2 pulmonary complications were noted in three (9 %) patients. During follow-up (range, 6–30 months; median, 13 months), two (6 %) patients exhibited local progression, and five (14 %) developed distant or regional lymph node metastases. The 2-year overall survival rates for all patients and medically operable patients were 58 and 83 %, respectively. The authors concluded that high-dose SRS is safe [79]. Also in 2004, Wolf and colleagues published their results [80].

A phase I dose escalation study of SRS which was performed to test the feasibility of an increase in local tumor control in patients (f/m) with functionally inoperable early-stage non-small cell lung cancer is feasible. Twenty patients were treated with SRS in three 10-Gy ($n = 19$) or 12–12.5-Gy fractions to the PTV enclosing the 100 % isodose line or one 26-Gy dose to the PTV enclosing the 80 % isodose line

($n=26$). The median follow-up duration was 11 months (range, 2–61 months). The actuarial local control rate was 92 %, and this was significantly improved by increasing the dosage from three 10-Gy fractions to three 12–12.5-Gy fractions or a single 26-Gy dose ($p=0.038$). The overall survival rates after 1 and 2 years were 52 % and 32 %, respectively. After 12 months, 60 % of the patients (f/m) did not exhibit systemic progression. No severe acute or late toxicity was observed, and only two patients (3 %) developed symptomatic grade 2 pneumonitis, which was successfully treated with oral steroids. The research team concluded that SRS for early-stage lung cancer is a very effective local treatment option that did not cause significant complications in medically impaired patients who were not amenable to surgery and stated that "patient selection is important, because those with a low risk of systemic progression are more likely to benefit from this approach" [80].

In 2006, Fritz and colleagues published the results of the first outcome and feasibility study of single-dose SRS for early-stage non-small cell lung cancer [73]. A prospectively reviewed study was communicated. The authors evaluated response rates, local control, and side effects in 33 cases after non-fractionated stereotactic high single-dose body radiation therapy for lung tumors. The standard dose prescribed to the isocenter was 30 Gy. The PTV was defined using three CT scans with reference to the phases of respiration such that the movement span of the clinical target volume was enclosed. The volumes of the lung cancer lesions varied from 4.2 to 125.4 ccm (median, 17.5 ccm), and the PTV ranged from 15.6 to 387.3 ccm (median, 99.8 ccm). The largest tumor diameters ranged from 1.7 to 10 cm. The follow-up periods varied from 6.8 to 63 months (median, 18 months). Local control was achieved in 94 % of the patients. No serious symptomatic side effects were observed. According to a Kaplan–Meier analysis, the overall survival probability rates of patients with lung metastases were as follows: 1 year, 83 %; 2 years, 63 %; 3 years, 53 %; and 4 years, 39 % (median survival, 20.4 months). The authors concluded that single-dose SRS is an effective and safe form of local treatment and might become a viable alternative to invasive techniques [73].

Timmerman and colleagues from the collaborative Radiation Therapy Oncology Group (RTOG) summarized the initial experiences from previous years [77].

These authors addressed quality assurance questions that had arisen since the activation of the RTOG 0236 trial, in which SRS (here, SBRT) was evaluated for medically inoperable patients with clinical stage I non-small cell lung cancer. They stated that "SBRT is not a black box, and the essence of the therapy had to be distilled via guidelines. Issues related to patient selection, method of dosimetry construction, equipment requirements, motion assessments and control, site accreditation, data exchange, and follow-up policies were worked out by compromise and consensus" [77].

The first phase II trial was published by Timmerman and colleagues in 2006 [78].

Building on a previously reported phase I trial [72], the authors conducted a prospective phase II trial of SRS (or SBRT) in patients (f/m) with clinically staged pT1 or pT2 (<7 cm) cN0cM0 biopsy-confirmed early-stage non-small cell lung cancer. Again, all patients (f/m) had comorbid medical problems that precluded lobectomy, meaning that the research team was working with a group of patients

(f/m) at risk for overall mortality. The total SRS dose was 60–66 Gy in 3 fractions over a 1–2-week period. All 70 enrolled patients completed the planned therapy regimen, and the median follow-up duration was 17.5 months. The 3-month major response rate was 60 %. The Kaplan–Meier estimated local control rate at 2 years was 95 %. Altogether, 28 patients died as a result of cancer ($n=5$), treatment ($n=6$), or comorbid illnesses ($n=17$). The median overall survival duration was 32.6 months, and the 2-year overall survival rate was 54.7 %. Grade 3–5 toxicity events occurred in a total of 14 patients. Among the patients who experienced toxicity, the median time to observation was 10.5 months. Patients treated for tumors in the peripheral lung had a 2-year severe toxicity-free rate of 83 % compared with only 54 % for patients with central tumors. This SRS regimen achieved high rates of local control in functionally inoperable patients (f/m) with stage I non-small cell lung cancer. Both late local recurrence and toxicity were found to occur after this treatment. The authors warned readers that "this regimen should not be used for patients with tumors near the central airways due to excessive toxicity" [78].

Onishi and colleagues, who had published a second paper in 2003, communicated the results of a Japanese multi-institutional study with a significantly increased number of patients (f/m) ($n=257$) in 2007 [81].

This study population had a median age of 74 years, and again, all patients (f/m) had comorbid medical problems that precluded lobectomy; in other words, this group of patients (f/m) was at risk for overall mortality. The cohort contained 164 patients with T1c N0cM0 disease and 93 patients with T2 cN0cM0 disease who were treated at 14 institutions in Japan. Stereotactic three-dimensional treatment was performed using noncoplanar dynamic arcs or multiple static ports. Total doses of 18–75 Gy at the isocenter were administered in 1–22 fractions. The median calculated biological effective dose was 111 Gy (range, 57–180 Gy). After a median follow-up of 38 months, pulmonary complications exceeding grade 2 occurred in 14 patients (5.4 %). Local progression occurred in 36 patients (14.0 %), and the local recurrence rate was 8.4 % for a biologically equivalent dose of ≥100 Gy compared with 42.9 % for a dose <100 Gy ($p< 0.001$). The 5-year overall survival rate of medically operable patients was 70.8 % among those treated with a biologically equivalent dose of ≥100 Gy compared with 30.2 % among those treated with <100 Gy ($p<0.05$). SRS with a biologically equivalent dose of less than 180 Gy was deemed safe; according to the authors, "the local control and overall survival rates in 5 years with a BED (biologically effective dose) of 100 Gy or more were superior to the reported results for conventional radiotherapy. For all treatment methods and schedules, the local control and survival rates were better with a BED of 100 Gy or more compared with less than 100 Gy" [81].

The first large European study was published in 2008 by Lagerwaard and colleagues [82]. Subsequently, Senan and colleagues continued to communicate their well-organized records, well-designed clinical protocols, and sophisticated personal experiences with one of the largest cohorts of SRS (SBRT, SABR)-treated patients with lung lesions worldwide [71, 83–97]. In addition to the high number of fully published papers, the real-world conditions under which this group practices are a convincing factor; these clinicians work in a rational, stepwise, courageous, and highly communicative manner.

Personal Comments

The group of physicians associated with Dr. Senan act in a highly professional manner that is based on best clinical practices, respects ethical commitments, and focuses on patient-based oncology. Additionally, this group is collaborative and cooperative. Our personal experience with the group, particularly Dr. Senan, was characterized by an open-minded, rational, highly focused investigative group of colleagues. We have learned much from this experience.

Bradley and colleagues reported on a significant inquiry that focused on the distant failure patterns and rates in patients (f/m) with early-stage non-small cell lung cancer [98].

These authors reviewed their experiences with either 3 or 5 fraction SRS (or SBRT) for peripheral or central tumors, respectively (total, 91 cases). All patients (f/m) were followed up for at least 6 months. Patients were referred for SRS because of underlying comorbidities (poor performance status, 31 or poor lung function, 52) or refusal of surgery (8 patients). Again, all patients (f/m) had comorbid medical problems that precluded lobectomy and were thus at risk for overall mortality. In this group, 83 lesions were peripheral and eight were central. Peripheral cancers received a mean dose of 18 Gy in 3 fractions. Lesions within 2 cm of the bronchus, esophagus, or brachial plexus were treated with 9 Gy in 5 fractions. The median follow-up was 18 months (range, 6–42 months). The TNM staging was as follows: T1 N0M0, 58 patients; T2 N0M0, 22 patients; T3 N0M0 (chest wall), 2 patients; and T1 N0M1, 6 patients. The median tumor diameter was 2 cm (range, 1–5 cm). The median forced expiratory volume in 1 s was 46 % (range, 17–133 %), and the median carbon monoxide diffusing capacity was 49 % (range, 15–144 %). Two-year local tumor control was achieved in 86 % of patients. The predominant failure pattern was the development of a distant metastasis or second lung cancer. The development of distant metastasis was the only significant prognostic factor for overall survival in a multivariate analysis. The results from this cohort have been identical to those of previous studies; according to the authors, "Local tumor control was shown to be high using SBRT for non-small-cell lung cancer. Overall survival is highly co-related with the development of distant metastasis" [98].

The American Society for Radiation Oncology (ASTRO) published a communication on this issue in 2010 [99].

Subsequently, a large number of reviews and definitions followed in the most recent 2 years; these have helped to refine the status of SRS for early-stage non-small cell lung cancer [68, 100–104]. These reviews and post hoc analyses mirror the realities of clinical routines that, astonishingly, have not led to practical guidelines for the entire community [105–110].

The basic clinical problems have not yet been solved. Nearly all patients (f/m) had comorbid medical problems that precluded lobectomy, and thus the research team faced the issue of a group of patients (f/m) at risk for overall mortality [89, 90, 93].

Interestingly, the publication of evaluations, definitions, and declarations continues [75, 100–102, 111], although unfortunately, as yet no real interdisciplinary

endeavors have moved beyond disciplinary frictions and interests to improve the statuses of patients (f/m).

Are plausible data available at the "level of evidence 2b" with particular regard to the use of SRS in comparison to surgery for early-stage lung cancer?

Yes, data are available, and we will discuss the details in the following paragraphs.

The meaning of systematic "comparative effectiveness research" has been expanded in the field of oncology [112]. This is of importance for clinical oncology, wherein randomization appears to be difficult [113–117]. Simultaneously, solid and valid results are urgently needed, particularly for lung cancer [8, 118–122].

Crabtree and colleagues compared the outcomes of SRS with those of conventional surgery in a paper published in 2010 [123].

This was the first reported comparison of outcomes between SRS (here named SBRT) and surgical resection. That study compared short-term outcomes between SBRT and surgical treatment in patients with non-small cell lung cancer. All patients who underwent surgery (January 2000–December 2006) or SBRT (February 2004–May 2007) for PET-CT-determined clinical stage IA/B non-small cell lung cancer were included. Comorbidity scores were recorded prospectively using the Adult Comorbidity Evaluation scoring system. Charts were reviewed to determine local tumor recurrence, disease-specific survival, and overall survival. A propensity score matching analysis was used to adjust the estimated treatment HRs for the confounding effects of patient age, comorbidity index, and clinical stage. A total of 462 patients underwent surgery, and 76 received SBRT. Overall, surgical patients were younger ($p < 0.001$), had lower comorbidity scores ($p < 0.001$), and had better pulmonary function (forced expiratory volume in 1 s and carbon monoxide diffusion in the lung; $p < 0.001$). Among the surgical and SBRT groups, 62.6 % (291/462) and 78.9 % (60/76), respectively, had clinical stage IA disease. The final pathology revealed upstaging in 35 % (161/462) of the surgery patients. In an unmatched comparison, the overall 5-year survival rate was 55 % with surgery, and the 3-year survival rate was 32 % with SBRT. Among patients with clinical stage IA disease, the 3-year local tumor control rates were 89 % with radiation therapy and 96 % with surgery ($p = 0.04$). There was no difference in local tumor control among patients with stage IB disease ($p = 0.89$). No disease-specific survival differences were observed among patients with stage 1A ($p = 0.33$) or IB disease ($p = 0.69$). A propensity analysis matched 57 high-risk surgical patients with 57 patients who underwent SBRT. In the matched comparison of these subgroups, no differences were observed in freedom from local recurrence (88 % versus 90 %), disease-free survival (77 % versus 86 %), and overall survival (54 % versus 38 %) at 3 years.

In an unmatched comparison of patients with clinical stage IA disease, the authors observed that "surgical patients were healthier and had better local tumor control compared with those receiving stereotactic body radiation therapy. Propensity analysis in clinical stage IA/B non-small cell lung cancer revealed

similar rates of local recurrence and disease-specific survival in patients treated with surgery compared with stereotactic body radiation therapy" [123].

We had already mentioned this idea. We had stated that almost all patients (f/m) in this setting suffered from other significant medical problems that precluded thoracic surgery, leaving them at risk for overall mortality [89, 90, 93].

Grills and colleagues reported and compared the outcomes after stereotactic radiotherapy or wedge resection in another cohort of patients with stage I non-small cell lung cancer [124].

A total of 124 patients (f/m) with T1–2 cN0 early-stage non-small cell lung cancer underwent wedge resection ($n=69$) or image-guided lung SRS ($n=58$). All were ineligible for anatomic lobectomy; of those receiving SRS, 95 % were medically inoperable, and 5 % refused surgery. The mean forced expiratory volume in 1 s and diffusing capacity of the lung for carbon monoxide were 1.39 L and 12.0 mL/min/mmHg for wedge, respectively, versus 1.31 L and 10.14 mL/min/mmHg, respectively for stereotactic radiosurgery ($p=$ not significant). The mean Charlson Comorbidity Index and median age were 3 and 74 years for wedge, respectively, versus 4 and 78 years for SBRT, respectively ($p<0.01$, $p=0.04$, respectively). SRS was volumetrically prescribed at a dose of 48 (T1) or 60 (T2) Gy in 4–5 fractions. The median follow-up duration was 2.5 years. At 30 months, no significant differences were identified between the groups in terms of regional recurrence, locoregional recurrence, distant metastasis, or freedom from any failure ($p>0.16$). Stereotactic radiosurgery reduced the risk of local recurrence (4 % versus 20 % for wedge; $p=0.07$). Although overall survival was higher with wedge, cause-specific survival was identical between the groups. After excluding synchronous primary tumors, non-biopsied tumors, or pathological T4 disease (wedge satellite lesion), SRS yielded reduced local recurrence (5 % versus 24 % for wedge, $p=0.05$) and regional recurrence rates (0 % versus 18 % for wedge, $p=0.07$). Both lung SBRT and wedge resection are reasonable treatment options for patients with stage I non-small cell lung cancer who are ineligible for anatomic lobectomy. SBRT and surgery, however, yielded identical cause-specific survival [124].

One early evaluation of the state of affairs came from Timmerman, who, as usual, displayed a high level of comprehension and coherence [125]. Other evaluations, definitions, and declarations followed [126, 127]. Interestingly, the writing of such evaluations, definitions, and declarations continues [75, 100–102, 111], unfortunately, as yet no real interdisciplinary endeavor has moved beyond disciplinary frictions and interests to improve the statuses of patients (f/m).

Summary

Noninvasive image-guided stereotactic radiosurgery is a safe and effective method for lung oligometastases (number <5, diameter <5 cm) of solid tumors.

Again, most patients (f/m) allocated to SRS had comorbid medical problems that precluded lobectomy and were thus at risk for overall mortality [89, 90, 93]. This has led to a serious selection bias that has affected overall survival.

The meaning of systematic comparative effectiveness research has been expanded in the field of oncology [112]. This is important for clinical oncology, where randomization appears to be difficult [113–117]. Simultaneously, concrete, valid results are urgently needed, particularly for lung cancer [8, 118–122].

Stereotactic Radiosurgery for Lung Metastases of Solid Tumors

Background

The status of surgery as a "standard" treatment was discussed in the first chapter of this section [128–130]. The issues related to surgery are identical for early-stage lung cancer and for lung metastases of limited number and size that derive from solid tumors such as breast cancer, colorectal cancers, autochthon lung cancer, or gastric cancer [131].

Large-scale registries have recorded data on patients (f/m) with lung metastases of various types of cancer [132]. The true issue is the proper interpretation and, more importantly, the contextualization of all acquired data into a consistent oncologic concept [133, 134]. To date, most surgical procedures for the removal of lung metastases of solid tumors have appeared to be based on pragmatic, practical, and empiric experience rather than systematic data exploitation and conceptual interposition in a coherent oncologic concept [135–147].

Even cases in which highly skilled thoracic surgical experts attempt to convince the respective local or regional community did not seem to be effective [132–134, 148–150].

Dr. Treasure, a widely recognized expert and well-known academic activist who has reflected on these issues for decades, unfortunately could not achieve an appropriate level of conceptual context within thoracic surgery communities and respective professional societies [136, 137, 147, 151–156].

Are plausible data available at the "level of evidence 1a" with particular regard to the use of SRS for lung metastases?
No, there are no data available at this level of evidence from meta-analyses or systematic reviews of randomized controlled trials (RCTs).

Are plausible data available at the "level of evidence 1b" with particular regard to the use of SRS for lung metastases?
No, there are no available data at this level of evidence from fully published texts of any randomized controlled trial.

Are plausible data available at the "level of evidence 2a" with particular regard to the use of SRS for lung metastases?
No, data are not available at this level of evidence from fully published meta-analyses or systematic reviews of valid cohort studies with sufficient numbers of patients (f/m).

Are plausible data available at the "level of evidence 2b" with particular regard to the use of SRS for lung metastases?
Yes, data are available at this level of evidence from fully published valid cohort studies with sufficient numbers of patients (f/m).

The first paper with only six cases concerning SRS was published by Morikawa and colleagues in 1995 [157].

In 1996, the first true cohort with a sufficient number of cases was presented by Okunieff and colleagues [158]. These authors reported their experiences with 50 patients (f/m) with lung oligometastases. Individuals with five or fewer total lesions were treated with curative intent. Most patients (62 %) received a total dose of 50 Gy in 5-Gy fractions. The number of targets treated per patient ranged from 1 to 5 (mean, 2.6). Maximum tumor diameters ranged from 0.3 to 7.7 cm (median, 2.1 cm). The mean follow-up period was 18.7 months. Local control of treated lesions was achieved in 42 of 49 evaluable patients (83 %). Of the 125 total lesions treated, eight progressed after treatment (94 % crude local control). Among curatively treated patients, the median overall survival duration from the time of treatment completion was 23.4 months. The progression-free survival rates in the same group of patients were 25 % and 16 % at 12 and 24 months, respectively. Grade 1 toxicity occurred in 35 % of all patients; 6.1 % developed grade 2 toxicity, and 2 % developed grade 3 toxicity. Excellent local tumor control rates and low toxicity rates were seen with SBRT. The median survival duration and progression-free survival rate both appeared to be superior to those achieved with standard care alone [158].

Hof and colleagues published their early experiences in 2007 [159]. A total of 61 patients (f/m) were included. The actuarial local progression-free rates were 88.6 %, 73.7 %, and 63.1 % at 12, 24, and 36 months after therapy, respectively. Although the majority of patients (70.4 %) developed changes in normal tissues, these were not related to clinically relevant toxicities. This method seemed to be a feasible, safe, and effective local procedure that could serve as a treatment option for solitary pulmonary metastases [159].

Two years later, Rusthoven and colleagues published their experiences with a Dutch population [160]. Patients (f/m) with fewer than four lung metastases and a cumulative maximum tumor diameter <7 cm were enrolled and treated in a multi-institutional phase I/II clinical trial in which they received SBRT delivered in 3 fractions. In phase I, the total dose was safely escalated from 48 to 60 Gy. The phase II dose was 60 Gy. The primary endpoint was local control. Lesions subjected to ≥6 months of radiographic follow-up were considered assessable for

local control. The secondary endpoints included toxicity and survival. Thirty-eight patients with 63 lesions were enrolled and treated at three participating institutions. Seventy-one percent had received at least one prior systemic treatment regimen for metastatic disease, and 34 % had received at least two prior regimens (range, 0–5). Two patients developed local recurrences after prior surgical resection. There were no episodes of grade 4 toxicity. The incidence of any grade 3 toxicity was 8 % (3/38). Symptomatic pneumonitis occurred in one patient (2.6 %). Fifty lesions were assessable for local control. The median follow-up duration of these lesions was 15.4 months (range, 6–48 months). The median gross tumor volume was 4.2 mL (range, 0.2–52.3 mL). The actuarial local control rates at 1 and 2 years after SBRT were 100 % and 96 %, respectively. Local progression occurred in one patient at 13 months after SBRT. The median survival duration was 19 months. This first prospective cohort demonstrated that high-dose SRS (here named as SBRT) is safe and effective for the treatment of patients with fewer than four lung metastases [160].

