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Controversies in the Treatment of Skin Neoplasias

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Controversies in the Treatment of Skin Neoplasias

Volume Editors

M. Sternemann *Berlin*
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Cutaneous Lymphomas – Radiotherapeutic Strategies

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Most cutaneous lymphomas present with either a B or T cell phenotype and constitute approximately 5–10% of all non-Hodgkin's lymphomas. Large series documenting most appropriate therapy are rather sparse compared to the nodal variety, and in general, the majority of cutaneous lymphomas tend to have a relatively indolent course compared to nodal lymphomas. Clinical behavior and presentation are closely related to cell type and location, and these factors are especially relevant in the case of cutaneous B cell lymphoma (CBCL). Although the cutaneous T cell lymphomas may also present with significant clinical variety based on the specific cell type, location is less important. The T cell lymphomas are dominated by mycosis fungoides (MF), which is the most common of all of the cutaneous lymphomas. Thorough clinical evaluation and staging are critical to ensure that patients have lymphoma confined to the skin.

According to the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) data through 2001, the annual incidence of MF appears to have stabilized and is approximately 5 per 1,000,000 persons in the United States [1, 2]. CBCL, though, has an increasing incidence, with a current annual rate of approximately 3.5 per 1,000,000 [1, 2]. The distribution and anatomic location of the cutaneous lymphoma contribute to the prognostic outcome for patients with CBCL. The SEER data reveal the following distribution by skin site: head and neck 50%, trunk 19%, upper extremity 12%, lower extremity (legs) 11%, and multifocal 8% [1, 2]. Although a variety of therapeutic modalities have been incorporated and studied in the management of patients with cutaneous lymphomas, radiotherapy remains the most effective with respect to complete response for both the B and T cell varieties. The most likely mode of cellular demise is apoptosis, which is induced through the exposure of

cells to ionizing radiation. Additionally, alterations in the cutaneous microenvironment, mediated by the interaction of ionizing radiation with antigen-presenting dendritic cells and cellular signaling mechanisms, may also be implicated in the complicated cascade of effects leading to high response rates [3].

Cutaneous B Cell Lymphoma

Patients thought to have CBCL undergo clinical evaluation that includes biopsy of the lesion or lesions in question. Documentation of lesion location, size and color is of critical importance in establishing response to therapy and for comparison in follow-up evaluation. Digital photography is recommended, and this subsequently becomes part of the medical record. The diagnosis may be suspected on clinical grounds, but biopsy material is typically evaluated through a variety of techniques that include histopathologic interpretation, immunophenotyping and flow cytometry. Additional evaluation incorporating methods such as polymerase chain reaction may be used to determine clonality. The disease is then generally classified by either the EORTC or WHO pathologic classification scheme.

CBCL responds rapidly and successfully to radiotherapy. Such treatment may take the form of either externally administered superficial/orthovoltage energies or electrons. When electrons are used, appropriate 'bolus' material is applied over the surface of the skin lesion, so that it may receive the proper prescription dose. The depth of the bolus material will be decided based on the electron energy utilized. The selection of electron energy is based on the vertical depth of the cutaneous lesion. The greater the energy of the electron beam, the deeper the penetration into tissue and the less surface or skin sparing. These concepts are important in determining the most appropriate energy for a particular patient, so that as much normal tissue as possible may be spared while providing adequate coverage of the target lesion. The design of the actual field for a single lesion is straightforward. The lesion is identified, and typically a 2- to 3-cm margin is designed to incorporate disease that may not be clinically apparent, and also to allow appropriate coverage given the dose constriction within tissue of the electron beam. The total dose range used to control most CBCL histologies is thought to be 30–40 Gy in fractionation of 1.8–2.0 Gy per day, 5 days per week.

In 1991, Santucci et al. [4] published a series of 83 patients with CBCL, 59 of whom were managed with radiotherapy alone. All patients treated with radiation had a complete response, and lesions were treated with orthovoltage radiotherapy via 6–8 Gy per week in 2 fractions, to a total of 40 Gy. Irradiated fields were 20×20 cm with a minimum 3-cm margin. The authors felt that

radiotherapy was the most subjectively well-accepted therapeutic option and, of the various treatment modalities offered, radiotherapy produced the most impressive results with a median disease-free survival of 20 months and mean of 30.5 months.

Two years later, in 1993, Piccinno et al. [5] reported on 31 patients with CBCL staged as IE. This cohort was treated similarly with orthovoltage and the total dose ranged from 10 to 40 Gy, with a median of 30 Gy and a 0.5- to 1.0-cm margin. A total of 28 patients received definitive radiation and 3 patients received radiotherapy as an adjuvant treatment following surgery. The entire group had a minimum follow-up of 2 years, and the complete remission rate was 100%, with a recurrence-free survival rate of approximately 40% at 30 months following therapy. Of those who failed, 68% were salvaged.

In 1996, Rijlaarsdam et al. [6] provided information on a specific group of patients with follicle center cell histology. There were a total of 55 patients and 40 were managed with radiotherapy. All 40 patients treated with radiotherapy had a complete response. Thirty-one of the patients were treated with electrons, and the remainder with photons. The radiation dose ranged between 30 and 40 Gy and the field design included a minimum of 2-cm margin. There did not appear to be a dose response between 30 and 40 Gy. The 5-year survival rate was estimated at 89% with a 2-year disease-free survival of 85%.

In 1999, Kirova et al. [7] reported on the radiotherapeutic treatment of 25 patients with CBCL. The mean follow-up time for this series was 3.9 years from completion of therapy. Extended field therapy was offered to 6 patients and localized field therapy to the other 19. The effective electron energy at the patient was 4 MeV, and the extended field was offered at 2.5-Gy fractions, 4 times per week to a total of 30 Gy. The localized fields were treated with 45–100 kV with a 0.55 aluminum filter. The doses for this group of patients ranged between 30 and 40 Gy via 2-Gy fractions, 5 times per week. A clinical margin of 2.5 cm was utilized. The overall survival rate at 5 years was 73%, with a complete response rate of 92%. There were no relapses within the radiotherapy field and all cutaneous relapses were salvaged with further radiation. Disease-free survival at 1 and 5 years was 91 and 75%, respectively. Ninety-two percent (23/25) of the patients developed a grade I reaction related to therapy, 1 suffered a grade II, and 1 a grade III reaction. Hence, this series documented the efficacy of radiotherapy for both localized lesions and for those with greater disease extension requiring an extended field technique.

Also in 1999, Bekkenk et al. [8] published a series of 29 patients with CBCL managed in a variety of ways. Five patients with primary cutaneous follicular center-cell lymphoma were treated with radiotherapy alone. Patients were offered 4- to 10-MeV electrons to a dose to 40 Gy. One patient with primary cutaneous large B cell of the leg was treated with radiotherapy. The

complete response rate for the 6 patients was 100%. It should be noted that all of these patients had multifocal disease. For those with follicular center-cell lymphoma, the median disease-free survival time was almost 5 years. None of the patients relapsed at last follow-up.

Piccinno et al. [9], in 2003, published additional results on a series of 104 patients with follicle center cell histology. Patients were managed with orthovoltage therapy and doses ranged from 14 to 35 Gy. Results were available for 102 patients and the follow-up period was 65 months. All patients achieved a complete response. The 2-, 5- and 10-year relapse-free rates were 43, 23 and 18%, respectively. The 5-year actuarial overall survival rate was 97%.

Eich et al. [10] published a series in 2003 that evaluated 35 patients with primary CBCL. Of these, 29 received radiotherapy alone and 6 had radiotherapy as part of their initial management. Of those receiving radiotherapy alone, 18 qualified as having primary follicle center cell lymphoma, 5 with cutaneous immunocytoma, 3 with primary large B cell lymphoma of leg, and 3 provisional. All but 1 patient achieved a complete response. The only individual who did not achieve a complete response developed pneumonia and died following a dose of just 16 Gy. The majority of patients were treated with electron beams (5–12 MeV), with a median fraction size of 1.8 Gy and a median total dose of 45 Gy. Bolus was used when necessary and the prescription was specified to the 95% isodose line. Grade I reactions were noted in 86% of the cohort, with 14% suffering grade II. The 5-year relapse-free survival and overall survival rates were 50 and 75%, respectively. Multivariate analysis identified disseminated primary lesions in at least two noncontiguous anatomic sites and large B cell lymphoma of the legs as unfavorable prognostic factors.

Smith et al. [11] published a series of 34 patients with CBCL in 2004 and endeavored to reconcile some of the issues between the EORTC and WHO classification systems, in addition to reporting results of radiotherapy for this group. Biopsy material was adequate for classification in 32 patients. A total of 17 patients or 53% were classified as follicle center cell by EORTC and diffuse large cell by WHO (FCC/DLB). A total of 8 patients or 25% were classified as follicle center cell by EORTC and follicular by WHO (FCC/Fol). Four patients or 13% were classified as marginal zone according to EORTC and WHO (MZ/MZ) and 9% (3/32) were classified as large B cell of the leg by EORTC and diffuse large B cell by WHO criteria (Leg/DLB). The doses of radiotherapy ranged from 20 to 48 Gy, with a median dose of 40 Gy, and electrons were used for 26 of the patients. The median fraction size was 2.0 Gy, with a range of 1.0–3.5 Gy. Patients were treated daily and the complete response rate was 100%. The 5-year relapse-free survival ranged from 62 to 73% for the patients with FCC/DLB, FCC/Fol, and MZ/MZ, but was only 33% for those with Leg/DLB ($p = 0.6$). Five-year overall survival was 100% for those with

FCC/DLB, FCC/Fol, and MZ/MZ, but was 67% for those with Leg/DLB ($p = 0.07$). Overall survival at 5 years for the entire group was 96%, with a 5-year relapse-free survival of 55%. At 5 years, 21% of the patients had developed extracutaneous disease. Patients who received less than 36 Gy appeared to be at increased risk for local recurrence with a 5-year local recurrence-free survival of 50%, compared with 90% for those receiving ≥36 Gy (unadjusted HR 0.163; 95% CI 0.026–1.0; $p = 0.05$). Covariates including age, sex, race, duration of symptoms, history of pseudolymphoma, number and location of lesions, size of largest lesion, presence of documented B cell clonality, number of radiotherapy fields, and administration of chemotherapy did not correlate with risk for any recurrence or local recurrence at a significance level of $p < 0.05$.

Although other modalities such as chemotherapy and surgery have been evaluated in a variety of patients with CBCL, it appears that radiotherapy provides the highest complete response rates and reasonable relapse-free survival rates. Salvage with radiotherapy is also highly efficacious. The therapy is readily accessible, of extremely low toxicity, and given as an outpatient procedure. Despite a lack of substantial data, the role of immunotherapy is emerging and may be synergistic to the results of radiotherapy. We will need to await the results of such investigations, as it is not well documented at this juncture.

In summary, localized CBCL lesions may be successfully managed with localized (and possibly extended or total skin techniques if the clinical situation mandates) fields incorporating fraction sizes of 1.8–2.0 Gy per day, to a total of 36–40 Gy with a 2- to 3-cm margin around the clinically apparent disease. Electrons with bolus or superficial/orthovoltage beams may be utilized successfully. Patients should be advised of the possibility of recurrence within the field, and the more likely possibility of disease recurrence out of the field. Routine follow-up is of significant importance given the opportunity for successful salvage using radiotherapy in an effort toward maintaining disease-free status and quality of life (table 1).

Cutaneous T-Cell Lymphoma-Mycosis Fungoides

Cutaneous T cell lymphoma is more commonly encountered than CBCL. MF is a cutaneous T cell lymphoma, and is the most common type. Given that MF represents the majority of cutaneous T cell lymphomas, the radiotherapeutic discussion will focus on this specific entity. Many of the same strategies that apply to CBCL are applicable to MF, but given the diffuse nature of MF, radiotherapy has often included larger fields or total skin electron beam therapy (TSEBT). The technical concepts are similar for the treatment of MF as for CBCL from a localized radiotherapeutic field standpoint. Such fields are used

Table 1. Radiotherapy for CBCL

	Patients n	Dose Gy	Response %	Relapse rate %	5 years' RFS %	5 years' OS %
Santucci et al., 1991 [4]	83	40	100	–	<50[a]	–
Piccinno et al., 1993 [5]	31	10–40	100	68	41[a]	–
Rijlaarsdam et al., 1996 [6]	40	30–40	100	20	85[a]	89
Kirova et al., 1999 [7]	25	30–40	92	–	75	73
Eich et al., 2003 [10]	35	27–54[b]	100[b]	31	50	75
Piccinno et al., 2003 [9]	104	14–35	100	75	23	97
Smith et al., 2004 [11]	34	20–48	100	38	55	96

RFS = Relapse-free survival; OS = overall survival.

[a]2 years' relapse-free survival.

[b]One patient did not complete the prescribed course because of intercurrent illness and is not included in this analysis.

for localized lesions, and electrons with appropriate bolus or superficial/orthovoltage beams are acceptable. Clinical margins of 2–3 cm are recommended and fractionation may range from 1.5 to 2.5 Gy depending on the nature and goals of therapy. An exception to this is when the TSEBT technique is utilized, which is best delivered in lower fraction sizes such as 1.0 Gy per day extended over 6–9 weeks to a total of 30–36 Gy. The total dose for localized lesions is generally slightly less than that recommended for CBCL, and is in the range of 30–36 Gy based on the retrospective data that are available.

Local radiotherapy is effective and well tolerated in the treatment MF. Cotter et al. [12] reported excellent results for a group of 14 patients with 110 lesions with a minimum of 1 year of follow-up. The local recurrence rate was 42% for those managed with a dose of less than or equal to 10 Gy, 32% for those managed with a dose of 10–20 Gy, and 21% for those receiving 20–30 Gy. There were no local failures in those treated with doses greater than 30 Gy.

In 1998, Wilson et al. [13] published an experience reviewing the success of such therapy for 21 patients (30 lesions) with stage IA MF. The median follow-up was 36 months, with a median dose of 20 Gy, but 17 patients received >20 Gy. The complete response rate was 97%, and the disease-free survival at 5 and 10 years was 75 and 65%, respectively. Local control at the 5-year evaluation point was 75%.

Micaily et al. [14] noted an 86% 10-year disease-free survival for a group of 18 patients with single lesion MF who were treated with a dose of 30 Gy.