More recent cohorts were presented by Filippi and colleagues [161]. These authors reported the clinical outcomes of a series of consecutive patients with five or fewer lung metastases that were been homogeneously selected and treated with single-dose SRS (here named SABR). The eligibility criteria were a maximum tumor diameter <50 mm, absent or controlled extrathoracic disease, adequate pulmonary function, no prior radiotherapy, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. All patients were treated with a single dose of 26 Gy prescribed to the 80 % isodose line. Follow-up comprised clinical evaluations and periodic CT scans. The primary endpoints were local control, toxicity, and progression-free survival. The secondary endpoints were cancer-specific survival and overall survival. Of the 102 treated patients, 67 patients with a total of 90 lesions were selected. The selection of this group of patients (f/m) remains unclear. The main primary tumor sites were the lung and colon–rectum (37.3 % and 43.3 % of lesions, respectively). The median follow-up duration was 24 months. Metastasis progression at the SABR site was observed in ten lesions (11.1 %), and the actuarial local control rates at 1 and 2 years were 93.4 % and 88.1 %, respectively. Systemic failure occurred in 37 patients (55.2 %) at a median interval of 8 months after SABR. The progression-free survival rates were 72 % and 55.4 % at 1 and 2 years, respectively. Seven and eight patients exhibited grade 1 (10.4 %) and grades 2–3 late radiological toxicity events (11.9 %), and six experienced late chest wall toxicity (two rib fractures, four chronic chest pain events; 8.9 %). The cancer-specific survival rates at 1 and 2 years were 90 % and 76 %, respectively, and the corresponding overall survival rates were 85.1 % and 70.5 %, respectively. The median survival duration was 40 months. In a multivariate analysis, a disease-free interval >24 months was nearly a significant predictor of improved cancer-specific survival (HR = 0.34 [95 % CI, 0.1–1.12], $p = 0.07$). The study included a cohort of patients treated with SRS in a single 26-Gy fraction and subsequently followed for a prolonged time. Single-fraction SRS appears to be an effective treatment option with little observed

acute toxicity and limited late toxicity (<15 %); further advantages include high patient compliance, short overall treatment time, and easy compatibility with systemic therapies. These results seem to support preexisting evidence for the use of single-dose SRS "as a valid and acceptable alternative to surgery for pulmonary metastases from different primary tumors" [161]. A study update revealed identical conclusions [162], suggesting certain degrees of safety and efficacy of SRS in patients (f/m) affected with lung oligometastases of colorectal cancer [162].

In 2015, Siva and colleagues published a study of 17 cases [163]. The setting of this study was highly sophisticated and involved the use of respiratory gating (4D) PET. Patients (f/m) received single-fraction SRS at a dose of 26 Gy. The mean time between scans was 62 days. At a median follow-up of 16 months, ten patients with 13 metastases had received SABR, and no patient exhibited local progression. The tumor motion vector was greater in patients with discordant 3D and 4D PET PERCIST responses ($p < 0.01$), with a mean (± standard error of the mean) motion of 10.5 mm (±0.96 mm) versus 6.14 mm (±0.81 mm) in patients with concordant 3D and 4D responses. The surrounding normal lung fluorodeoxyglucose tracer uptake at 70 days correlated strongly with the delivered radiation dose ($r^2 = 0.99$, $p < 0.01$), with significant elevations across all dose levels ($p \leq 0.05$), except the <2 Gy volume ($p = 0.30$). In conclusion, the authors demonstrated a high rate of interval progression between staging PET scans in patients with oligometastases. They found that the responses of tumors with large motion vectors were not concordant on conventional 3D PET and 4D PET. In addition, normal lung metabolic tracer uptake after SABR was strongly dose dependent, a novel finding that should be further validated [163].

Very recently (2015), Wang and colleagues published a large study [164].

A total of 134 lung metastases in 95 patients were treated with CyberKnife SRS. The number of lung metastases per patient ranged from 1 to 4 (single lesions in 63 patients, 66.3 %). The average tumor volume was 14.6 cm^3, and the prescribed radiation dose ranged from 30 to 60 Gy and was given in 1–5 fractions with a 60–88 % isodose line. The primary endpoint was local control; secondary endpoints were survival and toxicity. The median follow-up duration was 17 months (range, 4–46 months). The 1-, 2-, and 3-year local control rates were 97.6 %, 90.6 %, and 87.0 %, respectively. The median survival duration was 38.0 months, and the median progression-free survival duration was 14.0 months. The 2-year progression-free survival rate was 29.0 %, and the overall survival rate was 61.3 %. No grade 4 or higher toxicity events were encountered. CyberKnife SRS was found to be safe and effective for patients with lung metastases [164].

Another more recent paper was published by Aoki and colleagues in 2016 [165].

Here, the records of 66 patients with 76 oligo-recurrences in the lungs after SRS (here named SBRT) were retrospectively reviewed. The following lists the numbers of patients with oligo-recurrences at each primary site: lungs, 31; colorectal,

13; head and neck, 10; esophagus, 3; uterus, 3; and others, 6. The median SBRT dose was 50 Gy (range, 45–60 Gy) administered in a median of 5 (range, 5–9) fractions. Surviving patients had a median follow-up duration of 36.5 months. The 3-year rates of local control, overall survival, and disease-free survival were 90.6 %, 76.0 %, and 53.7 %, respectively. A longer disease-free interval from the initial treatment to SBRT and non-colorectal cancer were associated with favorable outcomes. Disease progression after SBRT occurred in 31 patients, most of whom had distant metastases ($n = 24$); of these, 87.5 % ($n = 21$) had new lung metastases. Among these 21 patients with new metastases, 12 were found to have developed a second oligo-recurrence. Additional SRS was performed for these 12 patients, and all 12 tumors were controlled without disease progression. Three patients (4.5 %) developed grade 2 radiation pneumonitis. No other late grade ≥2 adverse events were identified. Therefore, SRS for oligo-recurrence achieved acceptable tumor control [165].

Summary

The past decade has seen a considerable increase in the understanding of image-guided SRS and related publications and conference contributions.

Image-guided SRS is a safe and effective treatment method for limited lung oligometastases (fewer than 5, diameter <5 cm) of solid tumors.

Again, most patients (f/m) allocated to SRS had comorbid medical problems that precluded lobectomy and were thus at risk for overall mortality [89, 90, 93]. Therefore, serious selection bias was present, which would have influenced overall survival.

For more than two decades, maximally invasive or minimally invasive surgery has been the "standard" against which the safety and effectiveness of any new treatment method should be measured.

If the above evidence is considered seriously, image-guided SRS has been shown to be a safe and effective new method that is essentially noninvasive and cost-effective.

The meaning of systematic comparative effectiveness research has been expanded in the field of oncology [112]. This is particularly important for clinical oncology, where randomization seems to be difficult [113–117]. Simultaneously, solid and valid results are urgently needed, particularly for lung cancer [8, 118–122].

As it is embedded in a coherent, rational, and empirically reproducible oncologic concept, namely, the oligometastatic state concept first proposed by Hellmann in 1995, followed by extensive discussion, validation, and dispute, image-guided SRS will broaden the complex dialectics surrounding cure and palliation and lead toward the possible long-term control (and even cure) of cancer with limited metastases.


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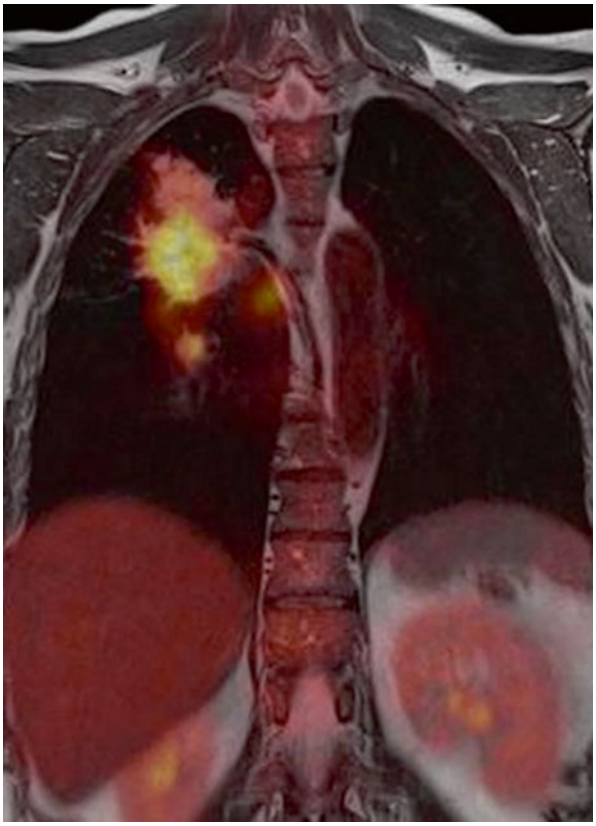

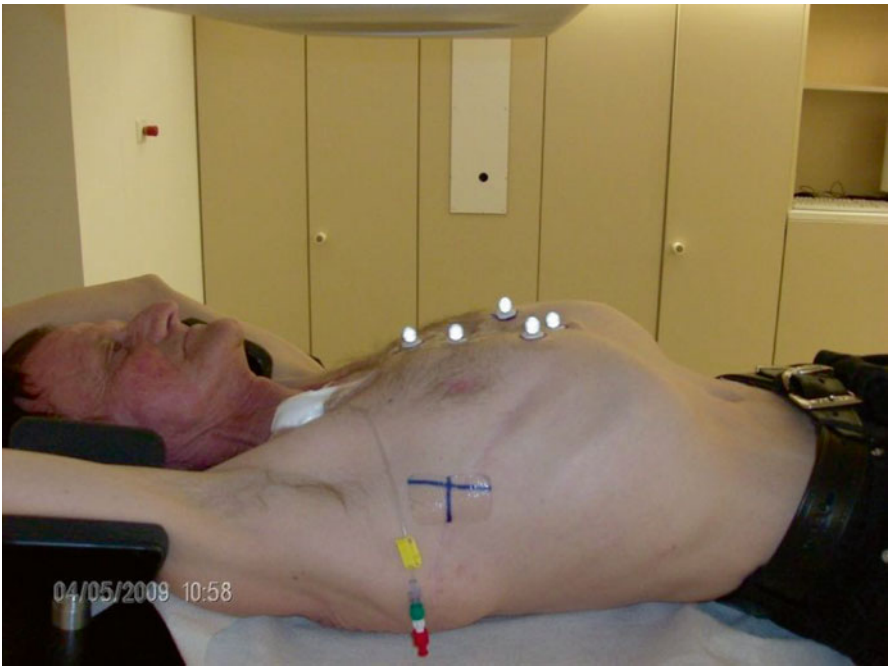
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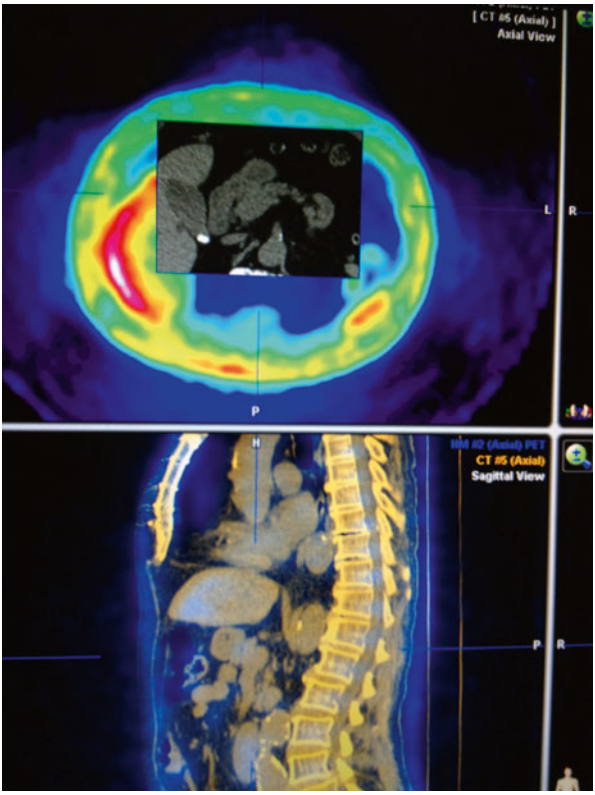
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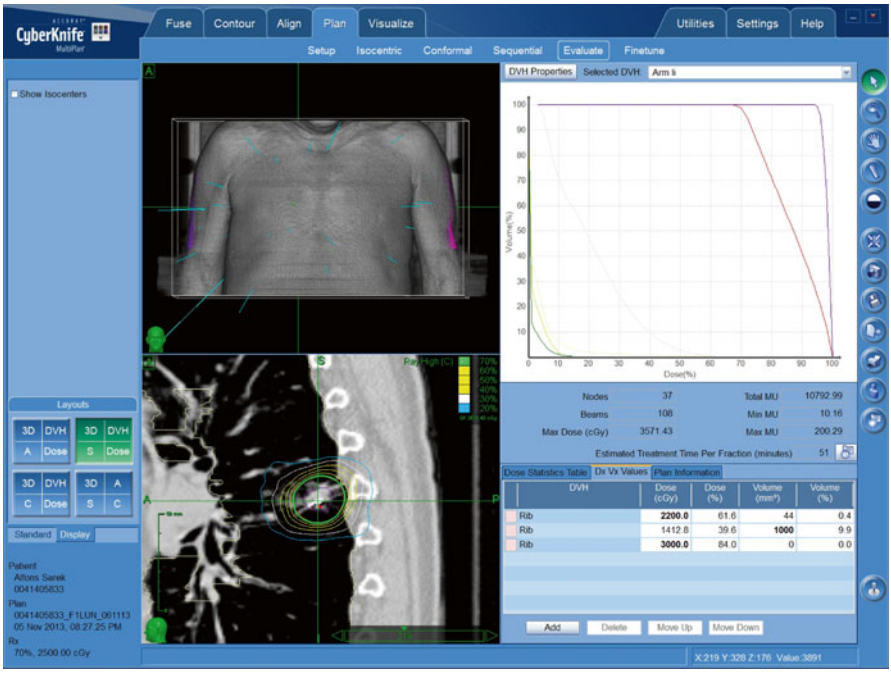
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Estimated Treatment Time Per Fraction (minutes) 51
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Dx Vx Values
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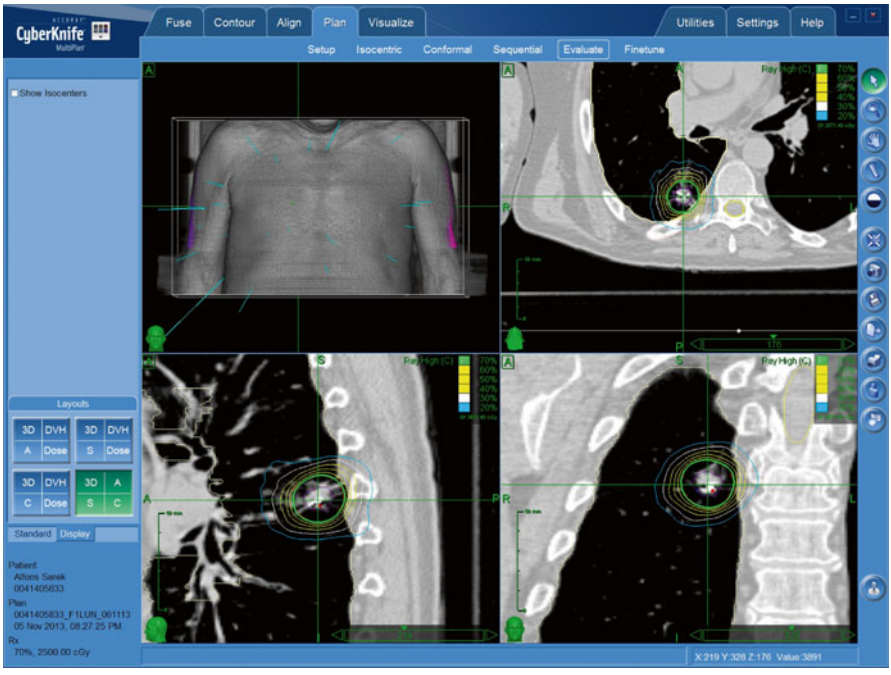
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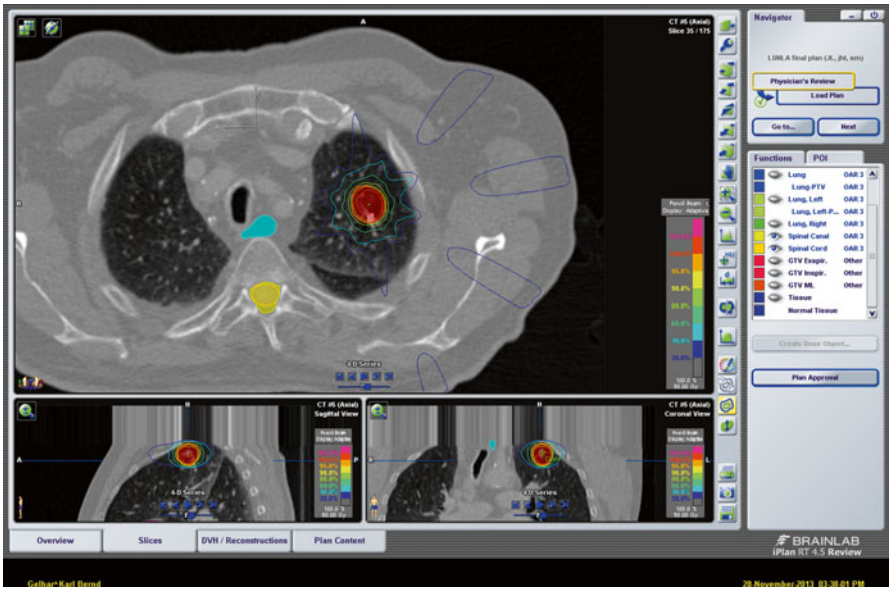
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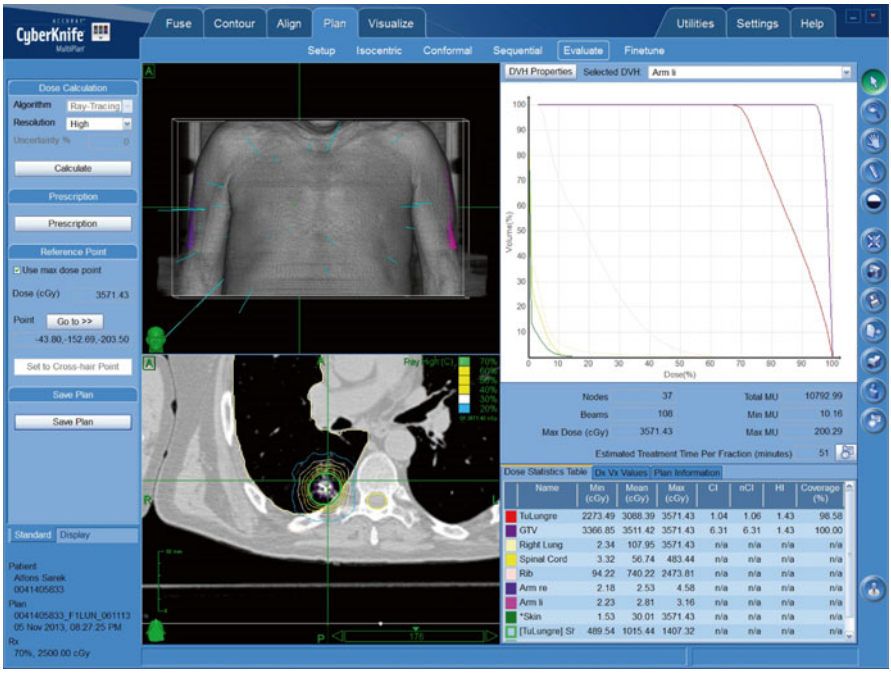
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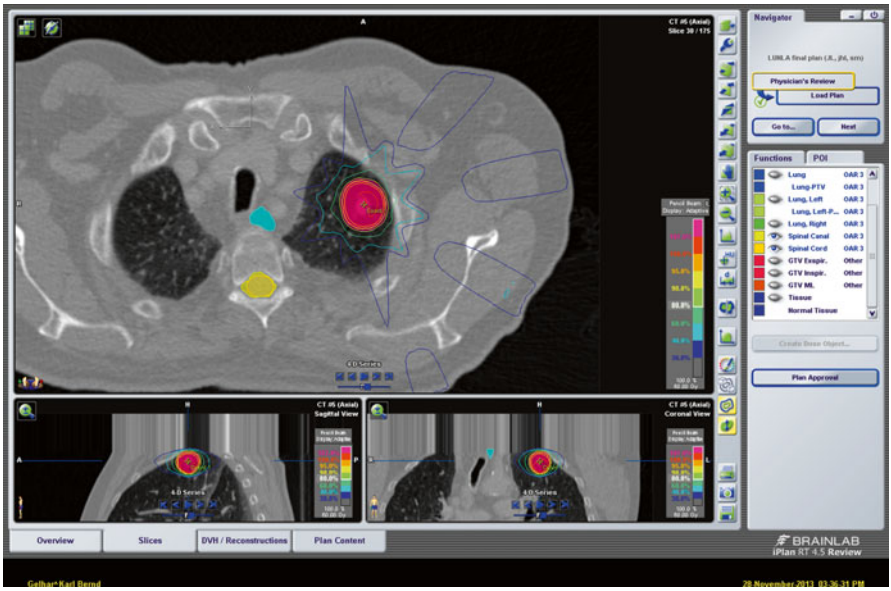
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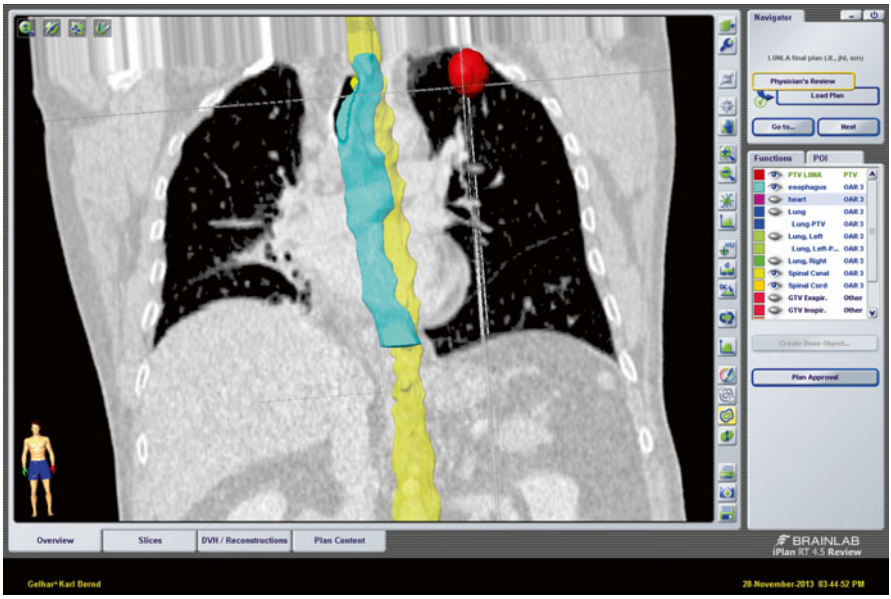
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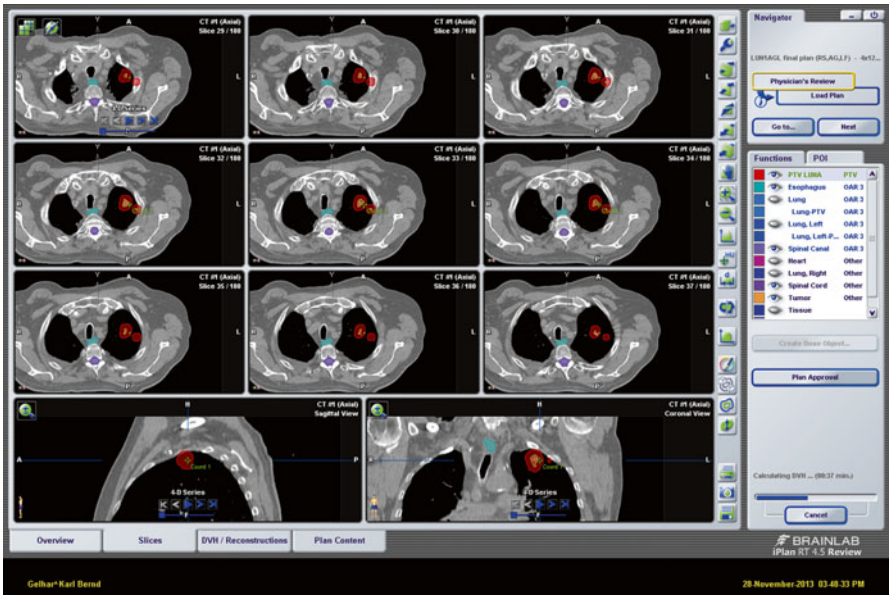
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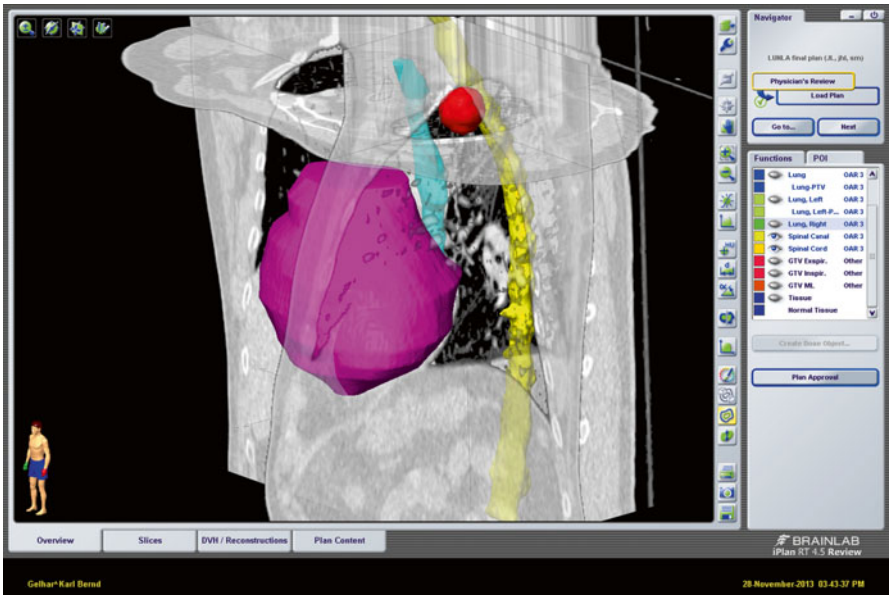
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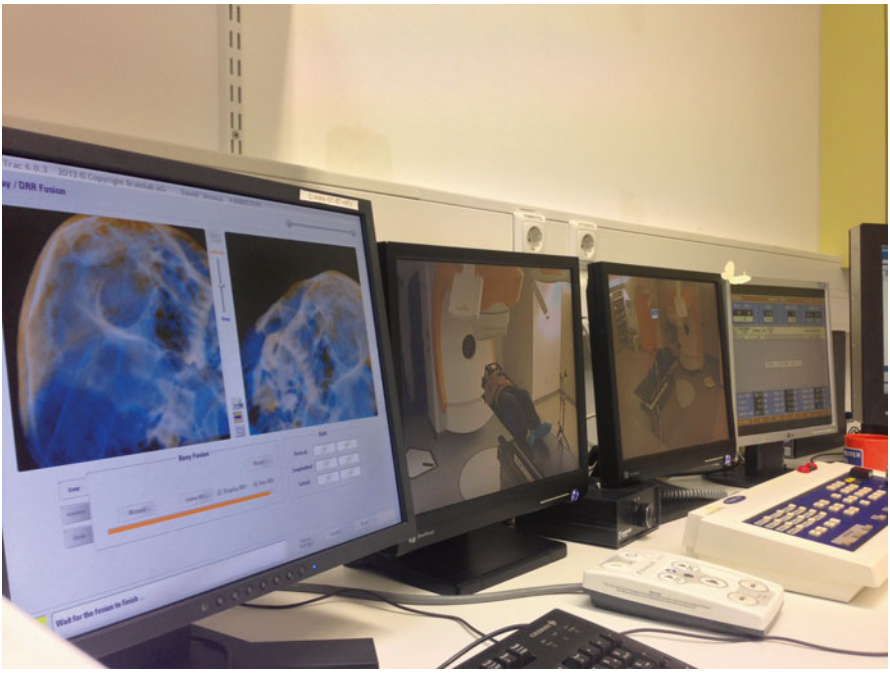
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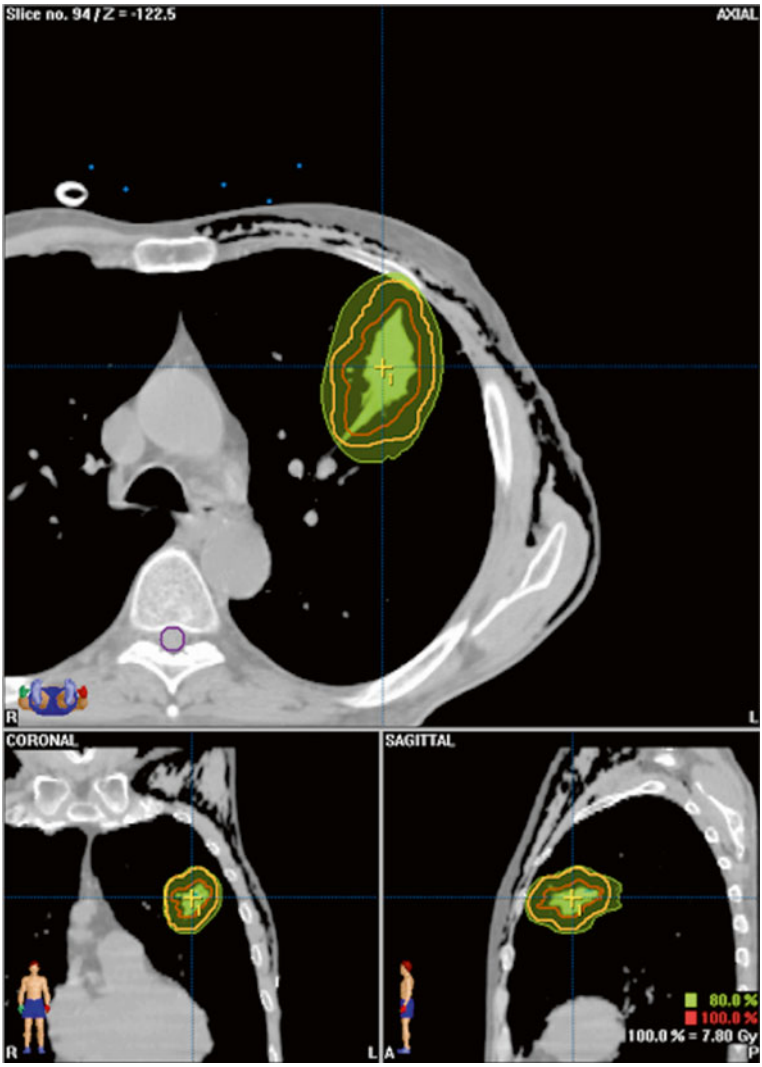

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Stereotactic Radiosurgery for Metastatic Lesions of the Spine

12

Abstract

Conventional radiotherapy can control spinal oligometastases. When lesions to the spine occur in diffuse pattern, conventional radiation is effective and it is a cost-efficient procedure. When spine metastases are limited by volume, number, and occurrence site, image-guided stereotactic radiosurgery might be a good alternative. It spares healthy tissue, especially the spinal cord.

Many patients (f/m) with metastasizing cancers like breast and lung cancer or prostate cancer could be controlled very well in long term.

Invasive surgical procedures indeed even when performed in a minimally invasive mode do not seem to be a good option. Any "standard" has to prove its superiority in terms of safety and effectiveness for patients (f/m), and it is true in the frame of cost efficiency too.

Image-guided stereotactic radiosurgery could affect spinal lesions by deactivating tumor cells because they are responsive to high-dose radiotherapy. The aim would be to prolong the time free of symptoms and, therefore, of a better quality of life.

Consecutively, it demonstrates a noninvasive high-precision and safe technique in treating patients (f/m).

Background

Spinal metastases occur often in patients (f/m) with cancer. The spine is the third most common site of metastasis, after the lung and liver. In some cases, infiltration of the vertebral column and the subsequent destruction and compression of the spinal cord cause severe morbidity [1].

Approximately 5–30 % of patients with cancer will develop spinal metastases [2]. Cancer patients with spinal metastases present a diagnostic and treatment challenge to clinicians of different disciplines. This challenge must be addressed using

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multidisciplinary, multimodal, and individualized management. The tumor cells that comprise bone metastases disrupt the homeostasis between bone formation and remodeling. Bone destruction is a late event in the formation of lytic bone metastases and begins with tumor cell proliferation; this subsequently activates osteoclasts, a process that is visible as trabecular destruction in imaging studies. Excessive bone destruction and increased bone formation may occur, thus producing blastic lesions [2]. One of 10 patients (f/m) has been symptomatic, and approximately 94–98 % of those patients (f/m) present with epidural and/or vertebral involvement [3, 4].

Metastatic spread from primary tumors (e.g., lung, breast, prostate cancer) occurs mainly through hematogenic mechanisms. Besides the mass effect, an epidural mass can cause cord distortion, resulting in demyelination or axonal destruction. Vascular compromise causes venous congestion and vasogenic edema of the spinal cord, resulting in venous infarction and hemorrhage [4, 5]. Approximately 70 % of symptomatic lesions are found in the thoracic region of the spine, particularly at the T4–T7 level. Of the remainder, 20 % and 10 % are found in the lumbar region and cervical spine, respectively. Several levels are involved in more than 50 % of patients with spinal metastases. Several noncontiguous segments are involved in approximately 10–38 % of patients. Intramural and intramedullary metastases are not as common as metastases of the vertebral body and epidural space. Most metastatic lesions are localized at the anterior portion of the vertebral body (60 %). In 30 % of cases, the lesions infiltrate the pedicle or lamina. A few patients present with disease in both the posterior and anterior parts of the spine. Some primary tumors have been associated with metastatic lesions of the spine at the following rates: lung cancer, 31 %; breast cancer, 24 %; gastrointestinal cancers, 9 %; prostate cancer, 8 %; and melanoma, 4 % [4, 5].

Clinically, potential morbidity from metastatic lesions of the spine is highly relevant. Patients (f/m) with lung or breast cancer and infiltration of the spine by metastatic lesions are at high risk for paralysis and/or bowel and bladder incontinence [6, 7]. The latter significantly compromises the quality of life of patients with cancer and places an additional burden on their caregivers. Normally, cord compression is falsely considered a preterminal event, rather than a challenge for oncologists [1, 8].

Computed tomography (CT), magnetic resonance imaging (MRI), and scintigraphy are used for diagnostic work-up in any case with a clinical suspension of spine metastases or during regular follow-up visits.

Regarding treatment options, invasive surgical procedures [9, 10] may compete with noninvasive radiotherapeutic procedures [11], or these procedures may complement each other under certain clinical circumstances [3].

The focus on radiotherapy reveals that a large number of available randomized controlled trials (RCTs) have evaluated the efficacies of single-fraction radiotherapy with different dose schemes (e.g., 8 Gy). Two highly sophisticated RT techniques—image-guided stereotactic radiosurgery (SRS) and intensity-modulated radiotherapy (IMRT)—have recently been adapted for the treatment of spinal bone metastases, and both have the potential to achieve excellent control while minimizing acute and late toxicity. Image-guided SRS and IMRT are particularly well suited

for the treatment of spinal bone metastases that are localized or require re-irradiation and may provide superior tumor control. It is important to both predict the prognosis [6, 12] of patients with bone metastases and assess spinal instability [13, 14] when selecting an optimal radiotherapy method and deciding whether to perform invasive surgery [3, 6, 12, 14].

Therefore, for the proper care of spinal bone metastases, patients require an interdisciplinary treatment approach [1, 2].

Current Concepts of Treatment

For more than three decades, maximally invasive or minimally invasive surgery has been the "standard" against which the safety and effectiveness of any new treatment method should be measured. This remains true for the other "standard" of conventional three-dimensional radiotherapy. In other words, image-guided SRS must be proven to be as safe and effective as the two standards.

We focus here on the role of image-guided SRS for the treatment of cancers with oligometastases to the spine.

Availability and Quality of the Scientific Evidence

A sufficient number of available publications have described the use of image-guided SRS for patients with spinal oligometastases. These publications could be used to promote a fair, patient-centered, and objectively differential approach in terms of recommending and discussing innovative treatment options that are safe, noninvasive, effective, and beyond the traditional "standard" method of surgery. This does not mean that a patient's preferences should be influenced, but rather that the patient should be able to provide informed consent based on the best available recent data.

Below, the degree of validity and quality of the available data regarding initial, postoperative, and hybrid SRS use are discussed in a question-and-answer format.

Are plausible and valid data available at the "level of evidence 1a" with particular regard to the use of image-guided SRS for oligometastatic metastatic lesions of the spine?
No, such data are not available from a proper and fully published meta-analysis of prospectively designed randomized controlled trials (RCTs).

Are plausible and valid data available at the "level of evidence 1b" with particular regard to the use of image-guided SRS for oligometastatic metastatic lesions of the spine?
No, such data are not available from properly conducted, fully published, prospectively designed randomized controlled trials (RCTs).

Are plausible and valid data available at the "level of evidence 1b" with particular regard to the use of image-guided SRS for oligometastatic metastatic lesions of the spine as a second-line radiation therapy (re-radiation)?

No, such data are not available from properly conducted, fully published, prospectively designed randomized controlled trials (RCTs).

Are plausible and valid data available at the "level of evidence 2a" with particular regard to the use of image-guided SRS for oligometastatic lesions of the spine?

Yes, there has been published one paper in 2014 by Bydon and colleagues, which was focused on the use of stereotactic radiosurgery for the treatment of spinal lesion [15]. Although it has not been a proper systematic review, it has included relevant literature.

We summarize in the following table the essential literature on postoperative stereotactic radiosurgery (Table 12.1).

Are plausible and valid data available at the "level of evidence 2b" with particular regard to the use of image-guided SRS for oligometastatic metastatic lesions of the spine?

Yes, available data support the indication of image-guided SRS for oligometastatic metastatic lesions of the spine.

Chang and colleagues initiated a phase I study that was published in 2004 [22].