In 2003, an updated experience was presented at the American Society for Therapeutic Radiation Oncology annual meeting. This report was a joint effort

between Yale and Hamilton and provided data for 29 unilesional, 5 bilesional, and 5 trilesional cases. The mean dose was 22 Gy, with a mean total number of 15 fractions. The mean follow-up was 6 years (0.5–21) and the average age of the patient group was 50 years. The 10-year progression-free experience for all cutaneous locations was 72%, while the local progression-free experience was 83%. Local failure was related to doses less than 24 Gy ($p = 0.06$) [15]. The Hamilton experience was updated and further reported at the EORTC task force meeting in 2004. Thirty-one patients with single patch or plaque lesions (average surface area of 87 cm^2) and 16 patients with 2–4 lesions (average surface area of 114 cm^2) were managed with a mean dose of 21 Gy and treated with a mean of 14 fractions. Failures at any location were noted in 4/31 and 8/16, respectively. Half of the failures were in distant skin only. The other half were local failures related to lower total dose but not plaque versus patch presentation. The 10-year all disease-free experiences were 82% (unilesional MF) versus 17% (2–4 lesions MF; $p = 0.005$). The 10-year distant relapse-free experiences were 95 versus 50%, respectively ($p = 0.08$). It appears that unilesional MF is well managed with local radiotherapy, whereas a decision to treat 2–4 lesions with circumscribed radiation fields should be undertaken with the understanding that distant relapse in the skin is most likely within 5 years of initial therapy.

Several centers in North America have extensive experience with TSEBT. The most common method, in use today at Yale, is the original 'Stanford technique' that consists of six total skin treatment positions. Substantial clinical data have been published from Stanford, Yale and Hamilton with relatively good consistency supporting the use of TSEBT for various stages of MF. Stanford investigators determined that response rates were improved with higher doses of TSEBT, a finding consistent with dose-response information gained in those with localized MF (as described above) [16–18]. TSEBT is technically very challenging, and technical/dosimetry consensus guidelines were recently established through the EORTC (table 2) [19]. Although a variety of therapies are available and commonly used to manage patients with MF, TSEBT provides the best opportunity for complete response. Given the technically challenging aspects of the treatment, lack of experience at most centers, and logistical challenges associated with TSEBT, a variety of other modalities are generally offered first.

TSEBT was first described by Trump et al. [20] in 1953. In 1960, Stanford published the method for linear accelerator-based TSEBT [21] and Szur et al. [22] published initial clinical data reporting results of TSEBT with a four-field technique in 1962. The Stanford group subsequently published larger data sets, and it became clear that TSEBT was a meaningful therapy for patients with cutaneous lymphoma from both a palliative and disease-free survival standpoint [23].

Table 2. EORTC guidelines for TSEBT

Dose inhomogeneity in air at treatment distance should be <10% within vertical and lateral dimensions
80% isodose line should be ≥4 mm deep to the skin surface to ensure that the epidermis and dermis fall within the high-dose region
80% isodose line should receive a minimum total dose of 26 Gy
20% isodose line should be <20 mm from the skin surface to minimize dose to underlying structures
30–36 fractions should be used to minimize acute side effects
Total dose to bone marrow from photon contamination should be less than 0.7 Gy
Patch treatments should be utilized to underdosed areas such as the perineum, scalp, and soles of feet
Internal and external eye shields should be used to ensure that the dose to the globe is not more than 15% of the prescribed skin surface dose

At Yale, a 'Stanford technique' is utilized that incorporates a dual gantry angle (252.5 and 287.5°) at an SSD of 3.8 m with an effective energy of 3.9 MeV. The six-field treatment technique requires an anteroposterior, posteroanterior, right and left anterior oblique, and a right and left posterior oblique field arrangement (fig. 1). The d-max is 0.8 cm, with an X-ray contamination of 0.43% [24]. The prescription dose is 36 Gy given over 36 fractions, over 9 weeks, 4 fractions per week. Shielding is used over the eyelids for 22 of the 36 treatments, with internal eye shielding for 14 of the fractions so that lids receive a therapeutic dose. The lips are shielded for the first 8 days, ears on an 'as needed' basis, and the hands are blocked every other cycle, as are the feet. Nails are blocked from the 'nail side' at all times. The soles of feet and perineum are boosted ('patched') with orthovoltage 1 Gy per day to a total of 14 and 18 Gy, respectively, as tolerated. Tumor lesions receive boosts via orthovoltage based on response to TSEBT. Tumor boosts are generally provided with orthovoltage via 2-Gy fractions to a total of 10–20 Gy given concomitantly with TSEBT, and this is performed at the completion of TSEBT.

TSEBT is provided in Ontario, Canada, in a similar fashion and with excellent results (table 3). We conducted multivariate regression analyses across 677 patients treated with TSEBT in Ontario (2–40 Gy), exploring the potential significance of age, sex, history of prior therapies, dose of TSEBT, and T classification. The greater rate of complete remission in the skin was associated with greater dose and lower T stage (both $p < 0.0001$), and possibly with treatment for new (i.e. first) diagnosis ($p = 0.06$). Progression-free survival was associated with greater dose ($p < 0.0001$), lower T stage ($p < 0.0001$) and new diagnosis ($p = 0.0006$). Overall survival was associated with all five variables, but

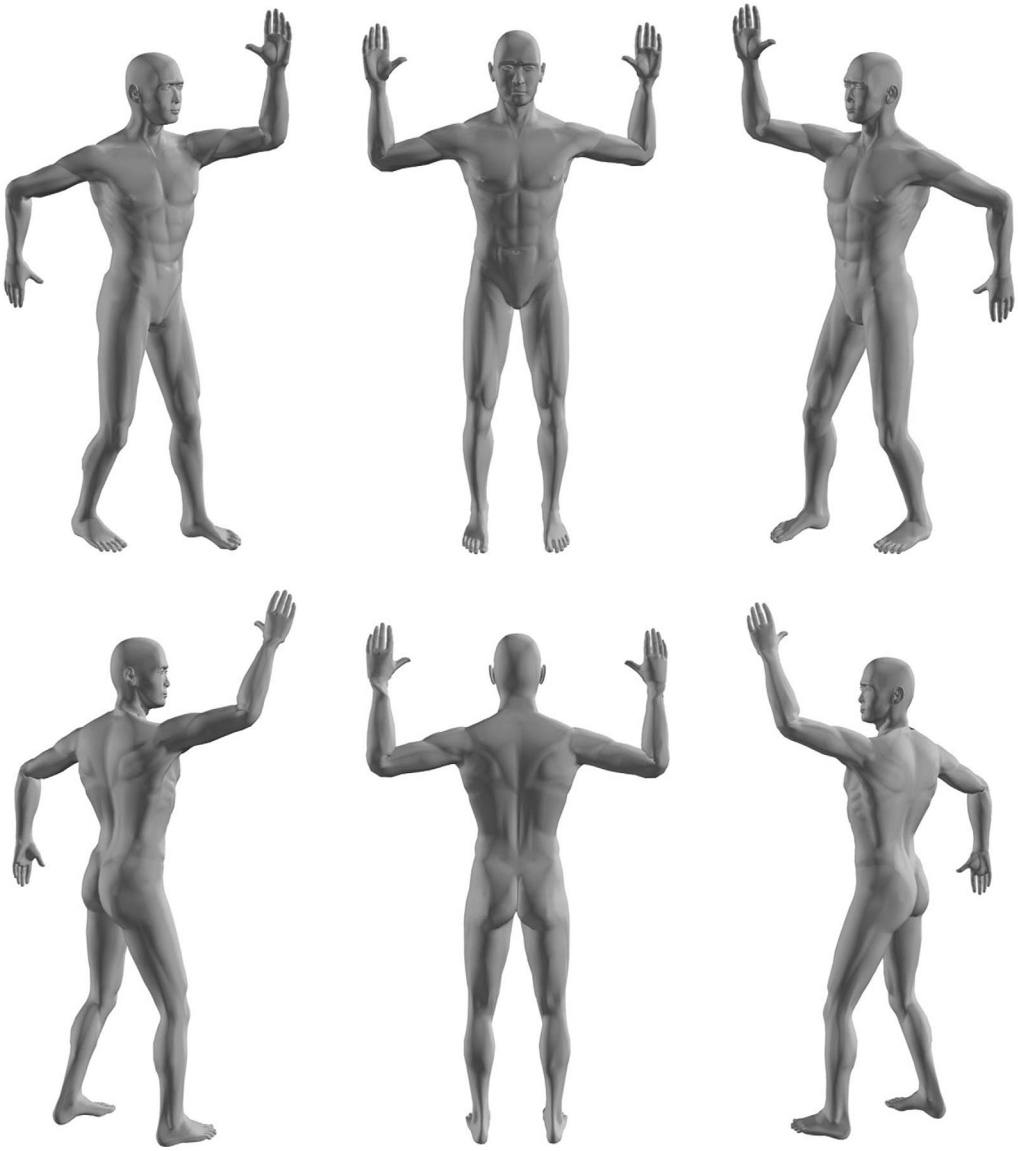

Fig. 1. Treatment positions used in TSEBT. Top row (from left to right): right anterior oblique, anteroposterior, and left anterior oblique treatment positions. Bottom row (from left to right): right posterior oblique, posteroanterior, and left posterior oblique treatment positions [reprinted with permission, 35].

Table 3. TSEBT results in Ontario, 1969–2004 (n = 677 patients)

DFT[a]	n	CR (0 year)	DFE, %		CSS, %		OS, %		Median OS
		%	5 years	10 years	5 years	10 years	5 years	10 years	years
D1	205	94	50	40	99	96	93	84	>25
D2	170	81	30	17	96	91	85	76	20
D3	44	64	32	16	64	59	49	39	4
D4	36	64	33	25	50	50	37	31	3
F1	63	83	37	34	93	85	88	75	>25
F2	77	78	29	14	86	78	72	51	12
F3	51	55	16	16	41	35	38	20	3
F4	31	36	14	14	53	39	34	25	4

TSEBT: A single course of 2–40 Gy of TSEBT using 2.95–5.2 MeV electrons, both horizontal and dual-beam techniques. CR = Complete remission; DFE = disease-free experience in those patients who attained a complete remission; CSS = cause-specific survival counting only deaths related to MF; OS = overall survival counting all deaths regardless of attribution (DFE, CSS and OS are presented as percentages estimated by the method of Kaplan-Meier).

[a]DFT: D = Newly diagnosed with MF; F = TSEBT after failing prior therapy(ies) for MF; T = T1, T2, T3 or T4 classification.

death secondary to MF (112 of the 246 deaths) was associated only with lower dose ($p < 0.0001$), greater T stage ($p < 0.0001$) and delaying TSEBT until after failing other therapies ($p = 0.0007$), and was not associated with age and sex. In patients who attained a complete clinical response to TSEBT (533/677 or 79%), only lower T stage ($p < 0.0001$) and administration of TSEBT for a new diagnosis of MF ($p = 0.01$) were significant predictors of improved survival. Overall, the complete response rate for a patient with T1 or T2 disease who receives TSEBT will be at least 80% with 35 Gy administered according to the consensus EORTC method. The 5-year relapse-free survival for patients with stage IA is expected to be 50%, and there is very good salvage with second-line therapy [25].

Acute toxicity of TSEBT may include pruritus, epilation, desquamation, hypohydrosis, xerosis, erythroderma, hyperpigmentation, lower extremity edema, bullae, alopecia and onychoptosis. Chronic toxicity may include atrophy, hypohydrosis, alopecia, telangiectasia, hyperpigmentation, and possibly second dermatologic malignancy.

When TSEBT is used in the management of patients with MF, it is critical to consider maintenance therapy for these individuals following completion of the TSEBT phase.

In 1995, Wilson et al. [26] reviewed the concept of adjuvant systemic therapy following TSEBT. It was determined that traditional systemic chemotherapy offered no benefit for disease control in the skin or survival for such patients. In 1997, Wilson and colleagues [27] evaluated a cohort of patients who had received TSEBT, followed by psoralen in combination with UVA light (PUVA) as adjuvant therapy on an ad hoc basis. This group was compared to a series of patients with similar T1 and T2 level disease (patches and plaques covering <10 or $>10\%$ of skin surface) who received only TSEBT. The findings revealed that PUVA improved 5-year disease-free survival to a level of 85% compared with 50% for those who did not receive the adjuvant therapy ($p = 0.02$). Similar benefits with adjuvant mechlorethamine were reported by Chinn et al. [28] from the Stanford group in 1999, but only for patients with T2 disease. The pilot study of Wilson and colleagues [27] has been replicated in Ontario, in a prospective nonrandomized study. There were 33 T1–2 patients treated with TSEBT plus adjuvant PUVA as compared with 59 treated only with an identical technique of TSEBT [19, 25]. Latest results reported at the EORTC task force meeting in 2004 indicated that disease-free survival at 2.5 years may be increased by 30% with adjuvant PUVA ($p = 0.01$), and a randomized trial is now in preparation in Ontario to confirm the effect with evaluation of toxicities and quality of life.

Adjuvant therapy for patients with advanced stages of disease such as tumor presentation is also critical in an effort to forestall recurrence and maintain control of disease. It is not clear which agents are most useful for this purpose, but PUVA, mechlorethamine, extracorporeal photopheresis (ECP), interferon-α, bexarotene, denileukin diftitox, and other targeted therapies, individually and in combination, have been utilized with some degree of success.

For those who do fail TSEBT, a repeat course of such therapy is well tolerated if offered with highly fractionated methods as those described above. Wilson et al. [29] and Becker et al. [30] evaluated the respective experiences from Yale and Stanford Universities. The response rates approached the excellent results observed following the initial course, and therapy was relatively well tolerated if provided with low daily fraction sizes of approximately 1 Gy. In the Yale series, patients received a median dose of 36 Gy for the first course, 18 Gy for the second, and 12 Gy for the third. Following the second course, 86% of the patients had a complete response and the median disease-free interval was 11.5 months. The best outcomes with respect to response were found in those who had longer time intervals between the two courses of TSEBT, a complete response following the first course, and diffuse cutaneous involvement at the time of relapse. Although this repeat course of therapy would likely not contribute to enhanced survival, the palliative benefits are substantial. In Ontario, 41 patients received second courses of TSEBT, and some of these were

managed with repeated low-dose TSEBT (4–6 Gy in 3 fractions, every 4–18 months, with no other therapies). This approach can maintain low or negligible disease burden and sustain quality of life in clinical situations where patients have failed many other therapies, topical and systemic.

There has been some concern over the efficacy of TSEBT in the management of patients with 'tumor' (TNM T3) stage disease. The staging system for MF takes into consideration the total skin surface area involved for those with patch and plaque level disease, with a break point of 10% skin surface area for determination of T1 versus T2 status. However, the extent of the total skin surface area involved by tumors has not been incorporated into the MF staging system. In 1996, Wilson and colleagues [31] sought to evaluate the influence of skin surface area involvement in a population of patients with tumors (T3 disease). The complete response rate was 78% for the entire group of patients with T3 disease. When patients were stratified between $<10\%$ tumor skin surface involvement or $>10\%$, all of those with $<10\%$ surface involvement were relapse-free at 18 months, whereas all patients with $>10\%$ surface involvement had relapsed by 18 months. The initial complete response rate for those with $>10\%$ surface involvement was 74%. Given these findings, we recommend careful consideration of total skin surface area involvement prior to making therapeutic decisions for those with T3/tumor stage MF.