The aim of that study was to investigate the safety, feasibility, and patient positioning accuracy. Fifteen cases were entered into a phase I clinical trial. Each patient received five treatments. Patients (f/m) uniformly received 30 Gy (if possible) of radiotherapy in five fractions to the clinical target volume. The total dose was

Table 12.1 Postoperative stereotactic radiosurgery for spinal lesions

Study (*n*)	Dose/fraction	Local control (%)	Comments
Mahadevan (*n* = 81) 2011 [16]	24–30/3–5	93	Lung, breast, renal cell, melanoma
Garg (*n* = 63) 2011 [17]	27–30/3–5	76	Renal cell, thyroid, sarcoma, breast
Damast (*n* = 97) 2011 [18]	20–30/5	61	Renal cell, lung, prostate, sarcoma
Choi (*n* = 51) 2010 [19]	10–30/1–5	73	Brest, lung, salivary gland, colorectal
Chang (*n* = 54) 2007 [20]	27/3	88	Renal cell, breast, sarcoma, lung
Gerszten (*n* = 347) 2007 [21]	12.5–25/1	88	Renal cell, breast, lung, colon, sarcoma

constrained by limiting the spinal cord to a maximum dose of 10 Gy. Toxicity was measured using the Common Toxicity Criteria, Late Effects of Normal Tissues scoring system, and a neurological function scale. Follow-up was conducted 4 weeks and 2, 3, 6, 9, and 12 months after the completion of stereotactic body radiotherapy (SBRT) and every 6 months thereafter. Technically, the procedure could be feasibly performed in all patients. No neurologic toxicity was observed in any patient. The median follow-up duration was 9 months (range, 6–16 months). The Clopper–Pearson upper limit of the probability of paralysis with 95 % confidence did not exceed 0.181. The positional setup error was determined to be within 1 mm of the planning isocenter. This phase I study demonstrated that this method is feasible and highly precise for the noninvasive treatment of spinal metastases [22]. The research team updated their results and published the outcome of a phase I/II study in 2007 [20]. A total of 36 patients (f/m) underwent image-guided SRS. Spinal MRI was conducted at the baseline and at each follow-up visit. The National Cancer Institute Common Toxicity Criteria 2.0 assessments were used to evaluate toxicity. Among 74 spinal metastatic lesions, the median tumor volume was 37.4 ccm (range, 1.6–358 ccm). No neuropathy or myelopathy was observed during a median follow-up period of 21.3 months (range, 0.9–49.6 months). The actuarial 1-year tumor progression-free incidence was 84 % for all tumors. A pattern of failure analysis identified two primary failure mechanisms: (1) recurrence in the bone adjacent to the site of previous treatment and (2) recurrence in the epidural space adjacent to the spinal cord. Grade 3 or 4 toxicities were limited to acute grade 3 nausea, vomiting, and diarrhea (one case), grade 3 dysphagia and trismus, and grade 3 non-cardiac chest pain. No acute or late grade 3 or 4 toxicity events were observed. An analysis of the data obtained in this study supported the safety and effectiveness of image-guided SRS for the treatment of spinal metastatic cancer. The authors suggested the routine treatment of pedicles and posterior elements posterior to the diseased vertebrae with a wide bone margin because of possible direct extension into these structures [20]. In 2005, Gerszten and colleagues published another initial study. A total of 48 cases involving 60 renal cell cancer oligometastases to the spine (6 cervical, 26 thoracic, 18 lumbar, and 10 sacral) were treated with single-fraction image-guided SRS and were followed up for a median of 37 months (range, 14–48 months). All patients (f/m) were successfully treated in an outpatient setting. The mean tumor volume was 61.9 ccm (range, 5.5–203 ccm). The maximum tumor dose was maintained at a mean of 20 Gy (range, 17.5–25 Gy). The mean spinal cord volume exposed to a dose >8 Gy was 0.64 ccm (range, 0.01–3 ccm); the mean spinal canal volume at the cauda equina level that was exposed to a dose >8 Gy was 0.65 ccm (range, 0.01–2.2 ccm). No radiation-induced toxicity occurred during the follow-up period. Axial and radicular pain improved in 34 (89 %) of 38 patients who were treated primarily for pain. Tumor control was observed in seven of eight patients treated primarily for radiographically documented tumor progression. Over time, six patients required open surgical intervention for tumor progression that had caused neurological dysfunction after radiosurgery. The conclusion was that “spinal radiosurgery can be a successful therapeutic modality for the delivery of large-dose single-fraction radiation to spinal metastases” [23].

In an intermittent review, Sheehan and colleagues evaluated the state of affairs concerning image-guided SRS of spinal metastases [24]. The authors stated that "the treatment of paraspinal and spinal metastasis with spinal radiosurgery represents a natural extension of the principles of intracranial radiosurgery. However, spinal radiosurgery is a far more complicated process than intracranial radiosurgery. Larger treatment volumes, numerous organs at risk, and the inability to utilize rigid, frame-based immobilization all contribute to the substantially more complex process of spinal radiosurgery. Beyond the convenience of a shorter duration of treatment for the patient, spinal radiosurgery affords a greater biological equivalent dose to a metastatic lesion than conventional radiotherapy fractionation schemes. This appears to translate into a high rate of tumor control and fast pain relief for patients. The minimally invasive nature of this approach is consistent with trends in open spinal surgery and helps to maintain or improve a patient's quality of life" [24].

In 2009, Sahgal and colleagues published a study with a focus on salvage therapy options for oligometastases to the spine [25]. A total of 39 consecutive patients (f/m) were treated with image-guided SRS (here named SBRT) and analyzed. Overall, 23 of 60 tumors had not previously received radiotherapy; the remaining 37 tumors had undergone previous irradiation. Of these 37 latter tumors, 31 were treated with the intent to salvage, according to image-based tumor progression. Local failure was defined as clinical and/or image-detected progression. At the last follow-up, 19 patients were deceased. The median patient survival duration was 21 months (95 % confidence interval [CI], 8–27 months), and the 2-year survival rate was 45 %. The median total dose prescribed was 24 Gy in 3 fractions prescribed to the 67 % and 60 % isodose lines for group without and with a previous history of radiotherapy, respectively. The median tumor follow-up durations for the groups without and with previous radiation were 9 months (range, 1–26 months) and 7 months (range, 1–48 months), respectively. Eight of 60 tumors progressed, and the 1- and 2-year progression-free rates were 85 % and 69 %, respectively. For the salvage group, the 1-year progression-free rate was 96 %. There were no significant differences in overall survival or the progression-free rate between tumors re-irradiated for salvage and all other treated tumors ($p = 0.08$ and $p = 0.31$, respectively). In six of eight failures, the minimum distance from the tumor to the thecal sac was $\leq$1 mm. Of 60 treated tumors, 39 underwent $\geq$6 months of follow-up, and no radiation-induced myelopathy or radiculopathy was observed. The authors concluded that image-guided SRS to the spine "has shown preliminary efficacy and safety in patients with image-based progression of previously irradiated metastases" [25].

Ahmed and colleagues reported their experiences in 2012 [26]. A total of 66 patients (f/m) were treated with image-guided SRS (here named SBRT) for spinal metastases. Twenty-two lesions (25.8 %) were treated for recurrence after prior radiotherapy. The mean patient age was 56.8 ± 13.4 years. Patients were treated with a median dose of 24 Gy (range, 10–40 Gy) in a median of 3 fractions (range, 1–5). Tumor sites included the thoracic, lumbar, cervical, and sacral spine ($n = 48$, 22, 12, and 3, respectively). The mean actuarial survival rate at 12 months was 52.2 %. A

total of seven patients experienced both local and marginal failure, one patient experienced marginal but not local failure, and one patient experienced local failure only. The actuarial local control rates at 1 year were 83.3 % and 91.2 % in patients with and without prior treatment, respectively. The median dose delivered to patients who experienced local/marginal failure was 24 Gy (range, 18–30 Gy) in a median of 3 fractions (range, 1–5). No cases of grade 4 toxicity were reported. In one of two patients experiencing grade 3 toxicity, SBRT had been administered after previous radiation. The results indicate the method to be "an effective measure to achieve local control in spinal metastases. Toxicity of treatment was rare, including those previously irradiated" [26].

In 2012, Balagamwala and colleagues published a study of single-dose image-guided SRS [27]. The authors reviewed the outcomes of image-guided SRS (here named SBRT) for the treatment of renal cell carcinoma oligometastases to the spine. A total of 57 patients (f/m) with 88 treatment sites were enrolled in the study. The median follow-up and survival durations were 5.4 months (range, 0.3–38 months) and 8.3 months (range, 1.5–38 months), respectively. The median times to radiographic failure and unadjusted pain progression were 26.5 and 26.0 months, respectively. The median time to pain relief (from the date of simulation) and duration of pain relief (from the date of treatment) were 0.9 months (range, 0.1–4.4 months) and 5.4 months (range, 0.1–37.4 months), respectively. Multivariate analyses demonstrated that multilevel disease (hazard ratio [HR] = 3.5, $p = 0.02$) and neural foramen involvement (HR = 3.4, $p = 0.02$) correlated with radiographic failure, whereas multilevel disease (HR = 2.3, $p = 0.056$) and vertebral body fracture (HR = 2.4, $p = 0.046$) correlated with unadjusted pain progression. One patient experienced grade 3 nausea and vomiting; no other grade 3 or 4 toxicities were observed. Twelve treatment sites (14 %) were complicated by subsequent vertebral fractures. The authors concluded that this method offers fast and durable pain relief with minimal toxicity and "seems optimal for patients who have solitary or few spinal metastases. Patients with neural foramen involvement are at an increased risk for failure" [27].

A report of a phase I/II trial was published in 2012 by Garg and colleagues [28]. All patients (f/m) in that study were evaluated by a multidisciplinary team. Single-fraction image-guided SRS (here named SBRT) was delivered at a peripheral dose of 16–24 Gy while limiting the dose to the spinal cord. Higher doses were used for tumors with renal cell histology. A total of 61 patients with 63 tumors of the non-cervical spine were enrolled. The mean follow-up duration was 20 months. The actuarial 18-month imaging local control and overall survival rates for all patients were 88 % and 64 %, respectively, and the median survival duration for all patients was 30 months. No significant differences in outcomes were noted with respect to tumor histology or dose. Two patients experienced adverse events (grade 3 or higher) related to radiation. The actuarial 18-month rate of freedom from neurologic deterioration of any cause was 82 %. The authors concluded that "additional studies that can prospectively identify predictive factors for spinal cord toxicity are warranted to minimize the incidence of this serious yet rare complication" [28].

In the same year, another phase I/II trial was published by Wang and colleagues [29].

This trial enrolled a cohort of 149 patients (f/m) with 166 mechanically stable, non-cord-compressing spinal metastases who were treated with image-guided SRS (here called SBRT). The patients (f/m) received a total dose of 27–30 Gy in 3 fractions. Symptoms were measured before treatment and at several time points up to 6 months after treatment. The median follow-up duration was 15.9 months (interquartile range [IQR], 9.5–30.3). The number of patients who reported no pain from bone metastases increased from 39 of 149 patients (26 %) before treatment to 55 of 102 patients (54 %) at 6 months after treatment ($p < 0.0001$). The reduction in BPI-reported pain from baseline to 4 weeks after treatment was clinically meaningful (baseline mean of 3.4 [standard deviation = 2.9] for the BPI pain-at-its-worst item versus 2.1 [2.4] at 4 weeks; effect size = 0.47, $p = 0.00076$). These improvements were accompanied by a significant reduction in opioid use during the first 6 months after treatment (43 [28.9 %] of 149 patients with strong opioid use at baseline versus 20 [20.0 %] of 100 patients at 6 months; $p = 0.011$). Ordinal regression modeling revealed that patients reported significant pain during the first 6 months after SBRT ($p = 0.00003$), as well as significant reductions in the composite score of the 6 items measuring symptom interference with daily life ($p = 0.0066$). Only a few non-neurological grade 3 toxicity events occurred, including nausea ($n = 1$), vomiting ($n = 1$), diarrhea ($n = 1$), fatigue ($n = 1$), dysphagia ($n = 1$), neck pain ($n = 1$), and diaphoresis ($n = 1$); two cases of pain associated with severe tongue edema and trismus were reported, and three cases of non-cardiac chest pain were reported. No grade 4 toxicities occurred. The progression-free survival rate after SBRT was 80.5 % (95 % CI, 72.9–86.1 %) at 1 year and 72.4 % (95 % CI, 63.1–79.7 %) at 2 years. The authors concluded that this method is "an effective primary or salvage treatment for mechanically stable spinal metastasis" [29].

A study that focused on long-term effects was published in 2014 by Mantel and colleagues [30]. A total of 32 patients (f/m) were included (median age, 55 years; 61 % male subjects; median Karnofsky Performance Scale score, 85). The median treatment dose was 60 Gy (range, 48.5–65 Gy) given in a median of 20 fractions (range, 17–33 fractions), and the median maximum dose to the planning risk volume for the spinal cord was 46.6 Gy. All patients suffering from pain prior to radiotherapy reported pain relief after treatment; after a median follow-up of 20.3 months, 61 % of treatment sites were pain-free, and another 25 % were associated with only mild pain. After 86 % of treatments, patients remained free from neurological symptoms at the time of the last clinical follow-up. Acute grade 1 toxicities were observed in 11 patients. Myelopathy did not occur in any patient. The radiologically controlled freedom from local progression rates were 92 % and 84 % after 12 and 24 months, respectively. The median overall survival duration was 19.6 months. The authors' interpretation was that the data indicated a long-term overall survival "despite metastatic disease, and dose-intensified fractionated radiosurgery for spinal metastases was safe and achieved long-term local tumor control and palliation of pain" [30].

In 2014, Ryu and colleagues communicated the preliminary results of the first large-scale multicenter trial conducted by the US-based Radiation Therapy Oncology Group (RTOG) [31]. This study assessed the feasibility and safety of image-guided SRS for limited spine metastases in a cooperative group setting. Patients (f/m) received a dose of 16 Gy via single-fraction image-guided SRS. The primary endpoint was feasibility, which included an image guidance targeting accuracy ≤2 mm, target volume coverage >90 % of the prescribed dose, maintenance of spinal cord dose constraints (10 Gy to ≤10 % of the cord volume from 5 to 6 mm above to 5–6 mm below the target or absolute spinal cord volume <0.35 cc), and other normal tissue dose constraints. A feasibility success rate <70 % was considered unacceptable for continuation of the phase 3 component. Forty-one patients were required according to a one-sample exact binomial test with an alpha = 0.10 (one sided). Acute toxicity was assessed according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0. Sixty-five institutions received credentials for spine phantom dosimetry and image-guided radiotherapy compliance. Forty-six patients were accrued, of which 44 were eligible. Tumors occurred at cervical, thoracic, and lumbar sites in 4, 21, and 19 patients, respectively. The median numerical pain rating scale score at presentation was 7. A final pretreatment rapid review was approved in 100 % of the cases. The accuracy of image-guided SRS targeting complied with the protocol in 95 % of cases. The target coverage and spinal cord dose constraint were in accordance with the protocol requirements in 100 % and 97 % of cases, respectively. The overall compliance rate of other normal tissue constraints with the protocol was 74 %. No events of grade 4–5 acute treatment-related toxicity were observed. The authors considered that the partial results of this phase 2 trial "demonstrate the feasibility and accurate use of SRS to treat spinal metastases, with rigorous quality control, in a cooperative group setting" [31].

The most recent paper again reported on experiences with single-dose versus multi-fraction spinal SRS for spinal metastases of renal cell carcinoma. This report was published by Ghia and colleagues in 2016 [32]. The results from a phase I/II trial were described in this publication.

Single-dose image-guided SRS was performed at 47 spinal sites of 43 patients. The median patient age was 62 years (range, 38–75 years). The most common histological subtype was clear cell ($n = 30$). Fifteen sites underwent surgery prior to treatment, of which laminectomy was the most commonly performed procedure ($n = 10$). A single dose of 24 Gy was delivered to 21 patients (f/m); multiple-dose regimens were either 27 Gy in 3 fractions ($n = 20$) or 30 Gy in 5 fractions ($n = 6$). The median overall survival duration for the entire cohort was 22.8 months. The median local control duration for the entire cohort was 80.6 months, with 1-year and 2-year actuarial local control rates of 82 % and 68 %, respectively. Single-fraction SRS correlated with improved 1- and 2-year actuarial local control rates relative to those achieved with multi-fraction SRS (95 % versus 71 % and 86 % versus 55 %, respectively; $p = 0.009$). In a competing risk analysis, single-dose image-guided SRS yielded superior local control relative to multiple-dose SRS (subhazard ratio = 6.57, $p = 0.014$). In a multivariate analysis of local control that

included tumor volume ($p = 0.272$), number of treated levels ($p = 0.819$), gross tumor volume (GTV) coverage ($p = 0.225$), and the GTV minimum point dose ($p = 0.97$) as covariates, multiple-dose image-guided SRS remained inferior to single-dose SRS (subhazard ratio = 5.26, $p = 0.033$). The authors concluded that image-guided SRS "offers durable local control for spinal metastases from renal cell cancer." Single-fraction image-guided SRS "is associated with improved LC over multiple-dose image-guided stereotactic radiosurgery for previously non-irradiated spinal metastases" [32].

Prognostic Factors

Tang and colleagues examined whether a prognostic index could be derived from their outcome data [8]. The assumption was that there is much uncertainty in the prognosis of patients (f/m) following spinal metastasis treatment. And the hypothesis was that the researcher team could figure out if they could create a scoring system that stratifies patients (f/m) based on overall survival. Patients enrolled in two prospective trials investigating stereotactic spine radiation surgery for spinal metastasis with more than 3-year follow-up were analyzed. After a median follow-up of 70 months, results were analyzed for 206 patients (f/m). The authors have been focused on seven patient and tumor variables such as female sex (hazard ratio [HR] = 0.7, $p = .02$), Karnofsky Performance Scale score (HR = 0.8 per 10-point increase above 60, $p = .007$), previous surgery at the SSRS site (HR = 0.7, $p = .02$), previous radiation at the SSRS site (HR = 1.8, $p = .001$), the SSRS site as the only site of metastatic disease (HR = 0.5, $p = .01$), number of organ systems involved outside of the bone (HR = 1.4 per involved system, $p < .001$), and >5-year interval from initial diagnosis to detection of spine metastasis (HR = 0.5, $p < .001$). The median overall survival for the entire cohort was 25.5 months and it was indeed significant. Overall survival for the respective groups are as follows: for group 1, excellent prognosis, median survival was not reached; group 2 reached 32.4 months; group 3 reached 22.2 months; and group 4 was those with a poor prognosis that reached 9.1 months ($p < .001$). The authors concluded that "the prognostic index for spinal metastases (PRISM) model, a new model that identified patient subgroups with poor and excellent prognoses" [8].

Another research group focused on the identical problem and communicated their results also in 2015 [33]. The assumption was that the "number of patients with spinal tumors is rapidly increasing; spinal metastases develop in more than 30% of cancer patients during the course of their illness. Such lesions can significantly decrease quality of life, often necessitating treatment" [33]. And the hypothesis was that the researcher team could figure out if they could determine prognostic factors that predicted pain palliation and report overall institutional outcomes after spine

treatment by noninvasive image-guided stereotactic radiosurgery. Data were collected at the initial visit just before treatment and at 1-, 3-, 6-, and 12-month follow-up visits. Collected clinical data included Karnofsky Performance Scale scores, pain status, presence of neurological deficits, and prior radiation exposure at the level of interest. Radiation treatment plan parameters (dose, fractionation, and target coverage) were recorded. A total of 99 cases were enrolled in the study. The median survival time was 9.1 months (95% CI 6.9–17.2 months). Significant decreases in the proportion of patients reporting pain were observed at 3 months ($p<0.0001$), 6 months ($p=0.0002$), and 12 months ($p=0.0019$) after treatment. Significant decreases in the number of patients reporting pain were also observed at the last follow-up visit ($p=0.00020$) (median follow-up time 6.1 months, range 1.0–56.6 months). Univariate analyses revealed that significant predictors of persistent pain after intervention were initial extent of epidural spinal cord compression grade, stratified by a Bilsky grade of 1c ($p=0.0058$); initial American Spinal Injury Association grade of D ($p=0.011$); initial Karnofsky Performance Scale score, stratified by a score of 80 ($p=0.002$); the presence of multiple treated lesions ($p=0.044$); and prior radiation at the site of interest ($p<0.0001$). The multivariate analyses revealed that the only predictor of pain at last follow-up visit was a prior history of radiation at the site of interest ($p=0.0038$), although initial extent of epidural spinal cord compression grade trended toward significance ($p=0.073$). Using pain outcomes at 3 months, at this follow-up time point, pain could be predicted by receipt of radiation above a biologically effective dose of 66.7 Gy. The authors concluded that pain reduction has been limited for patients (f/m) "with spinal tumors with epidural extension that deforms the cord and for patients who have previously received radiation to the same site."[33]

Summary

The past decade has seen a real increase in the understanding of image-guided SRS, as well as relevant publications and conference contributions.