Patients with erythroderma (T4) have significant pruritus and, subsequently, quality of life issues are substantial for this particular group. In 1999, Jones et al. [32] evaluated a group of 45 patients with erythroderma as part of a joint effort with Wilson from Yale. The group of 45 patients had not received any neoadjuvant, concomitant nor adjuvant therapies. The rate of complete response was 60%, and 26% of patients were progression-free at 5 years. Hence, TSEBT is a significantly beneficial modality for this group of patients. Since that time, a variety of targeted and immune-based therapies have been developed and further expanded such as ECP, which is especially useful in patients with erythroderma, and particularly in those with circulating abnormal CD4+ cells. In 2000, Wilson et al. [33] reported a series of patients with T4 disease and specifically evaluated the role of ECP as part of a combined modality treatment program. After adjustment for blood involvement and stage, the addition of ECP improved disease-free survival, progression-free survival, and cause-specific survival. The 2-year cause-specific survival was 100% for those receiving ECP and TSEBT compared to 69% for those treated with TSEBT alone ($p = 0.048$). The 3-year disease-free survival was 81 and 49%, respectively ($p = 0.024$).

Patients with visceral and nodal disease related to their cutaneous lymphoma present especially challenging problems. Although systemic therapies are offered to such patients, response duration is generally short lived. Such

patients may derive excellent palliative relief from short course photon beam radiotherapy in conjunction with localized therapy to the skin or TSEBT. Typically, courses of 20–30 Gy in fractions of 2.0–3.0 Gy provide rapid relief of symptoms.

Conclusion

Cutaneous lymphomas present challenging management issues for both clinician and patient. Therapeutic results based on phase III data are limited. Nevertheless, the weight of the evidence from various institutional experiences suggests that radiotherapy is an important curative and palliative modality in the management of a wide spectrum of cutaneous lymphomas. For the CBCLs that are localized, radiotherapy is most likely the best initial option for such patients. For patients with MF, similar efficacy is noted in managing those with localized disease, but many patients with MF present with more widespread involvement, or disease which is resistant to other forms of therapy initiated prior to radiotherapy. In such circumstances, TSEBT may be considered, and will likely offer excellent palliation and enhanced disease-free survival compared with other modalities, given its very high complete response rates. It is not clear that TSEBT offers an overall survival advantage in the management of MF, and this is a topic that is widely debated. Even if survival is not enhanced with radiotherapy for cutaneous lymphomas, these diseases constitute a group that, based purely on their presentation, merit efficient palliative therapy. The primary motives for most patients are to achieve complete remission and to have active lesions treated with minimal disruption in lifestyle or schedule, thereby assuring valuable quality of life [34]. Hopefully, with the establishment of more novel immunologic-based therapy, the benefit of radiotherapy may be further advanced. Given the extraordinary complete response and relatively durable remission rates, radiation will continue to play an important role in the management of patients with cutaneous lymphomas of both B and T cell origin.

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The Clinical Impact of T Cell Receptor Rearrangement Analysis in Cutaneous T Cell Lymphoma

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Cutaneous T cell lymphoma (CTCL) is a clonal lymphoproliferative malignancy primarily involving the skin. In contrast to primary nodal lymphomas, CTCL is characterized by a prolonged clinical course with a different clinical behavior and outcome. However, in a significant part of the patients, progression with involvement of the lymph nodes and/or visceral organs occurs [1].

The classical and most common forms of CTCL are mycosis fungoides (fig. 1) and Sézary syndrome. In addition, other rare variants of CTCL are known, e.g. cutaneous CD30-positive large cell lymphoma or lymphomatoid papulosis. Improved and clinically relevant CTCL classification approaches will be published by the forthcoming first consensus classification of the European Organization for Research and Treatment (EORTC) and the World Health Organization, the so-called EORTC-WHO classification for cutaneous lymphomas [2]. Formal staging is done according to the TNM classification system [3].

Diagnosis of CTCL may be especially difficult in cases of early stage or unusual clinical presentation. Rapid advances in molecular biological techniques have made it possible to study the disease at a genomic level. Using techniques such as Southern blot hybridization or polymerase chain reaction it has been possible to characterize T cell proliferations based on the detection of rearranged T cell antigen receptor (TCR) genes. In the following sections the impact of TCR rearrangement analysis on the initial diagnosis as well as on the staging procedure of CTCL, particularly lymph node analysis, will be reviewed.

Molecular Diagnosis of Initial Skin Lesion in CTCL

Routine diagnosis of CTCL is based on its characteristic clinical and histopathological features. However, the broad clinical and histological

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Classification of Primary Cutaneous Lymphomas

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Cutaneous lymphomas represent clonal proliferations of neoplastic T or B lymphocytes. They have been recognized as a heterogeneous group with distinct variability in clinical presentation, histopathology, immunophenotyping and prognosis. After the primary gastrointestinal lymphomas cutaneous lymphomas represent the second most common group of extranodal lymphomas, with an estimated annual incidence of 0.5–1/100,000 [1].

Primary cutaneous lymphomas often show a completely different clinical behavior and prognosis compared to histologically similar systemic lymphomas that may involve the skin secondarily. Therefore, primary cutaneous lymphomas require different types of treatment. For this reason, a new consensus classification based on both, the European Organization for Research and Treatment of Cancer (EORTC) classification [2] for primary cutaneous lymphomas and the World Health Organization (WHO) classification for tumors of hematopoietic and lymphoid tissues [3] as the first common classification, namely the WHO-EORTC classification [4], has been established. In the following review we will give an overview of the most frequent cutaneous T cell lymphomas (CTCL): mycosis fungoides (Mf), Sézary syndrome (SS), anaplastic large cell lymphoma and lymphomatoid papulosis (LyP), and of the most frequent cutaneous B cell lymphomas (CBCL): cutaneous follicle center lymphoma, marginal zone lymphoma and diffuse large cell lymphoma, which represent nearly 90% of all cutaneous lymphomas. Rare entities occurring primarily in the skin are included in table 1.

Cutaneous T Cell Lymphoma

CTCL are non-Hodgkin lymphomas characterized by a dominant skin-homing T cell clone. They represent approximately 80% of all cutaneous

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Basal Cell and Squamous Cell Carcinoma – Radiotherapeutic Approaches

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Radiotherapeutic Approaches to Basal Cell and Squamous Cell Carcinomas and Some Other Skin Tumors

Carcinomas of the skin are the most accessible cancers, the diagnosis is readily made and the limits of the lesion are usually easy to define. No single treatment method is best for all cancers of the skin. If the sole criterion of success is eradication of the lesion, surgery and radiotherapy yield similar results. Most cutaneous cancers are sufficiently sensitive to radiation to be eradicated by doses that are well tolerated by the surrounding normal tissue. If appropriate principles are followed and precautions are taken, X-irradiation is a safe and effective method of therapy [1, 2]. Our discussion is deliberately limited to radiotherapy of cutaneous cancers of moderate size that can be effectively treated with Grenz rays, superficial X-rays or contact therapy units. Larger and more complicated skin cancers should be referred to Mohs' surgery and/or radiation oncologists for treatment with higher kilovoltage, megavoltage, or electron beam techniques or for implants with radioactive isotopes.

In the first section, we want to stress the *advantages* of soft or superficial X-ray therapy:

- Possible on an outpatient basis
- Painless
- Possible for physically or psychologically handicapped patients (also patients over 90 years old) [3]
- Possible for anticoagulated patients
- In patients where there exists a contraindication for a surgical intervention
- Healthy tissue or certain organs can be protected

- The margin of normal appearing skin is usually wide (more than in surgical excisions)
- The intervention is not traumatic

The patient has to be informed that there are also *disadvantages* of radiation therapy:

- The treatment cannot be done in one single session
- If the patient has already received full tumor doses in a radiation field, this particular field cannot be irradiated a second time
- Radiation treatment is followed by alopecia (except if treated by Grenz rays)
- Chronic radiation dermatitis tends to be accentuated with time

What Is Then the Ideal Indication for Radiotherapy?

Radiotherapy is particularly valuable for medium-sized tumors of 1–4 cm in diameter in the face of elderly people, since smaller tumors are mostly treated by surgery and larger lesions are mostly treated either by Mohs' surgery or by a combination of surgery and megavoltage treatment.

What Are the Best Areas to Be Treated by Radiation Therapy?

The real superiority of irradiation over excision lies in its greater preservation of uninvolved tissue. In certain anatomic regions this may pose a problem for the surgeon but not for the radiotherapist who can easily adjust the size of the field to the required area of treatment. Therefore radiation is often the treatment of choice in areas where tissue cannot be readily sacrificed for cosmetic and/or functional reasons. There is general agreement that ionizing radiation is often preferable to other methods of treatment for cutaneous tumors of the following areas [1]: eyelids, medial or lateral canthi of the eyes, nose, ears and lips.

Excellent areas for radiotherapy are also the nasolabial fold and preauricular areas as well as larger tumors of the cheek. On the other hand, the skin of the trunk and extremities has a greater tendency to develop radiation sequelae, particularly telangiectasias and changes in pigmentation [4].

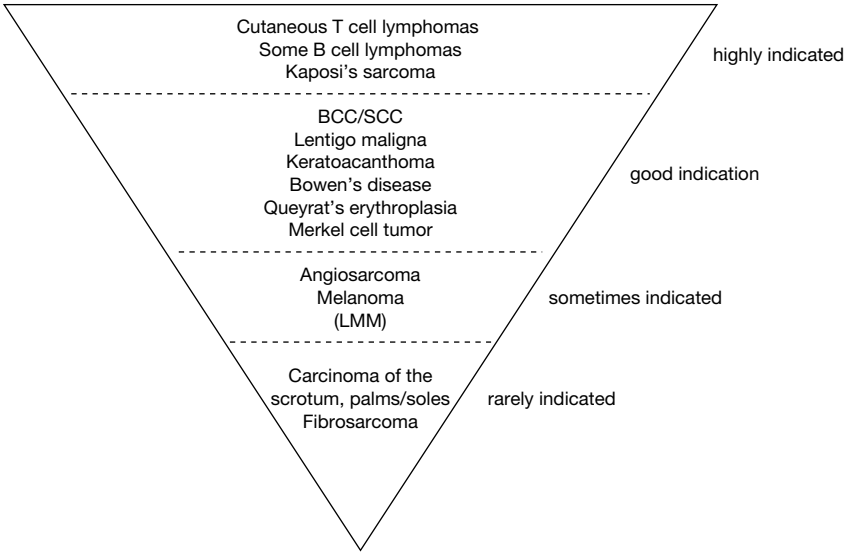
Before radiation therapy of a lesion is begun, the diagnosis must be confirmed by biopsy.

Why a Biopsy?

The histological examination determines the type of the tumor, the radiosensitivity of the tumor, the exact extension of the tumor, the depth of the tumor and the exclusion of an error.

Concerning the radiosensitivity of skin tumors we can distinguish four categories (see table 1), i.e. (1) highly indicated and unique advantage: Kaposi's sarcoma (KS), mycosis fungoides and other lymphomas of the skin, (2) good indication: basal cell (BCC) and squamous cell carcinomas (SCC), keratoacan-

Table 1. Indications/radiosensitivity of different skin tumors



thoma, Bowen's disease, Queyrat's erythroplasia, Merkel cell carcinoma, (3) sometimes indicated: angiosarcoma, melanoma and (4) rarely indicated: fibrosarcoma, carcinomas of the scrotum, soles and palms.

We also distinguish between *curative* radiotherapy in tumor's such as BCC, SCC, keratoacanthomas, precancerous lesions and melanomas of the lentigo maligna (LM) type, whereas radiation therapy is *palliative* in tumors such as Merkel cell carcinoma, KS and most lymphomas.

Are there *contraindications* for radiotherapy with soft X-rays? These are:

- Tumors penetrating into cartilage or bone
- Intraoral tumors
- Tumors penetrating into the nostrils
- Tumors in scars of osteomyelitis, burns, chronic ulcers or in chronic radiodermatitis
- No re-treatment of previously irradiated skin carcinomas
- Genodermatoses which are prone to neoplasms, such as basal cell nevus syndrome or xeroderma pigmentosum

Which Radiation Quality?

Since the work done in England, Germany and the United States and with the introduction of the beryllium-windowed X-ray units, i.e. soft X-ray therapy

in dermatologic radiotherapy, as a rule of thumb, radiation qualities with a half-value depth (HVD = D1/2) corresponding to the depth of the tumor were proposed. Most of the radiation will then be absorbed in the pathological tissue and the possibility of undesirable radiation effects on underlying uninvolved tissue will be markedly reduced. The depth of the tumor can either be reasonably estimated by inspection and palpation or by an exact histopathological description of the tumor depth, preferably by an experienced dermatopathologist. Several papers could show that 50% of all BCC and SCC infiltrate to a depth of only 2 mm or less, and 75% of these tumors to 5 mm or less [1].

With Grenz and superficial X-ray machines, the kilovoltage is in a fixed combination with filters in order to avoid filter mistakes and thus application of faulty dosages. These X-ray machines have a kilovoltage between 10 and 50 kV, sometimes up to 100 or even 150 kV. With filter combinations, an HVD (=D1/2) from 1 to 20 mm can be reached. For dermatologic purposes, it is rarely necessary to irradiate tumors thicker than 20 mm.

Why Fractionated Doses?

Fractionation of radiation dosage is based on the assumptions that tissues recover at different rates from the effects of radiation and that tumor tissue recovers more slowly than normal tissue. When a given dose of radiation is divided into several increments and delivered over a period of several days, the biological effect is usually less pronounced than that of the same radiation administered in a single dose. This lesser damage with fractionation appears to be related to cell recovery between increments and to the capabilities of recovering cells to adapt to radiation-induced alterations of the surrounding tissues. Small tumors and radiations fields, therefore, support higher single doses than large tumors with large irradiation fields which have to be irradiated with smaller single doses. In addition, in large irradiation fields, we have to consider an additional backscatter factor.

Much work has been done in an attempt to define optimum time-dose-volume relationships for carcinomas of the skin. There is no consensus as to the total dose needed to eradicate a cutaneous cancer and when to terminate radiotherapy. Different authors have recommended different dosages [1]. The tendency is to use *standardized schedules* (see table 2).

It is still worthwhile to observe the patient's reaction during radiation therapy and to look for an exudative or erosive reaction in the irradiated margin. When larger individual doses are administered, the recommended total dose is usually smaller than in cases where smaller individual doses were used.

In the following we will discuss the different types of cutaneous cancers.

Table 2. Recommended doses: malignant tumors

Diagnosis	kV	Field Ø cm	Fractionation Gy	Total dose Gy	Time interval days
LM	12	<2	5–6 × 20 or	100–120	4–7
		>2	10–12 × 10	100–120	3–4
Bowen's disease/	20	<2	3–4 × 8	24–32	4–7
Queyrat's erythroplasia		>2	8 × 10 × 4	32–40	3–4
Keratosis, actinic	12	<2	5–7 × 8	40–56	4–7
	20		2–3 × 8	16–24	4–7
			5–7 × 4	20–28	3–4
BCC/SCC	20–50	<2	5–6 × 8	40–48	4–7
		2–5	10–12 × 4	40–48	3–4
		>5	26–28 × 2	52–56	daily
Mycosis fungoides/			3–7 × 2	6–14	3–4
other malignant lymphomas/ leukemic infiltrates	20–50 teleroentgen		4–10 × 1	4–10	3–7
LMM/			7–9 × 6	42–54	4–7
melanoma metastases	20–50				
KS		<2	3–5 × 8	24–40	4–7
	20–50	>2	5–10 × 4	20–40	3–4

Disseminated Actinic Keratoses

Usually, there is agreement that small actinic keratoses are best treated by surgical excision or other equivalent methods. The problem arises in extensive and disseminated actinic keratoses such as on the scalp. Here again, there are possibilities with topical treatments such as 5-fluorouracil or imiquimod cream, but usually recurrence rates are higher or recurrences appear sooner than after treatment with radiotherapy. Since these lesions are intraepidermally and often in an atrophic epidermis, the ideal treatment is with Grenz rays. The treatment consists of 6 sessions of 6 Gy twice weekly applied on one or several divided fields [5]. At the end of the treatment, an erythema or an exudative reaction will occur. If there is marked pruritus topical corticosteroid cream may be of excellent help to the patient. One month after the end of treatment, the erythema has mostly gone. The patient has to be told to continue sun protection with a hat and application of a sunscreen. Rarely, it is necessary to perform a second treatment years later.

The dose schedule is shown in table 2, treatment results in figure 1.

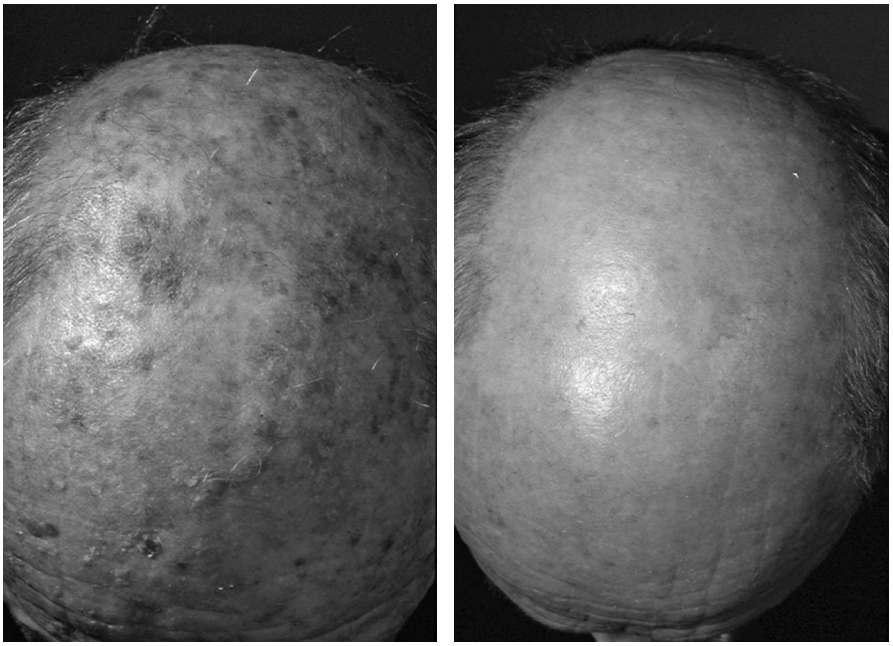


Fig. 1. Disseminated actinic keratoses of the scalp in a 78-year-old male patient, before (***a***) and 6 months after (***b***) Grenz ray treatment, 6 times 6 Gy (36 Gy), twice per week.

Bowen's Disease/Queyrat's Erythroplasia

This carcinoma in situ is to be treated similarly to actinic keratosis, but histopathologically these lesions are more acanthotic, i.e. these are thicker lesions. Even in elderly patients, it is possible to apply Grenz rays with a D1/2 of 1 mm. If the lesions are more infiltrated, soft X rays with the quality of 20 kV or more are necessary. The dose schedule can be adapted (see table 2): again fractions of single doses of 6 Gy up to a total dose which may be a little higher than for actinic keratoses, i.e. around 40 Gy. Single doses with soft X rays would be 4 Gy. Exudative reactions have to be expected a little earlier the genitoanal area. Treatment results are excellent [5].

The dose schedule is shown in table 2.

Lentigo Maligna

This is another precancerous lesion which is an excellent indication for radiation treatment, since extensive lesions in the face of elderly people are not

seldom. This treatment modality is not known too well because it has always been thought that this is not a curative treatment. Recent reports have shown that it is at least as good as surgical procedures [6–8]. As we mentioned above, the inclusion of a wide enough margin is not a problem for the radiation therapist and, therefore, large LM are an excellent indication for radiotherapy. The classical treatment schedule is called after Miescher who proposed 5–6 times 20 Gy Grenz rays for medium-sized lesions (around 2.5 cm in diameter); for larger lesions we would prefer 10–12 times 10 Gy Grenz rays (see table 2). Here again, we want to stress that the epidermis in the elderly is atrophic and with an HVD of 1 mm we even reach atypical melanocytes in the hair follicles!

Basal Cell Carcinoma, Squamous Cell Carcinoma, Keratoacanthoma

These tumors represent the classical indications for radiotherapy with soft X-rays or superficial X-rays, since most of them are well circumscribed and rarely larger than 2.5 cm, and as we described above, 75% of these tumors are less than 5 mm thick. Some treatment centers use the same treatment schedules for BCC and SCC, though one could imagine that SCC should be treated with a higher total dose, since they represent more aggressive tumors. Elderly patients prefer not to come every day for their treatment sessions. Therefore, medium-sized lesions may well be treated with e.g. a 4 Gy single dose in 3 fractions per week. There is the possibility for small lesions which cannot be excised for certain reasons, to apply an even higher single dose, e.g. 6–8 Gy per fraction twice a week. We absolutely agree that large lesions, i.e. lesions over 4 cm, are best treated with daily fractions of 2 or 3 Gy (see table 2). Treatment results are shown in figures 2 and 3.

We want to stress the importance of the histopathology of BCC or SCC for the outcome of the treatment result. We have seen in a large study that if the histopathology does not show a nodular type of BCC or SCC, but rather a sclerosing type the recurrence rate rises immediately. Therefore, these latter histological types are not well suited for the treatment with soft X-rays. There are two possibilities: (1) if the patient is operable, Mohs' surgery is the preferred method, or (2) if surgery is contraindicated megavoltage therapy should be chosen.

Metatypical carcinomas are considered as SCCs. For keratoacanthomas the same dose schedule is used as for SCCs [9, 10]. Carcinomas of skin appendages and, as we mentioned above, carcinomas penetrating into cartilage or bone, or localized in the mucous membranes or arising in chronic scars are not an indication for a soft X-ray therapy.

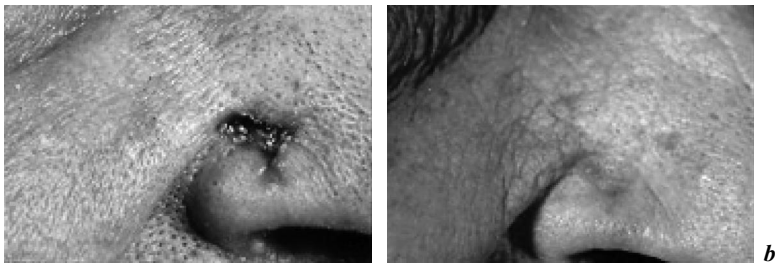


Fig. 2. BCC in a 70-year-old woman on the right nasolabial fold before (***a***) and 12 months after (***b***) soft X-ray treatment (40 kV), 6 times 8 Gy (48 Gy), once a week.

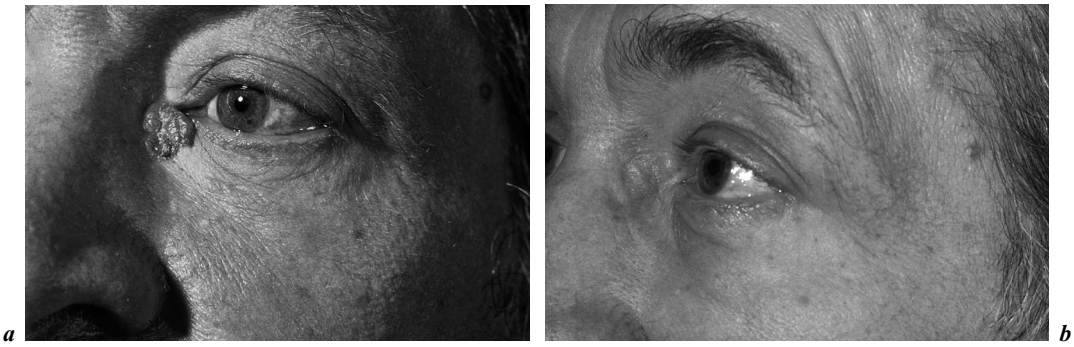


Fig. 3. BCC in a 64-year-old man on the left inner canthus before (***a***) and 6 months after (***b***) soft X-ray treatment (40 kV), 12 times 4 Gy (48 Gy), twice per week.

Radiation treatment is possible for BCCs, SCC's or keratoacanthomas, which were not completely excised or incompletely treated by electrodissection or cryotherapy. The techniques are the same as for primary tumors. The functional and the cosmetic results after irradiation of such treated tumors are usually satisfactory [1].

Melanoma of the LM Type

Since the time of Miescher, it has been well known that not only LM, but also lentigo maligna melanomas (LMM) respond well to radiation treatment and are thus considered curative indications [6–8]. In contrast to LMs, LMMs penetrate into the dermal tissues and, therefore, Grenz ray treatment is not recommended but rather soft or superficial X-rays, i.e. radiation qualities of at

least 20 kV or more. We want to stress that LM and LMM are not to be considered radioresistant, but are maybe tumors with a reduced radiosensitivity; the reasons discussed are [11]: a high percentage of nonproliferating cells, a high percentage of hypoxic cells, a high probability of potentially lethal repair, subpopulations of cells with different radiosensitivity in the 'shoulder' region of the survival curve, synthesis of the prostaglandins (radioprotectors) in the tumor cells, and melanin as a scavenger of 'radicals'.

Therefore, higher doses per fractions are recommended, mostly around 6 Gy per fraction. The proposed dose schedule is shown in table 2.

Our results of 64 patients show a similar outcome for radiation treatment and for surgical treatment with a cure rate of around 90% [7]. This is for LM, but also for LMM, especially large lesions in the face of elderly persons, and thus avoiding major surgical procedures and scarring. From a cosmetic and functional point of view the outcome is excellent.

Paget's Disease

We want to discuss Paget's disease in the context of carcinomas and not precancerous lesions, because at least Paget's disease of the nipple mostly shows an underlying carcinoma. We also agree that in extramammary Paget's disease, an underlying carcinoma is seldom found. In such situations, we deal with a superficial lesion and thus Grenz rays maybe used. The dose schedule is similar to that used for Bowen's disease.

Merkel Cell Tumor

Merkel cell tumor is a rare primary skin tumor and occurs most frequently in the 7th and the 8th decades. Tumors occur with greatest frequency in the head and neck region (50%). Tumors are characterized by a high rate of local recurrence after surgical excision (25–60%) and by frequent involvement of regional lymph nodes (45–79%); distant metastatic failure is common (22–48%) [12]. Several series have shown promising results when radiation therapy is added to the initial surgical management of Merkel cell carcinoma. At the MD Anderson Cancer Center, they found that 83% of patients showed disease control when they were treated with surgery and radiation therapy for palpable neck disease [13]. Doses of 50 Gy at conventional fractionation appear adequate for the treatment of subclinical disease, but when microscopic or gross residual disease exists, boost doses of 60–70 Gy are indicated [12, 14].

Cutaneous Lymphomas

In general, the lesions of cutaneous lymphomas, i.e. T cell or B cell lymphomas, are very radiosensitive [15, 16]. With the exception of certain circumscribed B cell lymphomas or localized CD30-positive lymphomas where radiotherapy is curative, the radiation treatment for lymphomas is palliative. Total doses in the range of 20–30 Gy have been commonly used and offer excellent palliation. Doses in this range may result in a relapse rate of up to 30%. Single doses of 2 Gy, either daily or 3 times per week, seem to offer the best local control (see also table 2).

Because of the possible need for subsequent treatment in adjacent areas, it is important to document the treated areas with Polaroid photographs, accurate drawings, and, if feasible, tattooing of the corners of the fields with India ink. In most patients, the lesions will not clear during or at the completion of irradiation and it may take up to 6–8 weeks for a complete response. For individual skin lesions, energies may be orthovoltage or electron beam. The depth of infiltration defines the energy of the beam required. Larger, bulkier lesions such as deep ulcers or lymph nodes may be treated with either cobalt or 4–6 MeV photons [for the total skin electron beam therapy, see 17–19].

Kaposi's Sarcoma

Here we distinguish between non-AIDS-associated and AIDS-associated KS.

Non-AIDS-Associated KS

Local irradiation of KS includes the lesion plus a normal tissue border of approximately 1–2 cm. Thin, cutaneous lesions can be effectively treated either by superficial X-ray therapy (e.g. 20–150 kV) or relatively low-energy electron beams, e.g. 4–6 MeV. Thick nodules are best treated by electron beams that encompass the entire lesion homogeneously but spare underlying normal tissues. Lesions on the eyelids are treated most easily by superficial X-rays and protective shields over the optic lens.

Based on the available evidence, both local therapy and elective regional therapy are effective techniques for the treatment of classical KS. The literature supports the use of a wide range of doses and fractionation patterns. As long as a sufficiently high dose is delivered, e.g. 20–30 Gy in ten fractions or even for small lesions 8 Gy in one fraction, a salutary outcome is likely. The treatment schedule is shown in table 2.