For more than two decades, maximally invasive or minimally invasive surgery has been the "standard" against which the safety and effectiveness of any new treatment method should be measured.

If the above-described evidence is taken seriously, image-guided SRS has been demonstrated as a safe, effective novel method that is essentially noninvasive and cost-effective.

Image-guided SRS has been embedded in a coherent, rational, and empirically reproducible oncologic concept, namely, the oligometastatic state concept that was first proposed by Hellmann in 1995 and has since been extensively discussed, validated, and disputed; accordingly, this technology will broaden the complex dialectics surrounding cure and palliation and lead toward the potential long-term control (and even cure) of cancers with limited metastases.

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Stereotactic Radiosurgery for Liver Lesions

13

Abstract

Oligometastases of solid tumors to the liver might lead to severe functional affections and, in some cases, to fatal organ failure in patients (f/m) with liver lesions.

Invasive surgical procedures like partial hepatectomy performed seem to be the historic "standard." Any "standard" has to prove its superiority in terms of safety and effectiveness for patients (f/m), and it is true in the frame of cost efficiency too.

Image-guided stereotactic radiosurgery with its multiple labels like stereotactic ablative radiotherapy (SABR) or stereotactic body radiotherapy (SBRT) could affect liver lesions by deactivating tumor cells. They are responsive to high-dose radiotherapy. Metastases, limited by volume, number, and occurrence site, react to radiation by stopping their growth. The aim would be the deactivation of lesions or, at least, to prolong the time free of hepatic symptoms and, therefore, to have a better quality of life.

Consecutively, it demonstrates a noninvasive high-precision and safe technique in treating patients (f/m).

Background

The liver is frequently the first site for metastasizing cancers because of its function as a filter in the portal blood circulation system. This statement is particularly true for gastrointestinal neoplasms. In addition, metastases of several cancer types with primary sites in other organs (i.e., beyond gastrointestinal neoplasms) exhibit a natural trajectory that includes development in the hepatic parenchyma.

Primary cancers of the liver, gallbladder, and bile duct are rare; although for decades, the "standard" approach was surgery and despite the hegemony of invasive

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mechanistic medicine, emerging valid, high-quality data demonstrate the use of stereotactic radiosurgery (SRS) for these cancers.

In this chapter, we will focus on different SRS methods used to treat cancers with oligometastases to the liver.

Historical Context

Since the 1980s, many research groups have obtained results indicative of improved clinical outcomes in patients (f/m).

As historically presupposed, the initial valuable efforts, which were undertaken between 1980 and 2000, were branded as pragmatic methods of execution by more experimental investigations. In a typically very slow manner, investigators' thoughts became engrossed with the notion of a systematic approach to the issue of the treatment of hepatic metastases. This transformation in scientific thinking was accompanied by fundamental changes in the features and widespread availability of imaging technologies. Computed tomography (CT) scanning became available outside of large university medical centers in the mid-1990s, followed by the availability of magnetic resonance imaging (MRI) for broad clinical usage in midsize medical centers. This progression was also true for ultrasound technology, although it occurred for different market-driven reasons. The rapid dynamics of imaging technologies had profoundly practical technological and conceptual implications on conventional surgery, minimally invasive surgery, and radiosurgery. In addition, array of so-called interventional radiology procedures was made available specifically for liver metastases.

Historically, the conventional "standard" of care for patients (f/m) with cancer and liver oligometastases has involved surgical resection techniques such as hemihepatectomy (right, left) and extended hemihepatectomy (right, left). Subsequent sophisticated techniques, such as segmentectomy or wedge resection, completed the invasive surgical arsenal. In the early 1980s, Wagner and colleagues reflected on the options and likelihood of treating colorectal cancers with a limited number and volume of metastases to the liver, which is a very frequently encountered clinical scenario [1]. These authors stated that the 5-year overall survival rate after the resection of hepatic metastases from colorectal cancer "is 25 %. Although resection palliates some patients who do not live that long, 50 % of patients so treated are not helped at all. Until ignorance of a cancer's real stage is resolved by improved techniques, the evaluation and choice of therapy can be based only upon knowledge of the natural history of untreated metastases and determinants of prognosis derived from treated patients. Analysis of the survival rates of 252 patients who had biopsy proven, unresected hepatic metastases that were the only evidence of residual disease shows the extent to which natural history, rather than resection, may determine length of survival– and indicates the need for critical analysis of 2- and 3-year survival rates reported after any therapy. Study of 141 patients who had hepatic metastases resected shows that the stage of the primary lesion, being female, and the absence of extra-hepatic metastases are significant determinants of favorable

prognosis after resection of hepatic metastases" [1]. At that time, the efforts of Dr. Wagner and colleagues comprised an avant-garde investigation [2]. The source outcome data for their analysis included archived information recorded from 1948 to 1982. The authors commented, "the overall 5-year survival rate was 25 %, significantly higher than that of a group of historical controls who had resectable metastases that were not removed. The size and nature of our extended sample allowed identification of some determinants of favorable prognosis: Dukes' stage of the primary lesion, absence of extra-hepatic metastases, and being female. Contrary to our earlier observations, this study justified removal of some multiple hepatic metastases" [2]. Interestingly, the term "multiple," which refers to the tumor burden, was not the focus of the attention in that paper.

At that time, the natural history of untreated metastatic colorectal cancer was considered the natural state against which the effectiveness of any new treatment method should be measured. Accordingly, surgery was found to yield better results [1, 2].

As we observed in the 1990s and beyond, the invasive surgical arsenal comprised the first therapeutic "standard" for hepatic metastases from colorectal cancer [3]. At the end of the 1990s, Fong and colleagues published one of the largest research series to date, in which they addressed the question of prognosis in 1001 such cases [4].

Clearly defined and widely applicable clinical criteria for the selection of patients who may benefit from hepatic resection for metastatic colorectal cancer are needed. Such criteria would also be useful for the stratification of patients in clinical trials for this disease. Fong and colleagues evaluated clinical, pathologic, and outcome data in consecutive patients undergoing liver resection for metastatic colorectal cancer between July 1985 and October 1998. In that study, the resections included 237 tri-segmentectomies, 394 lobectomies, and 370 resections encompassing less than one lobe. The surgical mortality rate was 2.8 %. The 5- and 10-year survival rates were 37 % and 22 %, respectively. In that study, seven factors were found to be significant and independent predictors of poor long-term outcomes in a multivariate analysis: positive margin ($p = 0.004$), extrahepatic disease ($p = 0.003$), node-positive primary disease ($p = 0.02$), disease-free interval from primary to metastases <12 months ($p = 0.03$), >1 hepatic tumor ($p = 0.0004$), largest hepatic tumor >5 cm ($p = 0.01$), and carcinoembryonic antigen level >200 ng/ml ($p = 0.01$). When the last five of these criteria were used in a preoperative scoring system (each criterion = 1 point), the total score was highly predictive of the outcome ($p < 0.0001$). No patient with a score of 5 was a long-term survivor. The resection of hepatic metastases of colorectal cancer might yield long-term survival and could thus be considered curative. The long-term outcomes of all patients considered for resection can thus be predicted using five readily available criteria [4].

For the past two decades, surgery has been considered the "standard" treatment. Although the prognostic factors mentioned above have since been frequently confirmed, these criteria have not comprised a constitutive factor in the decision-making processes of surgical departments worldwide.

The extent of the invasive surgical arsenal widened further in response to pragmatism, positivism, and progressivism, despite the lack of a solid foundational epistemic concept.

Sixteen years later, in a very recent "meta-analysis" of retrospective reports, Petrelli and colleagues examined the role of prognostic factors after the complete resection of liver metastases in patients (f/m) with colorectal cancer [5]. The aim of that study was to identify risk factors related to overall survival (OS) after the complete resection of liver metastases. Twenty-four publications, with a total of 4855 patients, were eligible. Through multivariate analyses, a disease-free interval <12 months (hazard ratio [HR] = 1.47, $p = 0.0002$), size of the largest metastasis (HR = 1.56, $p < 0.0001$), total number of metastases (HR = 1.73, $p < 0.00001$), primary tumor with a node-positive status (HR = 1.56, $p = 0.002$), rectal primary tumor (HR = 1.48, $p < 0.00001$), high carcinoembryonic antigen level (HR = 1.49, $p = 0.02$), high tumor grade (HR = 2.42, $p < 0.00001$), and extrahepatic disease (HR = 2.03, $p < 0.00001$) were associated with an increased risk of death after complete resection of liver metastases from colorectal cancer. The most interesting comment in that review was that "in particular burden of liver and extra-hepatic metastases and grade are those associated with a higher risk of death" [5].

Current Concepts of Noninvasive Image-Guided Stereotactic Radiosurgery for Metastatic Liver Lesion

For more than two decades, maximally invasive and minimally invasive surgeries have been the new "standards" against which the safety and effectiveness of any new treatment method should be measured.

We focus here on the role of image-guided SRS for the treatment of cancers with oligometastases to the liver.

The first report on the use of radiation for liver lesions was published in 1954 by Phillips and colleagues [6]. This was considered an archaic period of radiotherapy.

The first contemporary and clinically relevant paper was published in 2000 by Herfarth and colleagues of the Heidelberg group [7]. That well-designed clinical protocol represented the starting point for a new field of liver lesion treatment in terms of the use of noninvasive, highly precise image-guided SRS.

A high accuracy of repositioning and reduction in target movement were constructed for this technique. The accuracy of setup was evaluated in patients with liver metastases who were treated with single-dose radiation. A total of 24 patients (f/m) were treated using a self-developed stereotactic frame. Liver movement was reduced using abdominal pressure. The effectiveness was evaluated via fluoroscopy. CT scans were performed on the planning day and directly before treatment. Representative reference marks were selected, and the coordinates were calculated. In addition, target displacement was quantitatively evaluated after treatment. Diaphragmatic movement was reduced to a median of 7 mm (range, 3–13 mm). The final body setup accuracy limited a median of 1.8 mm in the latero-lateral direction (range, 0.3–5.0 mm) and 2.0 mm in the anteroposterior direction (range,

0.8–3.8 mm). Deviations of the body in the cranio-caudal direction were always less than the thickness of one CT slice (<5 mm). However, repositioning was necessary in 16 cases. The final target shift was a median of 1.6 mm (range, 0.2–7.0 mm) in the latero-lateral and 2.3 mm (range, 0.0–6.3 mm) in the anteroposterior direction. The median shift in the cranio-caudal direction was 4.4 mm (range, 0.0–10.0 mm). The authors concluded that in patients (f/m) "with liver metastases, a high set-up accuracy of the body and the target can be achieved. This allows a high-dose focal radiotherapy of these lesions. However, a control CT scan should be performed directly before therapy to confirm set-up accuracy and possibly prompt necessary corrections" [7]. An outcome update was reported 4 years later [8].

Availability and Quality of the Scientific Evidence

A sufficient number of available publications describe the use of image-guided SRS for patients with liver oligometastases. These publications could be used to ensure a fair, patient-centered, and objectively differential approach to the recommendation and discussion of innovative treatment options that are safe, noninvasive, and effective and that lie beyond the traditional "standard" surgical method. This does not mean that the patient's preferences should be influenced, but rather that the patient should be encouraged to provide informed consent based on the best available data from recent years.

The following text describes the degrees of validity and quality of the available data for the initial, postoperative, or hybrid usage of SRS in question and answer format.

Are plausible and valid data available at the "level of evidence 1a" with particular regard to the use of SRS for liver oligometastases?
No, there are no data in the context of a proper and fully published meta-analysis of prospectively designed controlled randomized trials (CRTs).

Are plausible and valid data available at the "level of evidence 1b" with particular regard to the use of SRS for liver oligometastases?
No, there are no data not in the context of proper and fully published controlled randomized trials with prospective designs.

Are plausible and valid data available at the "level of evidence 2a" with particular regard to the use of SRS for liver oligometastases?
Yes, there are data available that demonstrate the feasibility, safety, and effectiveness of noninvasive image-guided stereotactic radiosurgery for metastatic liver lesions.

In 2011, Chang and colleagues published the first systematic review of mostly prospective cohort studies. Patients (f/m) with liver oligometastases of colorectal cancer at three institutions were included if they had 1–4 lesions, had received 1–6 fractions of image-guided SRS (designated stereotactic body radiation therapy

[SBRT]), and had undergone radiologic imaging ≥3 months posttreatment. Sixty-five patients with 102 lesions were treated. A tumor control probability model was used to estimate the 3-fraction dose required for >90 % local control after converting the schedule into biologically equivalent doses, single-fraction equivalent doses, or linear quadratic model-based single-fraction doses. Forty-seven (72 %) patients had been treated with ≥1 chemotherapy regimen before SBRT, and 27 (42 %) had been treated with ≥2 regimens. The median follow-up duration was 1.2 years (range, 0.3–5.2 years). The median radiation dose was 42 Gy (range, 22–60 Gy). When evaluated separately in a multivariate analysis, the total dose ($p = 0.0015$), dose/fraction ($p = 0.003$), and biologically equivalent dose ($p = 0.004$) all correlated with local lesion control. In the multivariate analysis, non-active extrahepatic disease was associated with overall survival (OS; $p = 0.046$) and closely correlated with sustained local control ($p = 0.06$). By using a single-fraction equivalent dose, biologically equivalent dose, or linear quadratic model-based single-fraction dose in the tumor control probability model, the estimated dose range needed to achieve a 1-year local control rate >90 % was 46–52 Gy in 3 fractions. This regimen appeared well tolerated and effective for liver metastases of colorectal cancer [9].

Scorsetti and colleagues summarized the evidence available in 2014 [10] after assuming that "approximately 70–90 % of liver metastases, however, are unresectable and an effective and safe alternative therapeutic option is necessary" for these patients (f/m). These authors reviewed image-guided SRS data of oligometastatic patients (f/m) and found promising results that were attributed to the ability of this procedure to deliver a conformal high radiation dose to the target lesion and a minimal dose to surrounding critical tissues [10]. Subsequent reviews confirmed those statements [11].

In 2014, the German Society for Radiation Oncology (German acronym, DEGRO) summarized data in order to develop a guideline for clinical practice [12]. Recommendations were developed for patient selection, imaging, planning, treatment delivery, motion management, dose reporting, and follow-up. Radiation dose constraints to the critical organs at risk were provided. The authors concluded that image-guided SRS "is a well-established treatment option for primary and secondary liver tumors associated with low morbidity" [12].

Are plausible and valid data available at the "level of evidence 2b" with particular regard to the use of SRS for liver oligometastases?

Yes, there are data available that demonstrate the feasibility, safety, and effectiveness of noninvasive image-guided stereotactic radiosurgery for metastatic liver lesions.

In 2005, Schefter and colleagues reported a phase I study [13]. Phase I studies attempt to determine the maximum tolerated dose of the given interventional method, in this case image-guided SRS (SBRT). Patients (f/m) with 1–3 liver metastases, a tumor diameter <6 cm, and adequate liver function were included. The first cohort received 36 Gy to the planning target volume (PTV) in 3 fractions. Subsequent cohorts received higher doses up to a set maximum of 60 Gy/3 fractions. At least 700 mL of the normal liver volume was required to receive a total dose <15 Gy.

Dose-limiting toxicities included acute grade 3 liver or intestinal toxicities and any acute grade 4 toxicity. The maximum tolerated dose was considered to have been exceeded if two of six patients in a cohort experienced a dose-limiting toxicity. Eighteen patients were enrolled (ten men, eight women) with a median age of 55 years (range, 26–83 years). The most common primary tumor site was colorectal (6 patients), and the median aggregate gross tumor volume was 18 ml (range, 3–98 ml). Four patients had multiple tumors. No patient experienced a dose-limiting toxicity, and the dose was escalated to 60 Gy/3 fractions without reaching the maximum tolerated dose. The conclusion was that a biologically effective dose was well tolerated in patients with oligometastases to the liver [13].

In 2006, Wulf and colleagues reported on their experiences [14]. A total of 51 hepatic metastases were treated using image-guided SRS. Twenty-eight targets in a "low-dose" group were treated with three 10-Gy fractions ($n=27$) or four 7-Gy fractions ($n=1$) prescribed to the planned target volume enclosed within the 65 % isodose line. Patients in a "high-dose" group were treated with three 12–12.5-Gy fractions ($n=19$; same dose prescription) or one 26-Gy fraction to the planned target volume enclosed within the 80 % isodose line ($n=9$). The median follow-up duration was 15 months. Among 51 metastases, nine local failures (range to incidence, 3–19 months) were observed, resulting in actuarial local control rates of 92 % at 12 months and 66 % at ≥24 months. A borderline significant correlation between dose and local control was observed ($p=0.077$); the actuarial local control rates at 12 and 24 months was 86 % and 58 % in the low-dose group versus 100 % and 82 % in the high-dose group. In a multivariate analysis, a high versus low dose was the only significant factor predictive of local control ($p=0.0089$). The conclusion was that "patient selection is important, because those with low risk for systemic progression are more likely to benefit from this approach" [14]. The records of 69 patients who were treated for 174 metastatic liver lesions were reviewed. The most common primary tumors were colorectal ($n=20$), breast ($n=16$), pancreas ($n=9$), and lung ($n=5$). The mean number of lesions treated per patient was 2.5 (range, 1–6). The longest lesion diameters ranged from 0.6 to 12.2 cm (median, 2.7 cm). The dose per fraction ranged from 2 to 6 Gy, with a median total dose of 48 Gy (range, 30–55 Gy). The median follow-up duration was 14.5 months. Sixty patients were evaluable for response, based on abdominal CT scans obtained at a minimum of 3 months after treatment completion. The actuarial overall in-field local control rates of the irradiated lesions were 76 % and 57 % at 10 and 20 months, respectively. The median overall survival duration was 14.5 months. The progression-free survival rates were 46 % and 24 % at 6 and 12 months, respectively. None of the patients developed grade 3 or higher toxicities [15].

Image-guided SRS via CyberKnife was introduced in some publications. In 2009, Ambrosino and colleagues reported the local control of unresectable liver metastases from colorectal and non-colorectal cancer [16]. A total of 27 patients (median age, 62 years; range, 47–80 years) were enrolled in the study. The diagnoses were liver metastasis of colorectal cancer in 11 patients (41 %), and other secondary malignancies in 16 (59 %) patients. The patients were treated with 25–60 Gy (median, 36 Gy) delivered in 3 consecutive fractions, and the isodose value covering

the planning target volume was 80 % of the prescribed dose. Overall, the mean tumor volume was 81.6 ± 35.9 ml. Growth inhibition or size reduction was achieved in 20 (74.1 %) patients: seven with a complete response and 13 with a partial response. Three patients (11.1 %) achieved local complete responses in other single lesions, whereas four (14.8 %) exhibited disease progression. The median posttreatment tumor volume was 24 ml (range, 0–54 ml) among the responders. Mild or moderate transient hepatic dysfunction was detected in nine patients, and five patients developed minor complications. Two patients with progressive disease died of liver failure. In conclusion, "in patients with liver metastases, stereotactic radiosurgery achieves high rates of local disease control, representing an acceptable alternative therapy, but should be further studied in larger series" [16].