AIDS-Associated KS

Usually, the same dose schedules are used (see above) and apparently no difference was evident, apart from the fact that it may take 3–4 months in these patients for the tumors to resolve and that radiation-induced edema of the feet or face, as well as symptomatic mucositis are more severe in patients with AIDS than in other patients [20].

Radiation therapy may be reserved for specific indications such as pain, ulceration, bleeding, functional impairment (e.g. on the legs), or improvement of the appearance of cosmetically disfiguring lesions (e.g. the eyelids). Palliative radiation therapy for AIDS-associated KS are: (1) a sufficiently high dose should be delivered to accomplish the desired goal and maintain this state for as long as possible, (2) the treatment should be delivered as rapidly as possible, and (3) the treatment should not induce distressing side effects.

In conclusion, we would just like to stress that there are two possibilities of radiation therapy: (1) curative therapy for: precancerous lesions, BCC and SCC, LM and LMM, isolated B lymphomas, and Merkel cell carcinoma, and (2) palliative therapy for: lymphomas (T and B), KS, angiosarcoma, melanomas, leukemic infiltrates of the skin, and metastatic nodules of various carcinomas.

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Kaposi's Sarcoma – Radiotherapeutic Aspects

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Kaposi's sarcoma was first described by Moriz Kaposi in 1872 [1]. Later it became known that Kaposi's sarcoma is a malignant, multifocal proliferation of capillaries and perivascular connective tissue that may affect the skin and internal organs [2, 3].

Classic Kaposi's sarcoma most often appears in the elderly man of eastern European and Mediterranean origin. The foci mostly occur on the lower leg and tend to progress slowly. More advanced tumors may occlude the lymph vessels and thus cause edema of the limb involved. Endemic (African) Kaposi's sarcoma is a more aggressive form and frequently occurs in patients with younger age living in central Africa. The tumor is likely to involve lymph nodes, bones and viscera often leading to death within a few years. Transplant-related (iatrogenic) Kaposi's sarcoma occurs in immunosuppressed patients having received a transplant. Very often, the foci arise in the mucosa of the mouth or in the viscera.

Epidemic Kaposi's sarcoma has been the most frequent malignancy diagnosed in association with HIV infection. The manifestations range from asymptomatic bluish macules to nodules that may obstruct the lymphatic vessels and consequently cause edema in lesions of the gastrointestinal tract or life-threatening involvement of the lung or the liver. The frequency of this kind of Kaposi's sarcoma has decreased markedly due to improvements in the systemic therapy of AIDS infection, namely the highly active antiretroviral therapy (HAART).

The most adequate therapy has to be chosen according to the extent of the disease, the stage of AIDS infection, opportunistic infections and the general health status of the patient, knowing well that in the great majority of patients every kind of therapy tends to be palliative [4]. In a patient with a limited

number of superficial foci, local therapy will be appropriate ranging from surgical excision (mostly biopsy [5]) to intralesional administration of cytostatics, photodynamic therapy, and – last but not least – radiotherapy. Patients with far-advanced disease, limb edema or involvement of the gastrointestinal tract or the lungs require chemotherapy additionally to the application of HAART. However, it should be borne in mind that these patients often suffer from far-advanced AIDS disease and thus tend to tolerate chemotherapy very badly. Consequently, an individual interdisciplinary discussion and decision on a therapy plan is highly recommendable [2, 3].

Indication

In patients with classic or endemic Kaposi's sarcoma, radiotherapy may be indicated for lesions that are painful, itching or bleeding or cause severe burning sensations. In the face or other visible parts of the body, those lesions may cause cosmetic disfigurement or, if they are more advanced, limb edema and, consequently, functional disabilities.

In patients with the more aggressive epidemic Kaposi's sarcoma, HAART is the therapy of choice, often causing spontaneous remission of sarcoma foci when effective against HIV. Patients unresponsive to HAART should be irradiated for at least 2 or 3 months after the beginning of medication. The other indications are comparable to those in classic Kaposi's sarcoma (pain, itching, bleeding, disfiguring lesions, edema and functional disabilities). Lymph node involvement may be another indication for radiotherapy, as well as painful and bleeding mucosal lesions in the oropharynx, limited obstruction of the gastrointestinal tract and limited involvement of the lungs. In more advanced cases radiotherapy is not possible, due to a high risk of intolerable toxicity. In the case of an acceptable general health status, chemotherapy should be applied [2–12].

Before referral to the radiooncologist, a patient with Kaposi's sarcoma should have undergone a thorough dermatological examination with photographic documentation. The thickness of the foci can be measured easily by high-frequency ultrasound. In patients with epidemic Kaposi's sarcoma, a chest radiograph and an abdominal CT scan are recommendable.

Technique of Radiotherapy

The technique of radiotherapy is dictated by the extent and the thickness of the foci. In many cases of simple skin foci, soft X-rays (45–100 kV) are the technique of choice. The field can easily be shaped irregularly by using individual

collimators cut out from thin lead sheets and should include the focus together with a safety margin of 1–2 cm. In case of foci of the eyelids, the lens of the eye should be shielded by a special lead protector. The energy of the beam should be chosen using the depth-dose curves of the individual machine, being aware of the thickness of the focus.

Electron beam therapy can be an alternative to superficial X-ray therapy. Usually electrons produced by a linear accelerator with energies ranging from 5 to 10 MeV are used. It should be borne in mind that the depth-dose curve of those electrons shows a dose build-up effect in the first millimeters of tissue, so that a bolus layer (water-equivalent material) of 0.5- to 1.0-cm thickness placed over the lesion is highly recommendable in order to achieve a full dose to the skin surface. Individual collimation of electron beams can be performed using metal shields, for example made of Lipowitz metal poured into individual forms taken from the patients' foci to a thickness of approximately 1 cm.

For thicker plaques, patients with limb edema, lymph node enlargement, or involvement of the lungs or gastrointestinal organs, ^{60}Co gamma rays or high-energy photons produced by a linear accelerator are necessary. Commonly, simple techniques like parallel opposing fields are used. A bolus layer as mentioned above should be considered when applicable. In complex cases, a 3-dimensional treatment plan is recommended [3, 8, 10, 13–15].

Some special techniques have been developed in order to improve the dose distribution in selected patients. Weshler et al. [13] describe a technique of a large-field radiotherapy using ^{60}Co gamma rays and parallel opposing lateral fields, where the affected limbs are immersed in a basin with water in order to homogenize the dose distribution and to minimize the dose build-up effect. Bodner et al. [16] use a photon radiosurgery system which produces low-energy X-rays from the tip of a needle-like probe at a high-dose rate. Margaretic et al. [17] describe the successful use of total skin electron treatment for extensive cutaneous lesions. For mucosal foci, Caccialanza et al. [18] reported an intracavitary X-ray therapy using soft X-rays whereas Syndikus et al. [19] applied brachytherapy to the hard and soft gum using individual dental plates.

Dosage of Radiotherapy

The dosage of the radiotherapy – and thus the total duration of therapy – should be chosen according to the extension of the foci, the stage of the underlying AIDS disease, and the general health status of the patient.

In patients with a favorable general performance status, the main purpose of radiotherapy is the complete remission of the foci with an acceptable rate and intensity of acute or long-term side effects such as hyperpigmentation or

fibrosis. Thus, according to the radiobiologists' recommendations, fractionated radiotherapy is preferred. Table 1 shows some fractionation schedules frequently used in the literature.

Treating mucosal foci in the mouth cavity or the oropharynx, the radiooncologist often has to deal with intolerable mucositis which causes problems with swallowing and pain requiring medication together with difficulties in nutrition of the patient. Thus, commonly the total dose is limited to approximately 15 Gy applying daily single doses of not more than 1.5–1.6 Gy [20, 21] (see also table 1).

In patients with unfavorable general health status, who are mostly heavily affected by AIDS disease or opportunistic infections, the main purpose of therapy is a quick relief of pain or limb edema. Here one-fraction schedules with doses ranging from 6 to 10 Gy are recommendable in order to avoid longer inpatient periods or frequent transport of the patients to the clinic.

Results of Radiotherapy

An overview of the results of radiotherapy taken from the literature is given in table 1.

There is only one paper by Stelzer and Griffin [22], comparing different dose schedules in a randomized setting. Higher doses were regarded to yield better results than lower ones, whereas the local side effects were higher as well. It must be criticized that the patient collectives are very small, and in the meantime this paper is 13 years old. Evaluating the other nonrandomized papers, the question of the dose dependency of the effect of radiotherapy has not been answered yet. Brenner et al. [23] showed that there is no dependency of the remission rate of the foci on the radiotherapy technique.

In general, local total remission of Kaposi's foci can be achieved in 60–90% of the patients with an additional frequency of partial remission of 10–20%. Ten to 70% of the foci recur within some months. The life expectancy of the patients is often determined by the underlying AIDS disease or its complications such as opportunistic infections, whereas a certain number of patients die of far advanced Kaposi's disease of the lungs or the intestine [5, 7, 8, 23].

Side Effects of Radiotherapy

In the literature, acute and long-term side effects are mostly reported as mild to moderate. Most often acute skin reactions are seen as skin redness,

Table 1. Results of radiotherapy in the literature

Authors	Patients	Sites	Total dose Gy	Single dose Gy	Complete remission on %	Partial remission on %	Mean time to recurrence weeks	Side effects/remarks
Gressen et al., 1999 [29]	36	46	21	3.5	80	11		Mean follow-up: 8 months Worse results in patients with opportunistic infections
Piccinno et al., 1995 [30]	65	594	5–45 4–20	5.0 2.0	68	13	16	Mean follow-up: 9 months
Berson et al., 1990 [31]	187	375	6–8 30–50 18–37 15–16	6.0–8.0 3.0–5.0 1.8–2.5 1.5–1.6	62 (6 months)		64	Local control 55%/12 months independent of dose; side effects 17–23%, grade II Median survival 15 months
Piedbois et al., 1994 [32]	453	5015	20 20+10	2.0	79 85	21 11		No dose dependency
Stelzer and Griffin, 1993 [22]	14	24 24 23	8 20 40	8 2 2	50 79 83		13 26 43	Mean follow-up: 35 weeks Randomized trial, higher doses clearly better; skin toxicity grade 1, depending on dose; local failure in 48–84%
Saran et al., 1997 [33]	52	124	20	2	32 (6 months)	57 (6 months)		Toxicity: grade I 74%, none 26%
Conill et al., 1997 [34]	22	251	8 30	8 3	95	4		Mean follow-up: 6 months No dose dependency
Yildiz et al., 1997 [35]	12	72	8	8	90 (12 months)			Toxicity: hyperpigmentation, edema
Ghabrial et al., 1992 [36]	42	49	8 15–36	8 3	32 22	68 72	30 25	Recurrence 22 vs. 39%; local toxicity comparable
Harrison et al., 1998 [37]	57	596	8 16	8 4	78[a] 81[a]			Mean follow-up: 19 months

Westermann et al., 1990 [38]	15	68	20–40	1.8–2.5	66	31		Mean follow-up: 8.5 months Redness, hyperpig mentation, 5/68 sites recurred after 5–16 months
Metzmann et al., 1995 [39]	15	15	30	2	73	13		Mild to moderate side effects
Plettenberg et al., 1991 [40]	23	53	20–30	2	17 (4 weeks)	34 (4 weeks)		Recurrence in 15/23 patients, mean survival 17 months
Geara et al., 1991 [41]	149	149	20–30	2.5	63	30	20	64% recurrences Dermatitis II 60%, dermatitis III 26%, dermatitis IV 8%
Le Bourgeois et al., 1994 [20]								Oral toxicity: 63% mild, 15% moderate, 22% severe
Oral mucosa	27		15–30	2	11	89	23	
Eyelid	146	186	15–30	2	96			
Kirova et al., 1998 [21]								Mean follow-up: 8.2 months
Skin	581	6662	20+10	2.5	66	26	32	Local recurrence in 71% Toxicity: 16% severe, 18% moderate, 66% mild
Oral mucosa	62	115	15.2	1.6–1.9	18	82		
Cooper, 1988 [42]	34		6.5–35	3.5–6.5				Mean follow-up: 40 months Classic Kaposi's sarcoma
			<1200 ret		86	10		
			>1200 ret		28	8		
Cooper, 1991 [43]	129	226	30	3	68	20		

ret = Rad equivalent therapy.
[a]Overall response rate.

long-term side effects as hyperpigmentation or depigmentation of the irradiated skin areas or mild to moderate fibrosis of the subcutaneous tissue (see table 1).

Radiotherapy of the skin and especially of the mucous membranes should be performed with caution in patients with AIDS. Radiobiological experiments performed by Formenti et al. [24] showed a higher radiosensitivity of fibroblasts of uninvolved skin areas in patients with AIDS and Kaposi's sarcoma compared with healthy persons, but the mechanism still needs to be elucidated. These results have been confirmed by clinical findings. Thoma-Greber et al. [25] report three patients with bullous skin reactions after soft X-ray therapy for Kaposi's sarcoma using a total dose of 30 Gy in ten single fractions of 3 Gy. Smith et al. [26] report a patient with bullous lesions of the skin after radiotherapy for Kaposi's foci with a total dose of 39 Gy applying single fractions of 2–3 Gy, and another patient with an ulcer regarded to be radiogenous after a total dose of 8 Gy in two equal fractions of 4 Gy 1 week apart. Fogel and Gillaspy [27] and Watkins et al. [28] describe in total 7 patients with severe partly ulcerous side effects of the mucous membranes after a radiotherapy for mucosal Kaposi's sarcoma applying total doses between 12 and 15 Gy in daily single fractions of 2–5 Gy.

As stated above, the exact mechanism of the enhanced sensitivity of the healthy tissue in patients with AIDS remains unclear. Nevertheless, this special reaction of the skin and the mucous membranes should be carefully taken into account.

Conclusions

In our opinion and according to the results published in the literature, radiotherapy appears to be a very reasonable instrument in the local therapy for Kaposi's sarcoma. It should be borne in mind that this therapy often will not cure the patient but will be palliative. The radiotherapy technique and the beam quality should be chosen according to the extent and the thickness of foci. In patients with unfavorable health status a single dose of 6–8 Gy should be preferred. In patients with favorable health status a fractionated radiotherapy applying a total dose of 20–30 Gy and daily single doses of 2 Gy should be chosen. Mucosal foci should be treated applying a reduced dose (total dose 15 Gy, single dose 1.5 Gy) in order to avoid unacceptable side effects. More than half of the foci relapse within a few months. The patients' survival is influenced by the sarcoma itself, but mainly depends on the underlying AIDS disease and its complications.

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Pathogenesis and Clinical Manifestation of Kaposi's Sarcoma

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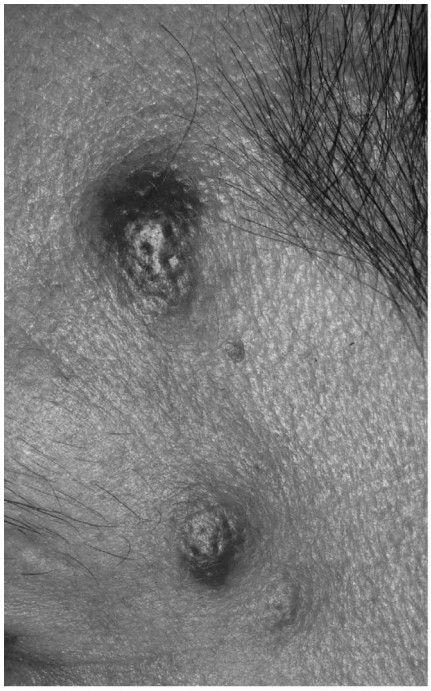
Kaposi's sarcoma (KS) was described by Moriz Kaposi in 1872 as a rare disorder of older men usually of Eastern European, Mediterranean, or Jewish origin. With the rise of the global HIV epidemic, the prevalence of KS began to increase dramatically and became the most common malignancy in AIDS patients. On this background, the scientific interest in this tumor was increased and new insights into its pathogenesis were obtained.

Until now, four particular variants of KS – classical, African, iatrogenic, and HIV-associated – have been distinguished. Classical KS predominantly affects elderly males of Jewish, Eastern European or Mediterranean descent. It has a low incidence in the general population. The male/female ratio has been reported to be around 10:1 and more than 65% of the patients are older than 50 years at time of first diagnosis [Rappersberger et al., 1999; Antman and Chang, 2000]. Classical KS is typically located at the lower extremities and shows a slow and benign course. The African or endemic KS occurs in different subvariants with a different clinical behavior and course, from slow and benign to fast and aggressive with visceral involvement. Under the condition of increasing numbers of HIV-infected people in some areas in Africa it shows equal incidence rates as the colon carcinoma in western Europe. In patients with severe immunosuppression iatrogenic KS can occur depending on the degree of immunosuppression. An ethnical background as in classical KS seems to be a predisposing factor. The HIV-associated or epidemic KS frequently presents at the beginning as a solitary lesion in an atypical location like the face or penis (fig. 1a), but in later stages the lesions may occur rapidly anywhere on the body (fig. 1b, c) and become nodular (fig. 1d). Its occurrence is approximately 20-fold higher in homosexual men than in other HIV-infected patients. The risk of HIV-infected homosexual men to develop KS has been calculated



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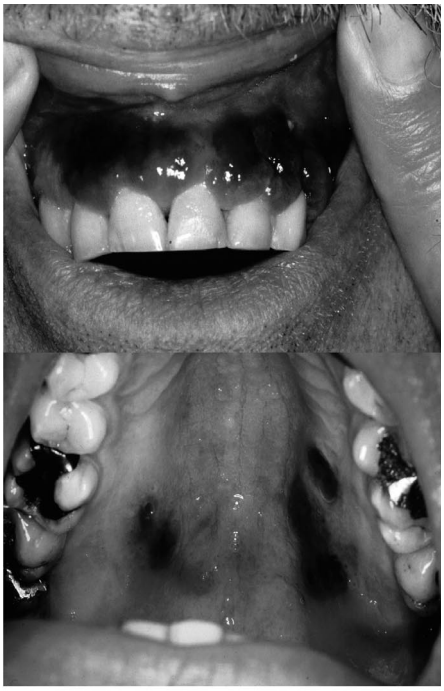

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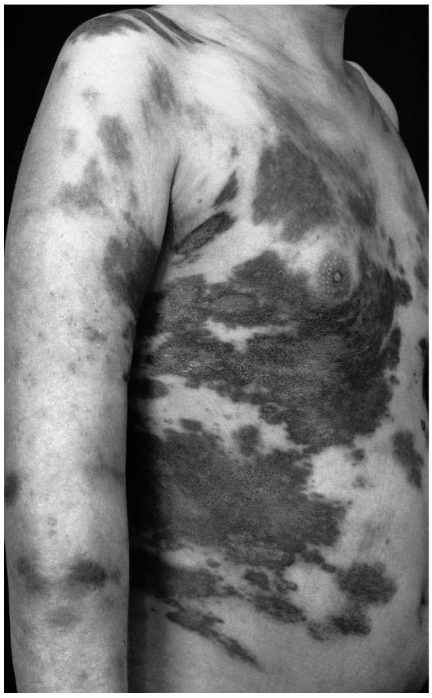

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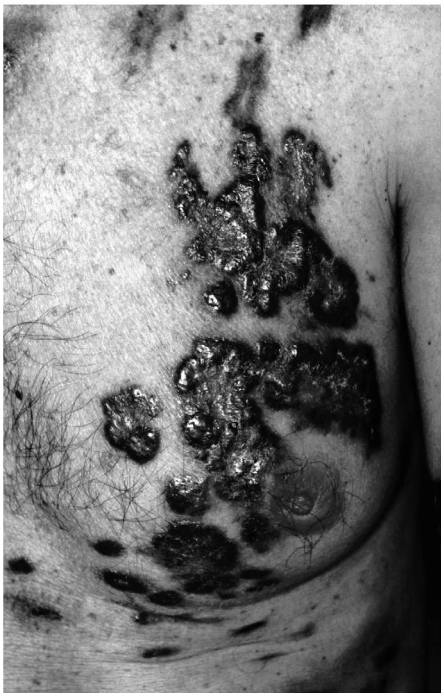

d

10,000–20,000× higher than in the general population and 300× higher than in other immunosuppressed groups. In case-control studies on the behavioral risks associated with the occurrence of KS, a relation to promiscuity with sexual partners has been seen, strongly supporting the hypothesis of an unknown infectious agent in KS [Beral et al., 1990]. Although a viral etiology for KS has been suspected since the early 1970s, Chang et al. [1994] reported on the presence of herpes virus-like DNA fragments in the lesions of a patient with KS and suggested a new virus for the first time in 1994. It was named Kaposi's sarcoma-associated herpes virus (KSHV). Human herpes viruses are classified into three subfamilies: Alphaherpesvirinae consisting of herpes simplex virus-1 (human herpes virus 1, HHV-1), herpes simplex virus-2 (HHV-2), and varicella zoster virus (HHV-3), Betaherpesvirinae consisting of cytomegalovirus (HHV-5, HHV-6, HHV-7), and Gammaherpesvirinae consisting of Epstein-Barr virus (HHV-4). On the basis of specific criteria like tissue tropism, molecular biological characterization, cytopathology and pathogenesis, KSHV was classified as a gammaherpesvirus, closely related to the Epstein-Barr virus and was designated as HHV-8. Gammaherpesviruses are known to be associated with increased benign and malignant cell proliferation. There is a strong epidemiological clue about a causative role of HHV-8 in the pathogenesis of all KS types, as, independently of the variants, most of patients with KS have high antibody titers against HHV-8.

Also histologically almost no differences are seen in the different variants of KS. KS is a tumor arising from cells sharing features of both vascular endothelial cells and of smooth muscle cells [Ensoli and Sirianni, 1998]. Therefore, vascular and spindle cell formations containing vascular slits are the two characteristic types of formations in KS (fig. 2a, b). The early patch stage of KS shows a proliferation of miniature vessels surrounding larger ectatic vessels. Their endothelial cells are large and may protrude into the lumen. Small groups of extravasated erythrocytes, hemosiderin deposits and a sparse infiltrate of lymphocytes and plasma cells are frequently seen. In the more advanced plaque and nodular stage vascular formations usually involve most of the dermis and may extend to the subcutis. There is an increasing predominance of spindle cell component, which is initially centered around the proliferating vascular formations. A rather typical feature is the presence of slitlike spaces containing erythrocytes, separating the spindle-shaped cells and the vascular channels (fig. 2b). In time the spindle-shaped endothelial cells predominate and produce the classic nodular KS lesion. Hemosiderin deposits accounting for the

Fig. 1. a-d Clinical manifestations of HIV-associated KS.

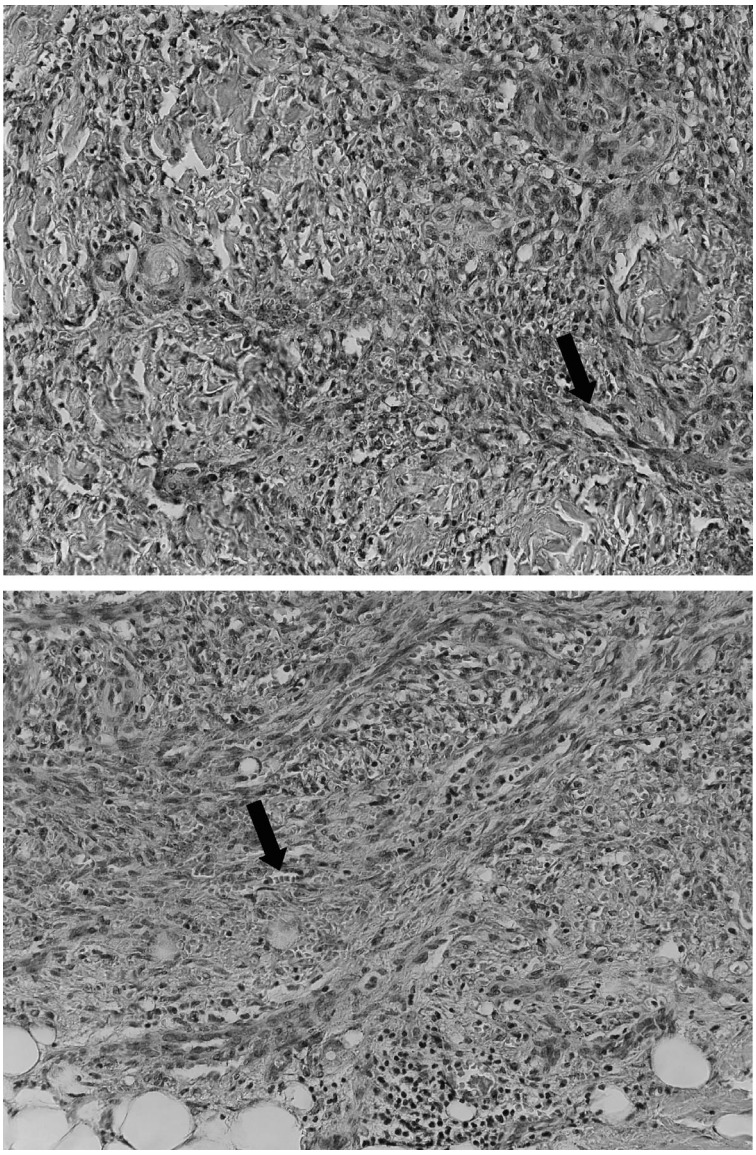

Fig. 2. Histopathologic findings of KS. Hematoxylin-eosin stain. Original magnification ×400. ***a*** KS (HE). Blood vessels (see arrow) appear within irregularly shaped vascular channels lined by endothelial cells. ***b*** KS (HE). Erythrocytes (see arrow) in single file between atypical endothelial cells. Vascular formations and spindle cells extend to the subcutis.

Table 1. HHV-8-encoded genes and their function in altering host signalling pathways

Viral encoded proteins	ORF	Function	Role in HHV-8 pathogenesis
vFLIP	ORF 71	Inhibition of apoptosis by interacting with the death-inducing signalling complex (DISC)	Persistence of HHV-8-infected cells
vBcl-2	ORF 16	Antiapoptotic effect by inhibiting mitochondrial cytochrome C release	Persistence of HHV-8-infected cells
vCyclin	ORF 72	Activation of cyclin-dependent kinase 6	Proliferation of HHV-8-infected cells
vIL-8 receptor	ORF 74	VEGF induction, mitogenesis	Angiogenesis, transformation
vIRF	ORF K9	Inhibition of interferon-induced p53 activation	Antagonization of the antiviral effect of interferon
vIL-6	ORF K2	Inflammation, mitogenesis	Cell proliferation

ORF = Open reading frame; FLIP = Fas/Fas-ligand-associated death domain protein-like inhibitory protein; Bcl-2 = B cell lymphoma; IRF = interferon-regulating factor

increased pigmentation characteristic of older lesions, and dilated vessels in the periphery of the nodular lesion are commonly seen in this stage. Immunohistologically the spindle cells are CD31 and CD34 positive. Electron-microscopic studies showed that KS cells are morphologically not homogeneous and that morphological differences are stage dependent, but not variant dependent.

The molecular biology of HHV-8 is complex and different mechanisms to interact with the metabolism of the host cells are described. HHV-8-infected KS cells elaborate a variety of pathogenetically important angiogenetic factors and proinflammatory cytokines [Ensoli and Stürzl, 1998]. Interestingly, on the other hand, cultured KS cells require cytokines like IL-6 to survive and proliferate [Miles et al., 1990] indicating a tight interaction between the virus and its host. Genomic sequencing has revealed that HHV-8 contains at least 81 open reading frames encoding several genes involved with cellular proliferation, differentiation, immune recognition, apoptosis and survival (table 1) [Yang et al., 2000; Klouche et al., 2004]. By expression of several virus-encoded cellular homologues, central pathways of cell cycle control and apoptosis were modulated and thereby a favorable microenvironment for the HHV-8 is created [Aoki and Tosato, 2003].

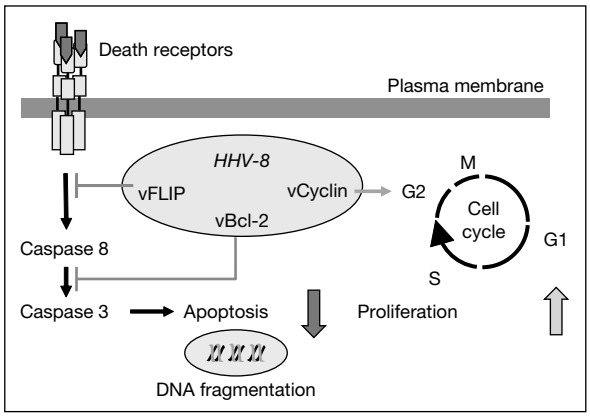

Fig. 3. Molecular mechanisms of HHV-8 pathogenesis.