In 2009, Lee and colleagues published another phase I study [17]. Individualized radiation doses were selected to maintain the same nominal risk of radiation-induced liver disease at three estimated risk levels (5, 10, and 20 %). Additional patients in an expanded cohort were treated at the maximal study dose. The median dose was 41.8 Gy (range, 27.7–60 Gy) in 6 fractions over 2 weeks. Sixty-eight patients with inoperable metastases of colorectal ($n = 40$), breast ($n = 12$), or other cancers ($n = 16$) were treated. The median tumor volume was 75.2 mL (range, 1.19–3,090 mL). The highest investigated radiation-induced liver disease risk level was safe, with no dose-limiting toxicities. Two grade 3 liver enzyme changes occurred, but no radiation-induced liver disease or other grade 3–5 liver toxicities was seen among patients with a low estimated risk of serious liver toxicity (95 % confidence interval [CI], 0–5.3 %). Six (9 %) patients developed acute grade 3 toxicities (gastritis, two; nausea, two; lethargy and thrombocytopenia, one each), and one patient (1 %) developed a grade 4 toxicity (thrombocytopenia). The 1-year local control rate was 71 % (95 CI, 58–85 %). The median overall survival duration was 17.6 months (95 % CI, 10.4–38.1 months). Image-guided SRS appeared to be safe and was accompanied by sustained local control in the majority of patients (f/m) [17].

Experiences with a Dutch study were published by Rusthoven and colleagues in 2009 [18]. In that multi-institutional phase I/II study, patients (f/m) with 1–3 hepatic lesions and maximum individual tumor diameters <6 cm were enrolled and treated with 3 fractions of image-guided SRS (SBRT). During phase I, the total dose was safely escalated from 36 to 60 Gy. The phase II dose was 60 Gy. The primary endpoint was local control. Lesions with >6 months of radiographic follow-up were considered assessable for local control. The secondary endpoints were toxicity and survival. A total of 47 patients (f/m) with 63 lesions were included. Among them, 69 % had received at least one prior systemic therapy regimen for metastatic disease (range, 0–5 regimens), and 45 % had extrahepatic disease at the time of study entry. Only one patient experienced a grade 3 or higher toxicity (2 %). Forty-nine discrete lesions were assessable for local control. The median follow-up duration of assessable lesions was 16 months (range, 6–54 months). The median maximal tumor diameter was 2.7 cm (range, 0.4–5.8 cm). Local progression occurred in only three lesions at a median of 7.5 months (range, 7–13 months). The actuarial in-field local control rates at 1 and 2 years after SBRT were 95 % and 92 %, respectively. Among lesions with maximal diameter of ≤3 cm, the 2-year local control rate was 100 %. The median survival duration was 20.5 months. According to the authors, this

multi-institutional phase I/II trial demonstrated "that high-dose liver SBRT is safe and effective for the treatment of patients with one to three hepatic metastases" [18].

In 2011, Rule and colleagues reported findings from a phase I dose escalation study [19]

Patients (f/m) with 1–5 hepatic metastases, a Karnofsky Performance Scale score of ≥60, the ability to spare a critical hepatic volume (volume receiving <21 Gy) of 700 mL, and adequate baseline hepatic function were enrolled into three dose escalation cohorts: 30 Gy in 3 fractions, 50 Gy in 5 fractions, and 60 Gy in 5 fractions. Dose-limiting toxicities included treatment-related grade 3 gastrointestinal, hepatobiliary/pancreatic, and metabolic/laboratory toxicities. Any grade 4 or 5 event attributable to therapy was defined as a dose-limiting toxicity. The local control and complete plus partial response rates were assessed. Twenty-seven patients with 37 lesions were enrolled (9 per cohort) and treated; the patients included 17 men and 11 women with a median age of 62 years (range, 48–86 years). The most common site of primary disease was colorectal (44.4 %). The median follow-up duration was 20 months (range, 4–53 months). There were no grade 4 or 5 toxicity or treatment-related grade 3 toxicity events. The actuarial 24-month local control rates for the 30-, 50-, and 60-Gy cohorts were 56 %, 89 %, and 100 %, respectively. There was a statistically significant difference in local control between the 60- and 30-Gy cohorts ($p=0.009$), but not between the 60- and 50-Gy cohorts ($p=0.56$) or the 50- and 30-Gy cohorts ($p=0.091$). The maximum tolerated dose was not reached. The authors concluded that a "dose of 60 Gy in 5 fractions can be safely delivered to selected patients with hepatic metastases as long as the critical liver volume is respected. A dose of 60 Gy in 5 fractions yields an excellent level of local control" [19].

A prospective phase II clinical trial was published by Scorsetti and colleagues [20]. In this trial, patients (f/m) with 1–3 liver metastases, a maximum individual tumor diameter <6 cm, and Karnofsky Performance Scale Score of ≥70 were enrolled and treated with SBRT. The dose prescription was 75 Gy on consecutive days. SBRT was delivered as volumetric modulated arc therapy via the RapidArc (Varian, Palo Alto, CA, USA) technique. The primary endpoint was in-field local control. The secondary endpoints were toxicity and survival. A total of 61 patients with 76 lesions were treated. Among these patients, 21 (34.3 %) had stable extrahepatic disease upon study entry. The most frequent primary sites were colorectal (45.9 %) and breast (18 %). Of the patients, 78.7 % had one lesion, 18.0 % had two lesions, and 3.3 % had three lesions. After a median of 12 months (range, 2–26 months), the in-field local response rate was 94 %. The median overall survival duration was 19 months, and the actuarial survival rate at 12 months was 83.5 %. None of the patients experienced grade 3 or higher acute toxicity events. No radiation-induced liver disease was detected. One patient experienced a late grade 3 toxicity event at 6 months due to chest wall pain. Image-guided SRS is "a therapeutic option, with excellent rates of local control and a low treatment-related toxicity" [20].

The research group later updated these data [21]. The updated median follow-up duration was 24 months (range, 4–47 months). In-field progression was observed in five lesions. The 24-month actuarial local control rate was 91 %. The median overall survival duration was 29.2 ± 3.7 months. The actuarial overall survival rate at 24 months was 65 %. The median progression-free survival duration was 12.0 ± 4.2 months,

with a 24-month actuarial progression-free survival rate of 35 %. No patients experienced radiation-induced liver disease or grade 3 or higher toxicity. The authors concluded that image-guided SRS "represents a feasible alternative for the treatment of colorectal liver metastases not amenable to surgery or other ablative treatments in selected patients, showing optimal local control and promising survival rate" [21].

Another well-designed study was communicated in 2015 by Goodman and colleagues, who reported the long-term safety and efficacy of image-guided SRS for hepatic oligometastases [22]. Eligible patients had 1–3 liver metastases, a maximum summed diameter of 6 cm, and no extrahepatic progression. We treated 106 lesions in 81 patients, of whom 67 % had colorectal primaries. The median dose was 54 Gy in 3–5 fractions. At a median follow-up of 33 months (range, 2.5–70 months), the overall local control rate was 94 % (95 % CI, indeterminate); Kaplan–Meier survival estimates were 96 % at 1 year and 91 % at 2, 3, and 4 years. Partial or complete response was observed in 69 % of the lesions and less than 3 % exhibited progression. The median survival time was 33.6 months (95 % CI, 29.1–38.4), and the Kaplan–Meier survival estimates at 1, 2, 3, and 4 years were 89.9 %, 68.6 %, 44.0 %, and 28.0 %, respectively. The incidence of grade 3 or higher liver toxicity was 4.9 %. The authors stated that image-guided SRS is "effective for selected patients with hepatic oligometastases with limited toxicities" [22].

Summary

The past decade has seen a real increase in the understanding of image-guided SRS, as well as related publications and conference contributions.

For more than two decades, maximally invasive or minimally invasive surgery was the "standard" against which the safety and effectiveness of any new treatment method were measured.

If the above evidence is taken seriously, image-guided SRS appears to be a good, safe, and effective new method that is essentially noninvasive and cost-effective.

As it is embedded in a coherent, rational, and empirically reproducible oncologic concept, namely, the oligometastatic state concept initially proposed by Dr. Samuel Hellmann in 1995, followed by extensive discussion, proof, and dispute, image-guided SRS will introduce a new pathway in the complex dialectics of cure and palliation and may lead toward a chance of long-term control (and even cure) of cancers with limited metastases.

Radiosurgery for Hepatocellular Carcinoma

Background

Invasive surgical procedures or palliative chemotherapy has been the standard treatment for hepatocellular carcinoma [23]. The potential effects of image-guided stereotactic radiosurgery for these lesions have been investigated, and the

implementation in the real-world scenarios remains controversial and difficult. The status of a noninvasive procedure seems to be complicated; even a significant number of patients (f/m) have declared as palliative without the attempt to execute image-guided stereotactic radiosurgery.

We, therefore, provide an overview on available data in this field, without an in-depth analysis.

Current Concepts of Noninvasive Image-Guided Stereotactic Radiosurgery for Hepatocellular Carcinoma

Availability and Quality of the Scientific Evidence

A certain number of available publications describe the use of image-guided SRS for patients with hepatocellular carcinoma. These publications could be used to ensure a fair, patient-centered, and objectively differential approach to the recommendation and discussion of innovative treatment options that are safe, noninvasive, and effective and that lie beyond the traditional "standard" surgical method. This does not mean that the patient's preferences should be influenced, but rather that the patient should be encouraged to provide informed consent based on the best available data from recent years.

The following text describes the degrees of validity and quality of the available data for the initial, postoperative, or hybrid usage of SRS in question and answer format.

Do we have plausible and valid data on the "level of evidence 1a" in special regard to the usage of SRS for hepatocellular carcinoma?
No, when we think of a proper and fully published meta-analysis of controlled randomized trials (CRT) with prospective design.

Do we have plausible and valid data on the "level of evidence 1b" in special regard to the usage of SRS for hepatocellular carcinoma?
No, when we think of proper and fully published controlled randomized trials (CRT) with prospective design.

Do we have plausible and valid data on the "level of evidence 2a" in special regard to the usage of SRS for hepatocellular carcinoma?
No. There is no systematic review available to date.

There has been one review that included most relevant papers published in recent years; it was published in 2015 by Meng and colleagues [24].

Herein, they discuss the emerging role of image-guided stereotactic radiosurgery (here named SBRT) as well as current indications, implementation, efficacy, and toxicities after the treatment. It was noted that image-guided stereotactic was a safe and effective therapeutic option for hepatocellular carcinoma lesions unsuitable for standard locoregional therapies, with acceptable local control rates and low treatment-related toxicity. The significant correlation between local control and higher doses and between LC and overall survival supports the clinical value of SBRT in these patients (f/m) [24].

Do we have plausible and valid data on the "level of evidence 2b" in special regard to the usage of SRS for hepatocellular carcinoma?

Yes, there are data describing in a prospective setting the effectiveness and safety of image-guided stereotactic radiosurgery for this indication. In the following paragraphs, we merely review the last two years, in terms of demonstration of feasibility, safety, and effectiveness of image-guided stereotactic radiosurgery in this specific scenario, even to date, besides Japan, few centers perform high-volume radiosurgery for hepatocellular carcinoma.

Lasley and colleagues reported on 38 patients (f/m) in 2015 [23]. Median follow-up was 33.3 months (2.8–61.1 months) for Child A group and 46.3 months (3.7–70.4 months) for Child B patients. Local control at 6 months was 92 % for Child A group and 93 % for Child B group. Kaplan–Meier estimated 2- and 3-year local control was 91 % for Child A group and 82 % for Child B group ($p = .61$). Median overall survival was 44.8 months and 17.0 months for Child A group and Child B group. Estimated overall survival after 2- and 3-years was 72 % and 61 % for Child A group and 33 % and 26 % for Child B group ($p = .03$). Overall, Child A patients with ≥grade III liver toxicity had 4.59 (95 % confidence interval, 1.19–17.66) times greater risk of death than those without toxicity ($p = .0268$). No such correlation was seen for Child B patients; however, three of these Child B patients (f/m) underwent orthotopic liver transplant. Child B patients (f/m) experiencing grade III/IV liver toxicity had significantly higher mean liver dose, higher dose to one-third normal liver, and larger volumes of liver receiving doses <2.5 to 15 Gy in 2.5-Gy increments. For Child A patients, there was no critical liver dose or volume constraint correlated with toxicity [23].

Yamashita and colleagues published in 2015 their experiences [25]. A total of 79 patients (f/m) were treated. The median age was 73 years, 76 % were males, and their Child–Pugh scores were grades A (85 %) and B (11 %) before SBRT. The median biologically effective dose (alpha/beta = 10 Gy) was 96.3 Gy. The median follow-up time was 21.0 months for surviving patients. The 2-year overall survival, progression-free survival, and distant metastasis-free survival were 53 %, 40 %, and 76 %, respectively. Sex and serum PIVKA-II values were significant predictive factors for overall survival. Hypo- or hypervascular types, sex, and clinical stage were significant predictive factors for progression-free survival. The 2-year progression-free survival was 66 % in stage I versus 18 % in stages II–III. Multivariate analysis indicated that clinical stage was the only significant predictive factor for progression-free survival. No grade 3 toxicities in the acute, subacute, and chronic phases were observed. Progression-free survival after image-guided stereotactic radiosurgery for liver lesions was, here too, satisfactory, especially for stage I, even though these patients were unsuitable for resection and ablation. The authors concluded that image-guided stereotactic radiosurgery is safe and might be an alternative to resection and ablation [25].

The Florence team of Dr. Scorsetti and colleagues who had published an image-guided stereotactic radiosurgery for liver metastases did this hepatocellular carcinoma too [26]. Patients (f/m) with 1–3 inoperable lesions with diameter ≤6 cm were treated. According to lesions' size and liver function, two prescription

regimens were adopted: 48–75 Gy in three fractions and 36–60 Gy in six fractions. Image-guided stereotactic radiosurgery was delivered using the volumetric modulated arc therapy technique with flattening filter-free photon beams. The primary endpoints of this study were in-field local control and toxicity. Secondary endpoints were overall survival (OS) and progression-free survival. A total of 43 patients (f/m) with 63 lesions were treated. All patients had Child–Pugh class A or B disease. Thirty lesions (48 %) were treated with 48–75 Gy in three consecutive fractions, and 33 (52 %) received 36–60 Gy in six fractions. Median follow-up was 8 months (range, 3–43 months). Actuarial local control at 6, 12, and 24 months was 94.2 ± 3.3, 85.8 ± 5.5, and 64.4 ± 11.5 %, respectively. A biological equivalent dose (BED) >100 Gy and GTV size were significant prognostic factors for local control in univariate analysis ($p<0.001$ and $p<0.02$). Median overall survival was 18.0 ± 5.8 months. Actuarial overall survival at 6, 12, and 24 months was 91.1 ± 4.9, 77.9 ± 8.2, and 45.3 ± 14.0 %, respectively. Univariate analysis showed that OS is correlated with local control ($p<0.04$), BED >100 ($p<0.05$), and cumulative gross tumor volume GTV <5 cm ($p<0.04$). Median progression-free survival was 8 months, with a 1-year progression-free survival rate of 41 %. A significant (≥ grade 3) toxicity was observed in seven patients (16 %) 2–6 months after the completion of the treatment. No classic radiation-induced liver disease was observed. The authors concluded that the noninvasive therapy is a safe and effective therapeutic option for lesions unsuitable to standard locoregional therapies, with acceptable local control rates and low treatment-related toxicity. The significant correlation between local control and higher doses and between local control and overall survival supports the clinical value of this treatment method [26].

Sanuki and colleagues reported with the special regard to toxicity of image-guided stereotactic radiosurgery in patients (f/m) with hepatocellular carcinoma in 2015 [27].

The study included 194 cases that were treated with image-guided stereotactic radiosurgery. Among them, patients followed up for more than 6 months were eligible. Laboratory results and Child–Pugh scores were obtained before treatment and at monthly follow-up visits. A total of 108 cases were evaluated with a median follow-up of 28.2 months. Fatal hepatic failure within 12 months occurred in eight patients (4 %). On univariate analysis, grade 3 or more elevated transaminases, Child–Pugh scores of 8 or more, and/or grade 3 or more decreased platelet count significantly predicted fatal hepatic failure within 12 months. Combinations of these factors (i.e., having at least one criterion) also predicted fatal hepatic failure within 12 months (16 % with criteria versus 1 % without criteria). Two-year overall survival rates for patients with and without radiation-induced liver disease was 64.9 % and 83.8 % ($p<0.001$), respectively. The authors concluded that the identified three criteria that affected overall survival in patients (f/m) may help to promote a better selection in future prospective trials [27].

Kimura and colleagues communicated their experiences in 2015 [28]. Overall, 65 patients with 74 lesions (median tumor size, 16 mm) were enrolled. They were treated at the prescribed dose of 48 Gy in four fractions at the isocenter. Child–Turcotte–Pugh (CTP) scoring was used to classify 56 and nine patients into classes A and B,

respectively. Local progression was defined as irradiated tumor growth on a dynamic computed tomography follow-up. The median follow-up period was 26 months. Tumor responses were assessed according to the modified Response Evaluation Criteria in Solid Tumors. Treatment-related toxicities were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0. The 2-year overall survival, progression-free survival, and local control rates were 76.0 % (95 % confidence interval [CI], 65.4–86.7 %), 40.0 % (95 % CI, 27.6–52.3 %), and 100 % (95 % CI, 100 %), respectively. At 6–12 months after SBRT, grade 3 or higher toxicities were observed in 15 (23.1 %) patients. The incidence of grade 3 or higher toxicities was higher in CTP class B than in class A ($p=0.0127$). The conclusion of the authors was that the method is "effective and relatively safe for patients with small hepatocellular carcinoma who were ineligible for resection or ablation therapies" [28].

Another team reported on image-guided stereotactic radiosurgery as an ablative treatment for inoperable hepatocellular carcinoma [29]. A total of 77 consecutive patients were treated for 97 liver-confined lesions. A total dose of 45 Gy in 3 fractions was prescribed to the 80 % isodose line. The median follow-up was 12 months. The median tumor diameter was 2.4 cm. The local control rate was 99 % at 1 and 2 years. The 1- and 2-year overall survival was 81.8 % and 56.6 %, respectively. The median time to progression was 9 months (0–38). The rate of hepatic toxicity was 7.7 % [1.6–13.7], 14.9 % [5.7–23.2], and 23.1 % [9.9–34.3] at 6 months, 1 year, and 2 years, respectively. In multivariate analysis, female gender (HR, 7.87 [3.14–19.69]), a Child B–C stage (HR, 3.71 [1.41–9.76]), a sum of all lesion diameters 2 cm (HR, 7.48 [2.09–26.83]), and a previous treatment (HR, 0.10 [0.01–0.79]) were independent prognostic factors of overall survival. The conclusion of the authors was that image-guided stereotactic radiosurgery (here named SBRT) leads to high local control rates for inoperable hepatocellular carcinomas and that "it should be considered when an ablative treatment is indicated in Child A patients" [29].

In a study in which patients (f/m) received image-guided stereotactic radiosurgery after incomplete transarterial chemoembolization, Zhong and colleagues reported on outcome data in 2014 [30]. A total of 72 patients with large hepatocellular carcinomas lesions were treated. The median total dose of 35.6 Gy was delivered over 12–14 days with a fractional dose of 2.6–3.0 Gy and 6 fractions per week. The patients were classified into those with tumor encapsulation (group A, $n=33$) and those without tumor encapsulation (group B, $n=39$). The clinical outcomes of tumor response, overall cumulative survival, and toxicities/complications were retrospectively analyzed. Among the 72 patients, complete remission was achieved in 6 (8.3 %) and partial remission in 51 (70.8 %), respectively, within a median follow-up of 18 months. The objective response rate was 79.1 %. The overall cumulative 1-, 3-, and 5-year survival rates and the median survival time were 38, 12, and 3 % and 12.2 months, respectively. In group A, the overall cumulative 1-, 3-, and 5-year survival rates were 56, 21, and 6 %, respectively, with a median survival of 19 months; in group B, the overall cumulative 1-, 3-, and 5-year survival rates were 23, 4, and 0 %, respectively, with a median survival of 10.8 months ($p=0.023$). The treatment was well tolerated, with no severe radiation-induced liver disease and no reported > grade 3 toxicity. In conclusion, it

"was shown to be a safe and effective treatment option for patients with unresectable huge hepatocellular carcinomas" [30].

A large study was recently published by Takeda and colleagues [31]. A total of 221 cases underwent image-guided stereotactic radiosurgery. Among them, patients (f/m) with untreated solitary lesions, treated only with this method preceded by transarterial chemoembolization, were eligible. Based on baseline liver function and liver volume receiving ≥20 Gy, 35–40 Gy in five fractions was prescribed to the planning target volume surface. Sixty-three patients were eligible, with a median follow-up duration of 31.1 (range, 12.0–88.1) months. No patients were lost to follow-up. Twenty patients were treated with only SABR. In 43 patients treated with SABR preceded by transarterial chemoembolization, accumulation of lipiodol in the lesion remained complete in five, a partial defect in 38 on pretreatment computed tomography. The 1-, 2-, and 3-year local control rates were 100 %, 95 %, and 92 %, respectively; the intrahepatic recurrence-free rates were 76 %, 55 %, and 36 %, respectively; and the overall survival rates were 100 %, 87 %, and 73 %, respectively. Grade 3 laboratory toxicities in the acute, subacute, and chronic phases were observed in 10, 9, and 13 patients, respectively, and ascites occurred in one patient. The author team concluded that "local control and overall survival… were excellent despite the candidates being unfit for resection and ablation [31]. The method "is safe and might be an alternative to resection and ablation" [31].

With focus on re-radiation, Lo and colleagues published a paper in 2014 [32].

A total of 14 patients (f/m) with local recurrence (18 lesions) after liver radiosurgery received repeated radiotherapy CyberKnife SRS. No patients experienced radiation-induced liver disease after the first treatment course. The median first dose was 41 Gy (range, 34–60 Gy); the median second dose, 40 Gy (range, 25–50 Gy); and the median interval, 12.9 months. Local recurrence was divided into in-field recurrence and outfield recurrence. Objective responses were observed in 11 tumors (61.1 %), including five tumors (27.8 %) with complete responses. Intrahepatic outfield failure was the main cause of treatment failure (7 of 14 patients). In-field failure had developed in 1 of 18 tumors (5.6 %), resulting in a 2-year in-field failure-free rate of 88.2 %. The median time to progression was 14.0 months, with 1- and 2-year progression-free survival rates of 68.6 % and 42.9 %, respectively. One- and 2-year overall survival rates were 76 % and 59.1 %, respectively. Of the 14 patients, one developed radiation-induced liver disease and three showed progression of the Child–Turcotte–Pugh class after the second SABR course. Other toxicities were generally mild and tolerable. Obviously, retreatment by using image-guided stereotactic radiosurgery again "is feasible with acceptable toxicity" [32].

Culleton and colleagues reported in 2014 on a prospective trial in patients (f/m) with Child–Pugh B or C hepatocellular carcinoma [33]. All patients (f/m) with Child–Pugh B7 or B8 unresectable lesions <10 cm were selected. A total of 29 patients with Child–Pugh B/C lesions were treated with a median dose 30 Gy in 6 fractions. The majority had Child–Pugh B7 liver function (69 %) and portal vein tumor thrombosis (76 %). The median survival was 7.9 months (95 % CI, 2.8–15.1). Survival was significantly better in patients with Child–Pugh = B7 and AFP less that 4491 ng/mL. Of 16 evaluable patients, 63 % had a decline in Child–Pugh score by

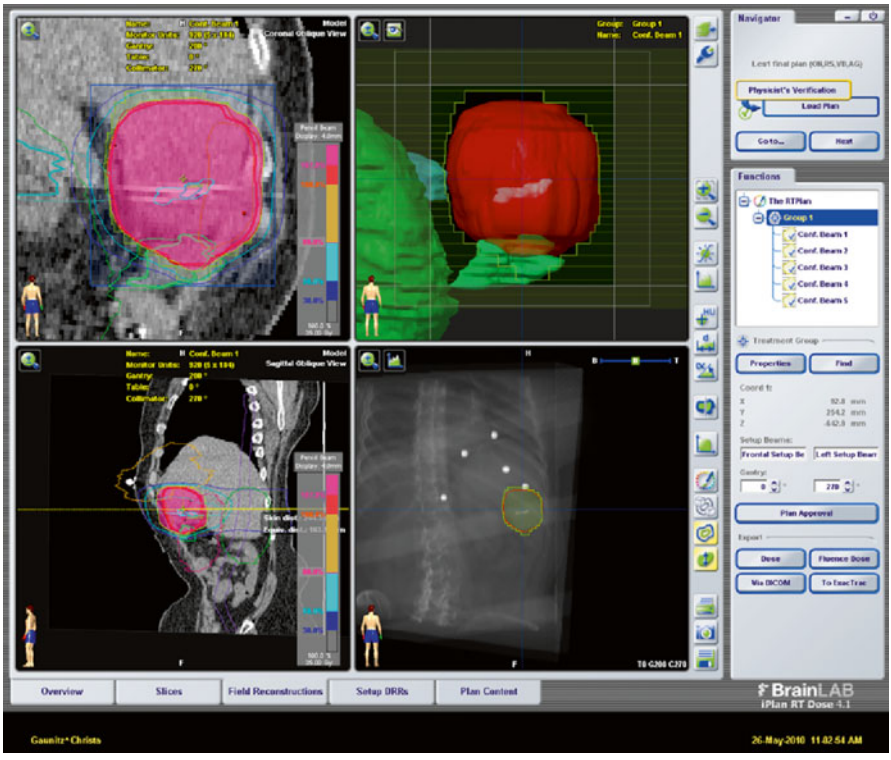
≥2 points at 3 months. They concluded that this method is a treatment option for patients (f/m) "with small hepatocellular carcinomas and modestly impaired liver function" [33].

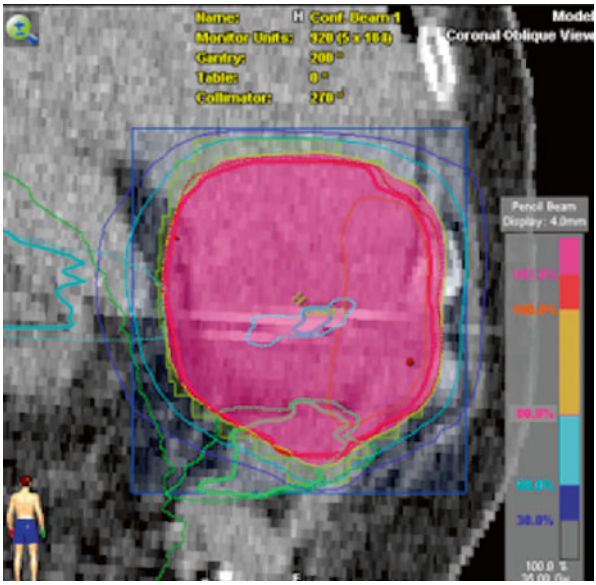
Summary

In the past decade, there has been a real increase of publications, conference contributions, and understanding of image-guided stereotactic radiosurgery for liver lesions. Cancer with oligometastases to the liver could be controlled by radiosurgery in a safe and effective way. Increasing number of patients (f/m) in this condition will undergo stereotactic techniques because they are not operable. Data outcome will convince even skepticism.

This is not true for hepatocellular carcinoma; in spite of data showed above, the clinical routine in large- and middle-sized medical centers is not reflecting the available evidence of grade 2b and less.

Image-guided stereotactic radiosurgery, in case we take evidence showed above seriously, is demonstrating the safety and effectiveness of a good and new method that is essentially noninvasive and cost-effective.

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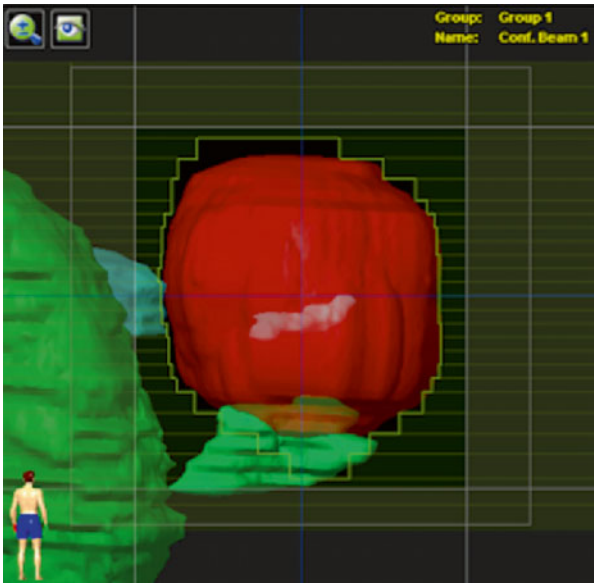
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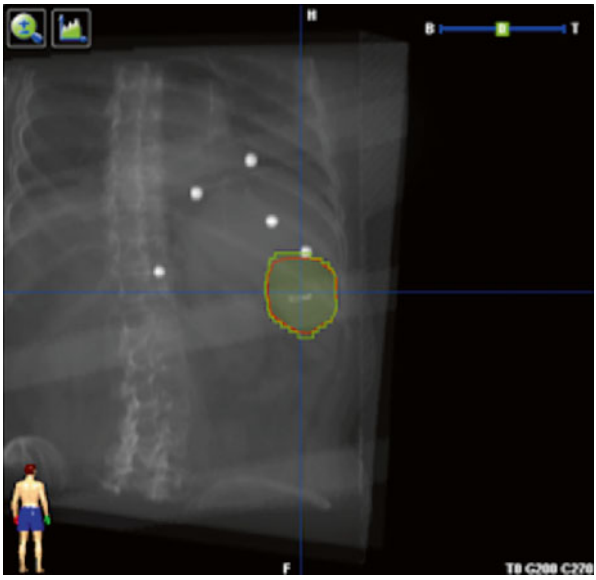
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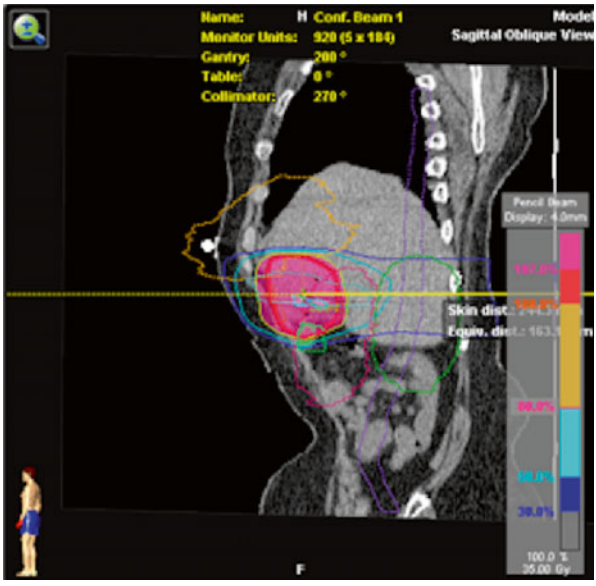
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Stereotactic Radiosurgery for Early-Stage Prostate Cancer

14

Abstract

Cancer of the prostate gland has been the most common cancer in men in the Western hemisphere. Not only because of its high incidence or comprehensive treatment costs that transgress each year frontiers but because of its potential mortality, prostate cancer is today a large-scale challenge to the medicine and healthcare systems.

Globally, prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in men.

Stereotactic radiosurgery seems to offer a safe and effective alternative method in relation to surgery, conventional external beam radiotherapy, and brachytherapy.

Data on non-invasive image-guided stereotactic radiosurgery for prostate cancer in its early stages are available. The method is feasible and cost-effective. It could be executed in outpatient setting and the treatment time extremely shorter than all other radiotherapeutic procedures.

Large-scale prospective controlled trials are in need.

Background

Cancer of the prostate gland has been the most common cancer in men in the Western hemisphere [1]. Not only because of its high incidence or comprehensive treatment costs that transgress each year frontiers but because of its potential mortality, prostate cancer is today a large-scale challenge to the medicine and healthcare systems.

Globally, prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males [2].

H. Badakhshi, *Image-Guided Stereotactic Radiosurgery*,
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There were around 47,300 new cases of prostate cancer in the UK in 2013; that's 130 cases diagnosed every day [3]. Prostate cancer is the second most common cancer in the UK (2013). Prostate cancer accounts for 13 % of all new cases in the UK (2013).

In males in the UK, prostate cancer is the most common cancer, with around 47,300 cases diagnosed in 2013. More than half (54 %) of prostate cancer cases in the UK each year are diagnosed in males aged 70 and over (2011–2013). Over the last decade, prostate cancer incidence rates have increased by less than a tenth (5 %) in the UK, which is similar in continental Europe too [3]. In Europe, around 417,000 new cases of prostate cancer were estimated to have been diagnosed in 2012. The UK incidence rate is the 17th highest in Europe. Worldwide, more than 1.11 million men were estimated to have been diagnosed with prostate cancer in 2012, with incidence rates varying across the world [1, 4]. One in eight men will be diagnosed with prostate cancer during their lifetime [1, 5].

Prostate cancer is the second most common cause of cancer death in UK men, after lung cancer. In 2012 in the UK, around 10,800 men died from prostate cancer; that's 30 every day. Almost three quarters of prostate cancer deaths occur in men aged 75 and over.

Prostate cancer death rates peaked in the early 1990s and have since fallen by around a fifth [3].

In Europe, around 92,300 men were estimated to have died from prostate cancer in 2012. The UK mortality rate is the 15th highest in Europe [3, 4].

Worldwide, more than 307,000 men were estimated to have died from prostate cancer in 2012, with mortality rates varying across the world [1, 4].

Therapeutic Options for Early-Stage Prostate Cancer

Two main competitive procedures for the clinical management of patients (f/m) with early-stage prostate cancer are provided to date: invasive surgical procedures and non-invasive radiation therapy procedures [2]. Both procedures are supported by a large body of scientific evidence [6–8].

A recent meta-analysis of 36 controlled randomized trials comparing non-invasive radiotherapy with invasive radical prostatectomy revealed that "there is no strong evidence to support one therapy over another" as conventional radiotherapy, brachytherapy, and radical prostatectomy, all "can all be considered as effective monotherapies for localised disease" and that with conventional radiotherapy also effective for postoperative management [2].

This systematic review of randomized controlled trials (RCTs) of radiotherapy and other non-pharmacological management options for localized prostate cancer revealed after the search of 13 databases that contained information till 2014. RCTs comparing radiotherapy (brachytherapy (BT) or external beam radiotherapy (EBRT)) to other management options, i.e., radical prostatectomy (RP), active surveillance, watchful waiting, high-intensity focused ultrasound (HIFU), or cryotherapy, each alone or in combination, e.g., with adjuvant hormone therapy (HT), were

included in the analysis. A total of 36 randomized controlled trials (134 references) were included. EBRT, BT, and RP were found to be effective in the management of localized prostate cancer. While higher doses of EBRT seem to be related to favorable survival-related outcomes, they might, depending on technique, involve more adverse events, e.g., gastrointestinal and genitourinary toxicity. Combining EBRT with hormone therapy shows a statistically significant advantage regarding overall survival when compared to EBRT alone (relative risk, 1.21; 95 % confidence interval, 1.12–1.30). Aside from mixed findings regarding urinary function, BT and radical prostatectomy were comparable in terms of quality of life and biochemical progression-free survival while favoring BT regarding patient satisfaction and sexual function. There might be advantages of EBRT (with/without HT) compared to cryoablation (with/without HT). No studies on HIFU were identified. Based on this systematic review, there is "no strong evidence to support one therapy over another as EBRT, BT and RP can all be considered as effective monotherapies for localised disease with EBRT also effective for post-operative management. All treatments have unique adverse events profiles" [2].

The authors comment that "these *will strengthen the evidence base for newer technologies*, help reinforce current consensus guidelines and establish greater standardization across practices" [2].

One of these *new technologies* could be image-guided stereotactic radiosurgery, as we show below.

What Would Be the Rationale for the Performance of Radiosurgery for the Early-Stage Prostate Cancer?

Dr. Kupelian, a well-known researcher in the filed of prostate cancer, described with his coauthors the rationale for stereotactic radiosurgery for early-stage prostate cancer [9].

One argument would be the radiobiology. The authors assume that there is a high intratumoral dose exposure with radiosurgery (here named SBRT) which might optimize antitumor mechanisms by stimulating local and direct immune responses in the local microenvironment and antigen-presenting cells. These high doses could induce "changes in the tumor stroma in vitro through activation of vascular endothelial cell apoptosis pathways. In addition to specific biochemical regulatory pathways, pathologic observations after radiosurgery also demonstrate greater obliteration of abnormal vasculature with high single doses, such as those used for managing arteriovenous malformations" [9]. As we stated in the chapter of this book dealing with arteriovenous malformations.

There are indications that direct immune changes, through the stimulation of toll-like receptors on antigen-presenting cells and of tumor cell characteristics, expose them more vulnerable to T-cell killing via therapeutic means as they are, e.g., vaccines. Higher doses per fraction, as compared to the conventional 2-Gy, can also prime T cells in lymphatic tissue, leading to more significant CD8+ T-cell-dependent disease control. That could be accompanied by the induction and expression of effector cytokines and other inflammatory mediators. Such a pro-inflammatory environment laden with cytokine production can increase permeability of local vasculature and stimulate antigen-presenting cells to mature more effectively [9].

The authors speculate that there may be an "*abscopal effect*, co-stimulatory molecules, cellular adhesion molecules, and death receptors to augment anticancer immune responses. As a result of tumor-specific T-cell responses and antigen-specific cellular immunity, innovative radiation dose–delivery strategies can be combined with modern immunotherapeutic interventions in the clinic" [9].

In regard to clinical experiences with any kind of hypofractionated radiotherapy, including radiosurgery, the authors demonstrate the recent outcome data, in order to reason for radiosurgery as a rational method that is safe, effective, and indeed non-invasive comparing to invasive surgical procedures.

It is a matter of fact that altered fractionation than the 2-Gy-dose schemes, e.g., hypofractionation, for early-stage prostate cancer has its clinical roots in high-dose rate brachytherapy [10] and external radiation therapy [11, 12], resulting in acceptable toxicity profiles and durable biochemical control rates with moderately hypofractionated schedules.

This has induced disputes questioning whether moderately hypofractionated schedules should be favored over traditional schedules in the treatment of localized prostate cancers if they are either equivalent or superior to conventional schedules [9–11, 13–22].

One interesting part of the discussion was to determine if the basal hypothesis or the primary premise is correct at all [11, 12, 15, 23–25].

These productive discussions result in a strategy shift toward more trials and experimental settings for altered fractionation schemes [26, 27]. Different approaches within the realm of hypofractionated radiotherapy came up [27–29].

A pooled analysis of 1100 patients from prospective phase II trials using radiosurgery techniques demonstrated a 95 % 5-year biochemical relapse-free survival rate for low-risk patients, with excellent long-term patient-reported outcomes with respect to urinary and bowel function [30, 31].

King and colleagues published this abovementioned pooled analysis in 2013 [30].

A total of 1100 patients with early-stage prostate cancer were enrolled in separate prospective phase 2 clinical trials of SBRT from eight institutions during 2003–2011 and pooled for analysis. SBRT using the CyberKnife delivered a median dose of 36.25 Gy in 4–5 fractions. Patients were low risk (58 %), intermediate risk (30 %), and high risk (11 %). A short course of androgen deprivation therapy (ADT) was given to 14 %. PSA relapse defined as a rise larger than 2 ng/ml above nadir was analyzed with the Kaplan–Meier method. With a median follow-up of 36 months, there were 49 patients with PSA failure (4.5 %), nine of whom were subsequently determined to be benign PSA bounces. The 5-year biochemical relapse-free survival rate was 93 % for all patients; 95 %, 83 %, and 78 % for Gleason score 6, 7, and 8, respectively ($p = 0.001$); and 95 %, 84 %, and 81 % for low-, intermediate-, and high-risk patients, respectively ($p < 0.001$). No differences were observed with ADT ($p = 0.71$) or as a function of total dose ($p = 0.17$). A PSA bounce of more than 0.2 ng/ml was noted among 16 % of patients. For 135 patients possessing a minimum of 5 years of follow-up, the 5-year biochemical relapse-free survival rate for

low- and intermediate-risk patients was 99 % and 93 %, respectively. Authors closed their study with statement that "PSA relapse-free survival rates after SBRT compare favorably with other definitive treatments for low and intermediate risk patients. The current evidence supports consideration of SBRT among the therapeutic options for these patients" [30].