HHV-8 encodes for a viral cyclin which drives the cell cycle by interaction with a host cyclin-dependent kinase (cdk 6) and which is insensitive to the regulation by cdk inhibitors like p16, p21 and p27. This kinase phosphorylates the retinoblastoma tumor suppressor protein (Rb) leading to the release of the transcription factor E2F. E2F is necessary for the transcription of S phase genes and the entry into G1/S transition [Swanton et al., 1997; Cannell and Mittnacht, 1999]. Host cell apoptosis is inhibited by an antiapoptotic viral Bcl-2 homologue and death receptor activation is counteracted by a viral form of the DISC (death-inducing signalling complex) inhibitor FLIP [Djerbi et al., 1999]. Figure 3 summarizes the described pathways [Boshoff et al., 1997; Barillari et al., 1999a, b; Stürzl et al., 1999; Kaaya et al., 2000]. In general, these signalling pathways are also altered in malignant tumors such as human melanoma [Raisova et al., 2001].

However, it is obvious that HHV-8 is necessary, but not sufficient to cause KS and that other factors such as immunosuppression and HIV viremia play a major role. For example in HIV-associated KS, HHV-8 interacts with the regulatory HIV-tat protein released from HIV-infected cells, which promotes angiogenesis, including activation of VEGF receptor expression and biosynthesis of the proinflammatory cytokine IL-6 [Dezube, 2000]. Additionally, HIV-tat protein is reported to activate tissue metalloproteases, thus facilitating contacts between monocytes and endothelial cells necessary for transmission and further replication of HHV-8 [Kumar et al., 1999]. It seems that the induction of angiogenesis is triggered by HIV and, on the other hand, the presence of HHV-8 leads to uncontrolled endothelial cell growth promoting their transformation into aggressive spindle cell tumors.

Therapeutic management of KS has been a target for intensive studies over recent years [Orfanos et al., 1995; Grunaug et al., 1998; Krown, 1998; Yarchoan, 1999]. Topical strategies such as cryotherapy, laser therapy and X-ray radiation are standard procedures for localized disease. For disseminated and visceral KS chemotherapeutics such as liposomal antracyclines, bleomycin, etoposide, paclitaxel and vinca alkaloids have been described to be successful [Gottlieb et al., 1997; Heimann et al., 1997; Schwartsmann et al., 1997; Nannan et al., 1999; Fumagalli et al., 2000; Gascon and Schwartz, 2000; Sgadari et al., 2000]. Furthermore, the antiangiogenic agent thalidomide was found to be effective in HIV-associated KS [Fife et al., 1998; Little et al., 2000]. Interferon-α has a beneficial long-term effect. In vitro studies pointed out that interferon-α reduces the proliferation of endothelial cells [Stadler et al., 1990; Schaart et al., 1991; Opravil et al., 1999]. However, antiherpes virus drugs, e.g. foscarnet, cidofovir and ganciclovir, are not sufficient as a monotherapy of KS [Devianne-Garrigue et al., 1998; Simonart et al., 1998; Fife et al., 1999; Willers et al., 1999].

A series of recent studies have shown that highly active antiretroviral therapy (HAART), particularly combinations including proteinase inhibitors, are effective in reducing the development of HIV-associated KS [Aboulafia, 1998; Benfield et al., 1998; Dupin et al., 1999; Dupont et al., 2000]. As a result, a substantial decrease of HIV-infected patients with KS has been noted after introduction of HAART [Jacobson et al., 1999]. It is interesting to note that the responses to HAART are more prolonged than those of other conventional chemotherapeutic strategies [Bower et al., 1999]. HAART, therefore, is strongly recommended as a first-line therapy of HIV-associated KS, in order to decrease the HIV load and to circumvent the obvious pathogenetic interaction of HHV-8 and HIV [Husak et al., 1999; Morini et al., 2000].

New insights into the pathogenetic molecular mechanisms of KS will generate new therapeutic strategies targeting paracrine factors, immune response, angiogenesis, cell cycle regulation and apoptosis [Whelan and Scadden, 2000].

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Merkel Cell Carcinoma – Clinical Presentation and Treatment

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Merkel cell carcinomas are dark blue-red soft tumors with a shiny nonulcerated surface, usually growing rapidly (fig. 1). Originally they have been described by Toker [1] and interpreted as carcinoma of eccrine glands. About 80% are localized to face/neck and extremities, and a few to the trunk, where the tumor is often reminiscent of subcutaneous infiltrations. The incidence is 0.2–0.3/100,000/year; 76% of patients are older than 65 years, and only 5% are younger than 50 years [2–5]. Very rarely children have been described suffering from a Merkel cell carcinoma [6]. Merkel cell carcinoma seems to be restricted to Caucasians and equally distributed among both genders [3].

Due to its unspectacular clinical features the differential diagnosis includes cutaneous metastases, lymphoma and adnexal tumors, but also basal cell carcinoma, malignant melanoma and others. The diagnosis is often made by routine histopathological investigation. It is a solid, noncohesive tumor within the dermis, but epidermis and adnexal structures are free from tumor infiltration. Tumor stroma and lymphocytic infiltrations are rare, if present at all. Three histomorphological types have been specified. The classical trabecular type was originally described by Toker [1, 7]. This type is rare and seems to have a somewhat better prognosis. About 80% of Merkel cell carcinomas belong to the intermediate cell type with a very homogeneous cell pattern of medium-sized cells and rare stroma (fig. 2). In addition a small cell type exists which seems to have the poorest prognosis. Therefore, in routine histology the diagnosis is often difficult and, for years, it had to be proved by electron microscopy by demonstrating the typical neuroendocrine granules of the tumor cells [8]. These granules are also common in the neuroendocrine

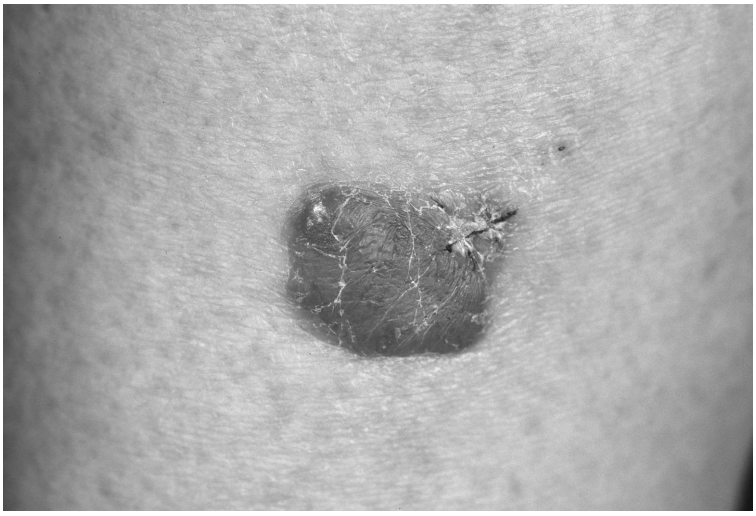
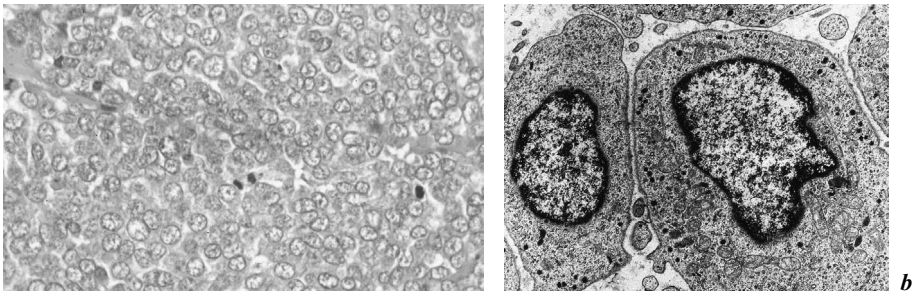


Fig. 1. Merkel cell carcinoma showing the typical shiny surface (81-year-old woman).



a ***b***

Fig. 2. Merkel cell carcinoma. ***a*** Intermediate-cell type (HE staining) showing homogenous small-to-intermediate-sized cells with vesicular nuclei. ***b*** Electron microscopy demonstrating the typical dense core granules in the cytoplasm.

Merkel cells disseminated within the basal layer of epidermis and the outer root sheath of hair follicles [9]. A second cellular feature, the cytoskeleton, biochemically made by low molecular cytokeratins 8, 18, 19 and 20 is also characteristic of Merkel cells and Merkel cell carcinomas. Especially cytokeratin 20 is highly selective (fig. 3a). The cytokeratin filaments make up a normal cytoskeleton but also paranuclear whirls (fig. 3b). The Merkel cell

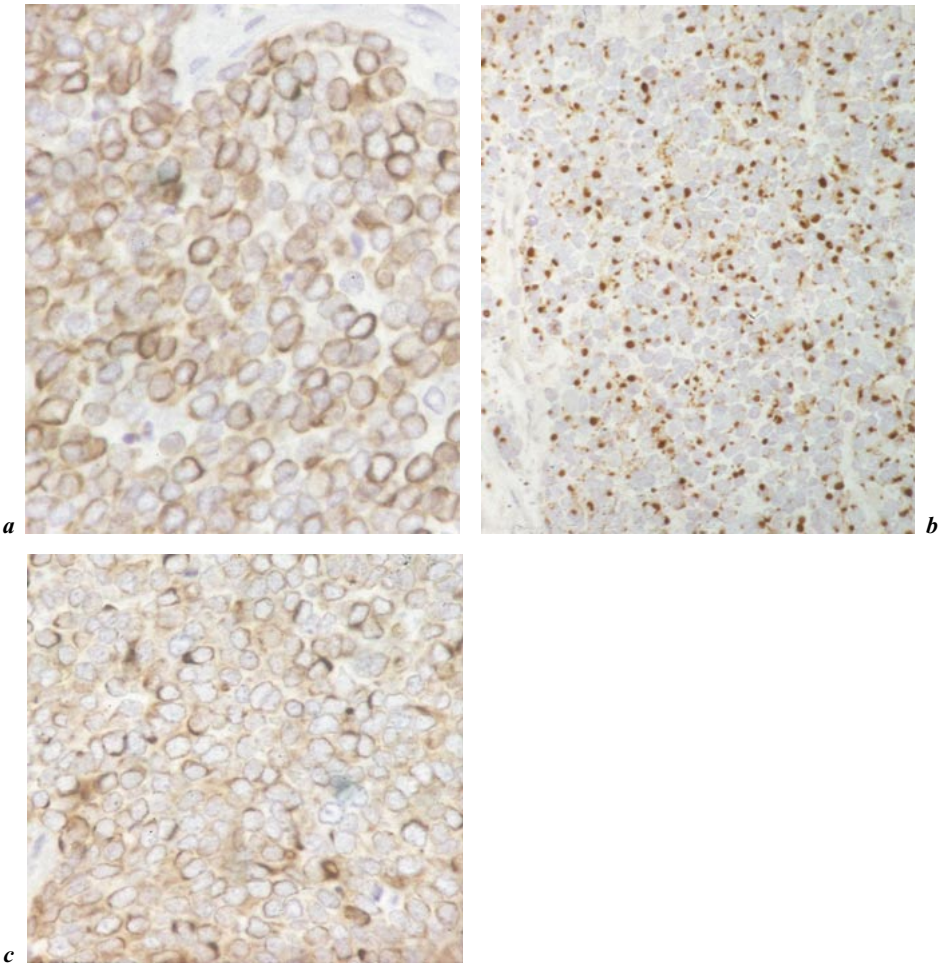


Fig. 3. Merkel cell carcinoma. Immunohistochemistry with antibodies to cytokeratin 20 (***a***, ***b****:* clone Ks IT 20.8) and neurofilament proteins (***c****:* NF-H, clone N 52). Note the staining of a typical cytoskeleton (***a***) and paranuclear whirls (***b***, ***c***) by intermediate filament antibodies.

carcinomas in addition coexpress neurofilament proteins, often prominent in paranuclear whirls (fig. 3c). Thus, the unique coexpression of cytokeratins and neurofilaments, a highly typical cellular feature of Merkel cell carcinoma, makes the immunohistochemical analysis of this tumor possible [9, 10]. Some neural and neuroendocrine markers are often present but in rather low amounts [5].

In the pathogenesis of Merkel cell carcinoma UV exposure and immunosuppression are main aspects. It is localized to the UV-exposed head, neck and extremities and gets more frequent with a higher UVB dose [3, 10, 11]. Patients with organ transplants develop a 50 times higher rate of Merkel cell carcinoma mostly within 5 years after transplantation at a younger age (<50 years) and the carcinoma is more aggressive [12]. In addition, after immunosuppressive therapy due to rheumatoid arthritis, HIV infection and other diseases the rate of Merkel cell carcinomas seems to be higher [13].

Moreover, Merkel cell carcinoma is the second carcinoma in about 25% of patients. This is a rather high amount compared to other tumors and mostly the first tumors are squamous cell carcinomas of the skin and ear-nose-throat area, leukemia or lymphoma [14].

During the last years neuronal paraneoplastic syndromes of Merkel cell carcinoma became evident [15]. Especially encephalomyelitis with rapid cognitive decline, behavioral disturbance and hallucinations seems to be often more or less intense. In addition, the Lambert-Eaton myasthenic syndrome and multifunctional neurological disorders have been described. It seems that in most cases of Merkel cell carcinoma neuronal disturbances are present to a greater or lesser extent. Up to now antibodies to acetylcholine receptors, substantia nigra and especially the neuronal Hu antibodies staining cytoplasm and nuclei of neurons have been described. The latter have not been characterized yet but seem to suggest a severe prognosis [15].