On the basis of the Stanford experience, recent fractionation regimens used are typically in the range of 35–40 Gy in 5 fractions with image-guided radiation therapy delivered every other day. When the linear quadratic model is applied and one assumes an alpha/beta ratio of two for prostate cancer, the biologically equivalent dose for a dose of 40 Gy delivered in 5 fractions (8 Gy per fraction) is 200 Gy, a substantially higher biologically equivalent dose than with conventionally fractionated schedules and similar to BED levels achieved with brachytherapy [9]. The limit of dose per fraction escalation appears to have been reached: as reported by Boike and colleagues, in the lone study that tested doses up to 50 Gy delivered in 5 fractions, toxicity (particularly rectal) was excessive, clearly demonstrating that SBRT with current techniques should be kept lower than 50 Gy in 5 fractions [32].

While the rationale seemed to be settled, it would be legitimate to ask about the patient's (f/m) preferences.

A meta-analysis was focused on decision-making processes in patients (f/m) with early-stage prostate cancer [33]. The paper was published in *CA: A Cancer Journal for Clinicians* that is the journal with highest impact factor to date and ever.

The role of decision aids in facilitating these decisions is unknown. Teams of two reviewers independently identified, selected, and abstracted data from 14 eligible trials ($n = 3377$ men), of which ten were conducted in North America. Of these, 11 trials compared decision aids with usual care, and three trials compared decision aids with other decision aids. In conclusion, "scant evidence at high risk of bias suggests the variable impact of existing decision aids on a limited set of decisional processes and outcomes. Because current decision aids provide information but do not directly facilitate shared decision making, subsequent efforts would benefit from user-centered design of decision aids that promote shared decision making" [33].

Radiosurgery (SBRT, SABR) not only requires much less of a time commitment by the patients (f/m), but it also incurs substantially less cost to the healthcare delivery system, which makes it an attractive approach in the USA and abroad [9].

Dr. Kupelian and colleagues argue to the end that "cost-effectiveness analyses demonstrated that SBRT was the least expensive option in terms of cost; payer costs were approximately two thirds those of IMRT and one third those of proton therapy. A similar magnitude of difference has been reported in terms of societal costs, including work productivity" [9].

Short-term treatment, so Dr. Kupelian and colleagues, "would be attractive not only to patients, who would return to work, family obligations, and general life commitments sooner, but also for health care providers such as busy radiation therapy departments in countries with limited access to state-of-the-art radiation therapy equipment. Long waiting lists, which invariably include prostate cancer patients, can be averted by use of such a technique" [9].

And, simultaneously, there are principles at stake. A recent meta-analysis published by Wallis and colleagues showed different aspects of the clinics and complex approach options [8].

The meta-analysis revealed 19 studies and data of 118 830 patients (f/m) were pooled. Most studies assessed patients treated with external beam radiotherapy, although some included those treated with brachytherapy separately or with the external beam radiation therapy group. The risk of overall (ten studies, aHR, 1.63; 95 % confidence interval, 1.54–1.73, $p<0.00001$) and prostate cancer-specific (15 studies, aHR, 2.08; 95 % confidence interval, 1.76–2.47, $p<0.00001$) mortality was higher for patients treated with radiotherapy compared with those treated with surgery. Subgroup analyses by risk group, radiation regimen, time period, and follow-up length did not alter the direction of results. The authors concluded that "radiotherapy for prostate cancer is associated with an increased risk of overall and prostate cancer-specific mortality compared with surgery based on observational data with low to moderate risk of bias. These data, combined with the forthcoming randomized data, may aid clinical decision making" [8]. It is relevant to state that all reviewed available studies used have a potential for bias due to their observational design [8].

Radiotherapeutic Options for Early-Stage Prostate Cancer

A large body of publications in regard to the radiotherapy for patients (f/m) with early-stage prostate cancer [34]. Different aspects of radiotherapy including tumor control, dose regimen, toxicity, and combination with hormonal manipulation have been enlightened [6, 7, 35, 36].

Prognosis and risk-related aspects including weight [37, 38] and life expectancy were studied [39–48]. It is true for mortality issues have been studies extensively [35, 36, 49–51].

The combination of radiotherapy and hormonal therapy including sequence, time, and interruption has also been investigated [42, 50, 52, 53].

Quality of life has been the focus of different study types and systematic reviews [54].

Hypothesis of cancer risk was the object of extensive studies and reviews that reveal some insights into the dynamics of this disease [55–59].

Besides conventional radiotherapy that is globally widespread and well studied [60, 61], the notion of high dose, hypofractionated and specially of image-guided stereotactic radiosurgery came in recent years into the focus of scientific endeavors.

A differential approach was selected to face the challenge of prostate cancer, notably early-stage cancer.

The peculiar standing of hypofractionated radiotherapy and high-precision radiosurgery is the matter of ongoing disputes and discussions.

Sanchez-Gomez and colleagues published results of a meta-analysis in 2015 in which they compared hypofractionated radiation therapy versus conventional

radiation therapy in prostate cancer. The hypothesis was that "new therapeutic alternatives can improve the safety and efficacy of prostate cancer treatment" [62].

The systematic review of the literature through searches on PubMed, Cochrane Library, CRD, ClinicalTrials, and EuroScan, collecting indicators of safety and efficacy. They included two systematic reviews and a clinical trial. In terms of efficacy, there is considerable heterogeneity among the studies, and no conclusive results were found concerning the superiority of the hypofractionated option over the normal fractionated option. In terms of safety, there were no significant differences in the onset of acute genitourinary complications between the two treatments. However, one of the reviews found more acute gastrointestinal complications in patients treated with hypofractionated radiation therapy. There were no significant differences in long-term complications based on the type of radiation therapy used, although the studies did have limitations. The result was that to date "there are no conclusive results that show that hypofractionated radiation therapy is more effective or safer than normal fractionated radiation therapy in the treatment of localized prostate cancer" [62].

A very recent publication by Sharieff and colleagues was communicated in 2016; it was focused on the technique, resources, and costs of image-guided stereotactic radiosurgery (here named SBRT) in patients (f/m) with prostate cancer [63]. They write that "robotic system has been used for stereotactic body radiotherapy of prostate cancer. Arc-based and fixed-gantry systems are used for hypofractionated regimens (10–20 fractions) and the standard regimen (39 fractions); they may also be used to deliver ablative therapy" [63]. They performed sensitivity analyses to examine the effects of daily hours of operation and in-room treatment delivery times on cost per patient. In addition, we estimated the budget impact when a robotic system is preferred over an arc-based or fixed-gantry system. Costs of SBRT were $6333/patient (robotic), $4368/patient (arc based), and $4443/patient (fixed gantry). When daily hours of operation were varied, the cost of robotic SBRT varied from $9324/patient (2 h daily) to $5250/patient (10 h daily). This was comparable to the costs of 39 fraction standard regimen which were $5935/patient (arc based) and $7992/patient (fixed gantry). In settings of moderate to high patient volume, robotic SBRT is cost-effective compared to the standard regimen. They stated that "If SBRT can be delivered with equivalent efficacy and safety, the arc-based system would be the most cost effective system" [63]. That is important in so far that all notions mentioned above will determine outcome of disease management the next decades.

Availability and Quality of Scientific Evidence

A sufficient number of publications using image-guided stereotactic radiosurgery for patients with liver oligometastases are available. These publications could be used to have a fair patient-centered and objectively differential approach in terms of recommending and discussing innovative treatment options with your patients that are safe, non-invasive, and effective and that lie beyond the traditional method of the

"standard" method, surgery. This cannot mean to influence patient's preferences, but to have an informed consent based on best available data of recent years.

Maximally invasive or minimally invasive surgery has been for more than two decades the new "standard" against which the safety and effectiveness of any new treatment method should have been measured.

Below you can see the degree of validity and quality of available data for upfront and postoperative or hybrid usage of SRS formulated as questions.

Do We Have Plausible and Valid Data on the "Level of Evidence 1a" in Special Regard to the Usage of SRS for Prostate Cancer?

No, when we think of a proper and fully published meta-analysis of controlled randomized trials (CRT) with prospective design.

Do We Have Plausible and Valid Data on the "Level of Evidence 1b" in Special Regard to the Usage of SRS for Prostate Cancer?

No, when we think of a proper and fully published controlled randomized trials (CRT) with prospective design.

Do We Have Plausible and Valid Data on the "Level of Evidence 2a" in Special Regard to the Usage of SRS for Prostate Cancer?

No, when we think of a proper and fully published meta-analysis of controlled randomized trials (CRT) with prospective design.

However, there are some recently published papers which attempt to provide an overview on a body of highly heterogeneous study types.

A recent "meta-analysis" of very heterogeneous study types accessed the status of image-guided stereotactic radiosurgery in the management of patients (f/m) with early-stage prostate cancer [64].

Stereotactic radiosurgery for early-stage prostate cancer allows overall treatment times to be reduced to as little as 1 week while maintaining a non-invasive approach. A total of 14 phase I–II trials and retrospective studies using radiosurgery. Three studies were identified which addressed cost. Dose fractionation, radiotherapy procedures, biochemical progression-free survival, toxicity, cost, and quality of life were critically appraised. A total of 1472 patients were examined. Median follow-up ranged from 11 to 60 months. The most common dose fractionation was 35–36.25 Gy in 5 fractions, used in nine out of 14 studies. Ten of 14 studies used CyberKnife. The overall biochemical progression-free survival ranged 81–100 %. Acute grade 2 urinary and rectal toxicities were reported in 5–42 % and 0–27 % of patients, respectively. Acute grade 3 or more urinary and rectal toxicities were 0.5 % and 0 %, respectively. Late grade 2 urinary toxicity was reported in 0–29 % of patients, while 1.3 % had a late grade 3 urinary toxicity. There were no late grade 4 urinary toxicities seen. Late grade 2 rectal toxicity was reported in 0–11 %, while 0.5 % had a late grade 3 rectal toxicity. Late grade 4 rectal toxicity was reported in 0.2 % of patients (f/m) [64]. They concluded that image-guided stereotactic radiosurgery (here called SBRT) "remains a promising new treatment for the future, with high local control rates and toxicity rates comparable with fractionated radiotherapy. The duration of

treatment is significantly shorter and significantly cheaper" and that "research is required to refine optimal patient selection, dose constraints and delivery setup" [64].

Zaorsky and colleagues reflect on the "ideal" type of radiotherapy for patients (f/m) with prostate cancer [65]. This "meta-analysis" of biologically equivalent dose escalation included data of 12,756 prostate cancer patients (f/m) from 55 studies published from 2003 to 2013 who were treated with non-dose-escalated conventionally fractionated external beam radiation therapy, dose-escalated conventionally fractionated external beam radiation therapy, hypofractionated radiotherapy, and high-dose rate brachytherapy with 5-year actuarial follow-up. Biologically equivalent dose was calculated based on the following formula: (nd[1 + d/(alpha/beta)]), where n is the number of fractions and d is dose per fraction, assuming an alpha/beta of 1.5 for prostate cancer and 3.0 for late toxicities. Mixed effects meta-regression models were used to estimate weighted linear relationships between BED and the observed percentages of patients experiencing late toxicities or 5-year freedom from biochemical failure. Data pooling revealed that increases of 10 Gy increments in biologically equivalent dose (at alpha/beta of 1.5) from 140 to 200 Gy were associated with 5-unit improvements in percent freedom from biochemical failure. Dose escalation of biologically equivalent dose above 200 Gy was not correlated with freedom from biochemical failure. Increasing biologically equivalent dose (at alpha/beta of 3.0) from 98 to 133 Gy was associated with increased gastrointestinal toxicity. Dose escalation above 133 Gy was not correlated with toxicity. The conclusion was that an "increase in the biologically equivalent dose to 200 Gy (at alpha/beta of 1.5) was associated with increased disease control. Doses above 200 Gy did not result in additional clinical benefit" [65].

Woo and colleagues focused on the appropriate patient-reported outcome for clinical trial design [66]. They state that "consensus regarding the appropriate patient-reported outcome endpoints for clinical trials evaluating radiation modalities for early stage prostate cancer is lacking" [66]. In order to structure clinical trial design, this study presents patient-reported outcome over a 36-month period following image-guided stereotactic radiosurgery (here named as SBRT) for early-stage prostate cancer. A total of 174 hormone-naive patients (f/m) were treated with 35–36.25 Gy with CyberKnife, delivered in five fractions. Patients (f/m) completed the validated Expanded Prostate Cancer Index Composite (EPIC)-26 questionnaire at baseline and all follow-ups. The proportion of patients developing a clinically significant decline in each EPIC domain score was determined. Per Radiation Therapy Oncology Group (RTOG) 0938, they tested the patients (f/m) who experienced a decline in EPIC urinary domain summary score of >2 points (unacceptable toxicity defined as ≥60 % of all patients reporting this degree of decline) and EPIC bowel domain summary score of >5 points (unacceptable toxicity defined as >55 % of all patients reporting this degree of decline) from baseline to 1 year. A total of 174 patients at a median age of 69 years received radiosurgery with a minimum follow-up of 36 months. The proportion of patients (f/m) reporting a clinically significant decline (MID for urinary/bowel are 5.5/4.4) in EPIC urinary/bowel domain scores was 34 %/30 % at 6 months, 40 %/32.2 % at 12 months, and 32.8 %/21.5 % at 36 months. The patients reporting a decrease in the EPIC urinary domain summary

score of >2 points were 43.2 % (CI, 33.7 %, 54.6 %) at 6 months, 51.6 % (CI, 43.4 %, 59.7 %) at 12 months, and 41.8 % (CI, 33.3 %, 50.6 %) at 36 months. The patients reporting a decrease in the EPIC bowel domain summary score of >5 points were 29.6 % (CI, 21.9 %, 39.3 %) at 6 months, 29 % (CI, 22 %, 36.8 %) at 12 months, and 22.4 % (CI, 15.7 %, 30.4 %) at 36 months. The authors concluded that, after treatment, clinically significant urinary symptoms are more common than bowel symptoms. Notably, between 12 and 36 months, they stated "the proportion of patients reporting a significant decrease in both EPIC urinary and bowel domain scores declined, suggesting a late improvement in these symptom domains" [66].

Do We Have Plausible and Valid Data on the "Level of Evidence 2a" in Special Regard to the Usage of SRS for Prostate Cancer?

Yes, there are data from well-designed studies that have been published recently.

Pontoriero and colleagues reported on their experiences with image-guided stereotactic radiosurgery in 2016 [67]. The primary endpoint was the evaluation of both acute and late toxicities; the secondary endpoint was the observation of prostate-specific antigen (PSA) nadir. Patients (f/m) with early-stage prostate cancer having prostate volume ≤90 cm^3 were enrolled in the present study. Patients were treated with radiosurgery alone, or in combined modality, radiosurgery with conventional radiotherapy was performed using a CyberKnife and fiducial tracking system. A total of 21 patients (f/m) were treated with image-guided stereotactic radiosurgery (38 Gy/4 fractions) and five for combined modality (9.5 Gy/2 fractions plus 46 Gy/23 fractions conventional radiotherapy). Androgen deprivation therapy was administered in 16 of the 26 patients. The median pretreatment PSA was 9.4 (range, 4.5–14.3) ng/mL. All patients completed the planned therapy. Acute grade 1 toxicity was observed in 18 patients, genitourinary in 12/26 patients and gastrointestinal in 6/26 patients. Acute grade 2 genitourinary toxicity was reported in 1/26 patients, and grade 2 gastrointestinal toxicity was observed in 2/26 patients. The median PSA nadir was 0.15 ng/mL. Late toxicities were observed in 5/26 patients: grade 1 genitourinary (3 of 26), grade 2 genitourinary (1 of 26), and grade 1 gastrointestinal (1 of 26). Median follow-up was 21.5 (range, 8–65) months. The authors concluded that image-guided stereotactic radiosurgery seems "stimulating" [67].

With regard to safety of stereotactic radiosurgery, Seymour and colleagues in 2015 contextualize dose–volume data and the temporal nature of toxicity with radiosurgery [68]. A total of 56 patients diagnosed with low- to intermediate-risk prostate cancer treated with radiosurgery alone were reviewed retrospectively. All patients received a total dose of 38 Gy in 4 fractions with a planning target volume expansion of 2 mm. Overall, acute, and late genitourinary toxicities were documented according to the Common Terminology Criteria for Adverse Events (version 4) and International Prostate Symptom Scores (IPSS). The median age at treatment was 68 years, and the median prostate volume was 45.5 mL, with a median baseline IPSS of 9.95. The median prescription isodose line was 68 %. The median clinical follow-up was 35.49 months. Acute grade 1, 2, and 3 genitourinary toxicities occurred in 41.1,

35.7, and 0% of patients. All acute genitourinary toxicities resolved except one patient with grade 2 toxicity that progressed to grade 3 late toxicity. No dose–volume relationships were associated with acute genitourinary grade 2+ toxicity. Late grade 1, 2, and 3 genitourinary toxicity occurred in 19.6%, 19.6%, and 3.6% of cases, respectively. Of the cases with late toxicities, 16.7% were persistent. Late grade 2+ genitourinary toxicity was associated with prostate volume more than 50 mL, lower homogeneity index, and urethral maximum point dose more than 47 Gy. The overall risk of any grade 2+ genitourinary toxicity was associated with baseline IPSS >7, prostate volume more than 50 mL, urethral volume receiving 44 Gy, and bladder volume receiving 19 Gy. The authors commented that radiosurgery for early-stage prostate cancer "appears well tolerated," with low-grade toxicity. "Urethral sparing should be used with a maximum point dose <47 Gy, volume receiving 120 Gy less than 50% of the prostate, and bladder volume receiving 19 Gy less than 15 mL in four fraction treatments" [68].

Summary

In the 5 years, there has been a real increase of publications, conference contributions, and understanding of image-guided stereotactic radiosurgery for early-stage prostate cancer. It could be controlled by radiosurgery in a safe and effective way. Increasing number of patients (f/m) in this condition will undergo stereotactic techniques because they are not operable.

Image-guided stereotactic radiosurgery, in case we take evidence showed above seriously, is demonstrating the safety and effectiveness of a good and new method that is essentially non-invasive and cost-effective.

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Future Perspectives

Clinical radiation therapy is safe and effective in the treatment of patients (f/m) with tumorous lesions, including cancer and its oligometastases.

The already racy expanding field of image-guided stereotactic radiosurgery will accelerate for many reasons.

First, the industrial drive of the first decade of the twenty-first century will induce more innovation with special regard to industry 4.0 with rising interest in robotics and more precision.

Second, an increasing number of patients (f/m) with cancer will survive after successful primary multimodal therapy; thus, cancer becomes, in a part of cases, a chronic condition rather than being deadly. Unavoidably, more and more patients (f/m) will develop metachronous metastases in the trajectory of their cancer disease. If oncologists of all disciplines would select patients (f/m) with limited metastatic capacity, thus in an oligometastatic state, in the right time and treat them with a clearly declared curative intention, that could lead to the improvement of survival outcome. Image-guided stereotactic radiosurgery, as a noninvasive, safe, and effective method will be a method of choice in these scenarios not only by physicians than but the patients (f/m) too.

Third, a concept as the base for therapeutic strategies, e.g., the oligometastatic concept, will be the epistemic ground for therapeutic technologies.

This dialectics of cure and palliation will change the face of cancer.

H. Badakhshi, *Image-Guided Stereotactic Radiosurgery*,
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Index

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