The therapy of Merkel cell carcinomas is often drawn from individual or very few cases, but no prospective double-blinded studies do exist in any tumor stage. Commonly, Merkel cell carcinoma is staged according to Yiengprugsavan et al. [16]: stage 1 means the primary tumor, stage 2 regional tumors and stage 3 metastases. In stage 1 there is consensus to do an excision with safety margins of about 2 cm; radiation and sentinel node biopsy should be done if possible [10, 17]. A meta-analysis (including n = 60) revealed that many more recurrences developed in cases with positive sentinel node biopsy including total lymph node dissection compared to negative sentinel nodes [18]. In stage 2 total lymph node dissection and radiation are generally accepted. Perfusion of the extremities (melphalan, TNF-α or others) and chemotherapy in diseases with a severe prognosis and/or rapid recurrence are to be discussed. However, the benefit of any chemotherapy in adjuvant situations has not yet been proven. Stage 3 is the phase of chemotherapy and mostly combinations established in small cell carcinoma of the lung are used. They are often based on etoposide, cisplatin, or cyclophosphamide among others [10, 19–23]. For octreotid, a somatostatin analogue, some case reports have shown beneficial effects but this is under discussion [24]. Radiation of metastases might be added. As the appearance of distant metastases and lethality is 40%, it has to be

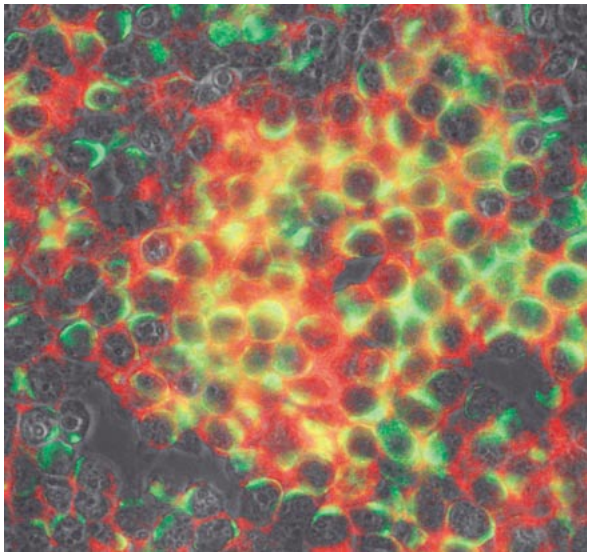


Fig. 4. Merkel cell carcinoma. Double immunofluorescence microscopy using monoclonal mouse cytokeratin 20 (clone IT-K_s20.10, green) and polyclonal rabbit c-kit antibodies (anti-CD117, red). A large amount of tumor cells is expressing c-kit.

stated in general that Merkel cell carcinoma is biologically more aggressive than malignant melanoma [11]. Thus, innovative future therapies should be initiated. Various Merkel cell lines in culture are available [25, 26], which might be helpful for further studies. However, the chemosensitivity tests are poor because of the slow and irregular doubling time of Merkel cell carcinoma cells in culture [10, 25, 26]. We tried Bcl-2-antisense oligonucleotides in a mouse experiment, where we were able to reduce tumor growth and to induce regression impressively [27]. A further concept might be CD117 (c-kit receptor tyrosinkinase) which as published is present in most Merkel cell carcinomas (fig. 4) [28]. However the benefit of an inhibitor of this tyrosine kinase (e.g. imatinib) has to be clarified in the future. As regards therapies to be established in Merkel cell carcinomas, it should always kept in mind that patients are rather old and often multimorbid.

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Merkel Cell Carcinoma – Uncommon and Aggressive Cutaneous Tumour

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The Merkel cell was initially described in 1875 by Friedrich Merkel [1] as an epidermal non-dendritic non-keratinocyte cell, which he called a tactile cell. The Merkel cell carcinoma (MCC), which belongs to the family of neuroendocrine tumours, was described for the first time by Toker [2, 3] in 1972 as a trabecular carcinoma of the skin found in 5 patients. Because of the unclear origin, the tumour was differently named like primary small cell tumour of the skin, primary neuroendocrine carcinoma of the skin, cutaneous apudoma, extrapulmonary carcinoid of the skin, and finally MCC [4–6] since a malignant transformation of Merkel cells, which are the skin pressure receptors, located in the basal layer of the epidermis [7, 8] became the supposed origin of this tumour.

Histological Diagnosis

Histologically, the epithelioid cells are small, round and blue, with a small basophil cytoplasmatic rim and a nuclear pattern of chromatin. Their dense, neurosecretory, submembranous granula evidenced with electron microscopy pointed to the neuroendocrine origin of the Merkel cells [3, 4, 9], which migrate from the neural crest to the skin and express a number of epithelial and neuronal markers after maturation [10]. Therefore, today the histopathological diagnosis of MCC is not merely based on morphological criteria [7] but mainly on the immunohistochemical assessment, which shows a specific expression spectrum of neuron-specific enolase, cytokeratin 20, neurofilament protein, synaptophysin, CD57, and chromogranin A [6, 9, 11–13]. As a chromosomal

abnormality the deletion of the short arm of chromosome 1 (1p36) is known, which is a common deletion in neuroblastoma and melanoma [14], whereas a conclusive gene, suppressor or oncogene, has not yet been positioned [13]. The expression of somatostatin receptors in addition to all the other markers is a further aspect to specify the diagnosis. About 78% of the primary tumours had a positive octreotid scan [15]. The results may be more promising with the new ligand (90) Y-DOTATOC and PET imaging, even in a therapeutic sense [16].

Epidemiology and Clinical Aspects

Commonly, it seems that the MCC as a specific tumour entity and especially its aggressiveness are still not well recognized. But the tumour has meanwhile become known to the specialists as a malignant, neuroendocrine, or cutaneous neoplasm, with a high rate of recurrence, propensity for lymphangiosis in the dermal lymphatic system, spread to regional lymph nodes and metastases. MCC is presumably the most malignant, most deadly primary skin tumour with a higher mortality rate than melanoma.

The histomorphological difficulties of the interpretation of an MCC and the several differential diagnoses, such as melanoma, lymphoma, extraskeletal Ewing sarcoma, and metastases from endocrine tumours (carcinoma of unknown primary origin), are well known [7]. MCC must already have existed at the time before the first description of its entity in 1972 [2]. Therefore, it may have been interpreted at those times as one of those other diseases. In the data base of our department there is no patient with MCC treated before 1988. Interestingly, Gillenwater et al. [17] from the MD Anderson Cancer Center reported on 66 patients with MCC seen between as early as 1945 and 1995. The earliest MCC patients out of 251 in a recent publication from the Memorial Sloan-Kettering Cancer Center (MSKCC) [18] were treated in 1970 (the largest number of patients from a single institution). The first time when radiotherapy of MCC was published was only in 1986 [19], followed in the next 5 years by just three further reports from the United States and Australia [20–22].

In spite of the growing intense interest of the oncologists and the increasing number of clinical publications, the MCC is still a relatively rare tumour entity, which presents primarily in Caucasians [23]. Poulsen [13] cites the US Surveillance, Epidemiology, and End Results (SEER) Program with an estimated incidence of 0.23 per 100,000 people in the white population [24]. The prevalence of MCC relative to melanoma in the Caucasian population was less than 1:60 [25]. Nevertheless, it seems that MCC became more frequent and more aggressive [25]. Allen et al. [18] from the MSKCC report on about 3 patients treated per year between 1970 and 1990, about 7 patients treated yearly

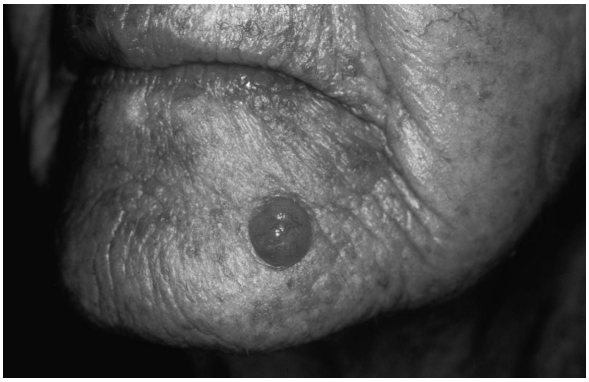

Fig. 1. Apparently harmless MCC nodule.

between 1991 and 1995, and finally a mean number of 23 patients treated yearly between 1995 and 2002.

There are only a few imaging reports [26], most of them concentrated on the use of nuclear medicine with somatostatin (octreotide) and PET imaging. With some exceptions [17, 27–30] the disease is reported mainly by case presentations, in spite of the growing literature. The high numbers of 875 patients in the publication of Akhtar et al. [31], who attributed just 10 patients from their own institution, and of 1,024 patients in that of Medina-Franco et al. [23], who reported on 16 of their own patients, represent the results of reviews of the literature.

The most frequent clinical presentation of an MCC is a nearly always painless, reddish or flesh-coloured, often fast growing, subcutaneous nodule (papule) with an iceberg-like effect, broadening in the depth, nevertheless often underestimated as non-malignant because of its innocuous appearance (fig. 1). But the variation of the clinical features is broad, from a slowly growing, small nodule up to rather large plaques (fig. 2, 3). At presentation, the tumour is most commonly less than 20 mm [25]. In the literature there is a broad agreement concerning the typical patient who is between 65 and 70 years old; patients younger than 50 are rather rare, the incidence being 24 times lower [25, 32]. The incidence of MCC is probably slightly higher in men [24, 25, 31]; in most publications, however, there is no clear gender predominance.

The tumour develops preferably in the skin areas exposed to the sun: 50–60% in the regions of head and neck [25], especially periorbital [13] and frequently at the eyelids [25], in 20–40% the extremities are involved [31], and the rest occurs in the skin of the trunk, mostly of the buttocks [31]. Twelve percent of the MSKCC patients were diagnosed with metastases and unknown primary tumour [18].

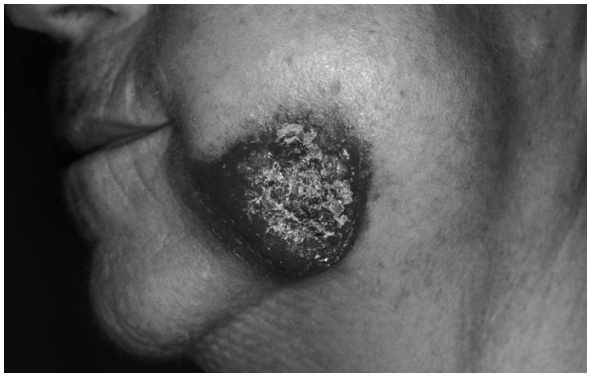

Fig. 2. Huge, fast-growing MCC with invasion of the skin.

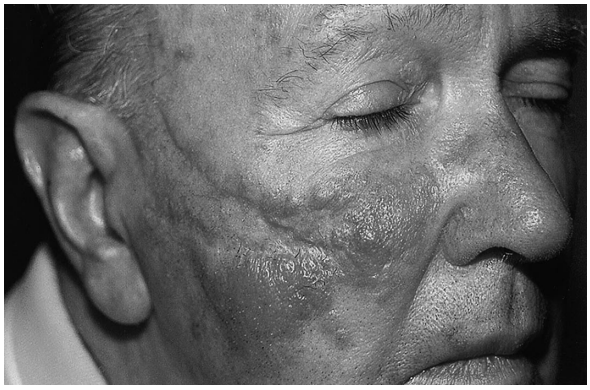

Fig. 3. Extensive local recurrence after incomplete resection of an MCC nodule on the cheek.

Seventy to 80% of the patients present with clinically negative regional lymph nodes [18, 25, 27, 29, 31], less than 10% with metastatic disease. However, the aggressiveness of the disease has been proved by the incidence of micrometastases in 100% of prophylactic lymph node dissection [32].

The preference for the areas exposed to the sun and the predominance of the elderly people clarify the dominant role of the UV radiation for the development of the MCC. This carcinogenic effect is obviously intensified in patients with immunosuppression, especially after organ transplantation and with acquired immunodeficiency [23, 25, 31, 33–35]; the latter may themselves be the causes of the disease.

Staging and Prognosis

The nodotrophic behaviour of the MCC, the early invasion of the adjacent subdermal lymphatic net system and the tendency for haematologic spreading need a very careful clinical examination with special attention to the lymphatic ways and a consequent and systematic staging with CT, supplemented with MR imaging [26], like that of a small cell lung cancer. The spectrum of the diagnostic possibilities has been extended with the demonstration of somatotropin receptors in the fast majority of the patients [16] and the use of the FDG-PET scan.

The challenge for the organization of the staging measures is the optimized timing between the first intervention, which was often not performed in an oncological department and therefore may often confront with an unexpected or even unknown histological diagnosis, the next definite therapeutic procedure and the right staging course. The key note in organizing must be not to lose time. For the definition of the right therapeutic procedure a multidisciplinary discussion is needed.

Commonly, the clinicians use the proposal from Yiengpruksawan et al. [36] for the clinical staging definition: stage I = localized disease of the skin, stage II = tumour in the regional lymphatic area, lymph nodes and/or dermal lymphatic spread, and stage III = tumour beyond the region, metastatic disease. At the MSKCC, a four-tiered staging system is used for patients with MCC [18]. The diameter of the primary tumour was identified as an additional predictor of survival in node-negative patients and the tumours were separated in tumours <2 cm in any diameter and tumours >2 cm. The staging system was enlarged from three to four categories: stage I = localized tumour, <2 cm; stage II = localized tumour, >2 cm; stage III = regional lymphatic spread, and stage IV = dissemination beyond the region, metastatic disease.

Allan et al. [18] went a step further to separate patients with clinically negative nodes. When nodes were pathologically staged and the disease was confirmed as node-negative, the probability of survival of this group of patients was 97%, the rate of nodal recurrence was 11%. When clinically negative nodes were not pathologically staged, the survival rate was 75% ($p = 0.009$) and the rate of nodal recurrence was 44% ($p = 0.001$).

The staging data of Allan et al. [18] reporting on the largest single-institution number of 251 patients with MCC demonstrate the variable natural history of MCC dependent on the stage of disease at presentation. Disease stage was the only independent predictor of survival (stage I: 81%; stage II: 67%; stage III: 52%; stage IV: 11%). Also the review of the literature of 1,024 patients by Medina-Franco et al. [23] concludes with the statement that the only factor significantly associated with overall survival was the stage of disease at

presentation: median survival for patients with stage I (localized disease of the skin) was 97 months, and for patients with stage II (dermal or nodal lymphatic disease) it was 15 months (log rank, $p = 0.02$). Poulsen [13] writes that multivariate analysis indicated the presence of lymph nodes as the major factor affecting survival but this was not a significant factor for locoregional control, which would confirm the effectiveness of radiation in securing locoregional control even in the presence of nodal disease.

Categorizing into stages does not give sufficient information concerning the differences in locoregional control dependent on the localization of the disease. Poulsen [13] points to the possible difficulties to control lesions of the legs. Reasons were the poor blood supply in elderly patients, which may limit a wide surgical resection and the low tolerance of the lower limbs of high-dose radiation. There are reports which find that patients with head and neck disease have the highest risk of local recurrence [36] and that head and neck location of the tumour is an unfavourable prognostic factor [27].

Treatment of Choice

Due to the low incidence of MCC there are no prospective studies, which validated the different modalities of treatment. Great numbers of review patients [23, 25, 31] are very helpful as to epidemiological data but the huge diversities of treatment strategies, the different staging measures, the differences in technical skill and quality and the long time scale involved give no really useful information for any superior treatment strategy adapted to the clinical situation. The main reasons for the divergence in the proposed therapeutic procedures are the natural history of the disease and the development of distant metastases associated with the stage of the disease at presentation [13, 18] and the different high local and high nodal recurrence rates, to which these proposed procedures are related. In the literature there are no data on how these recurrences may influence the rate of distant metastatic disease.

Authors with experience of low rates of local recurrences after surgical treatment of the primary tumour see no need for any adjuvant treatment [25, 30, 36–38], especially those who report on the follow-up of patients treated with Mohs micrographic surgery [30, 37], whereas authors confronted with high recurrence rates of up to 62% [17, 18, 25, 29, 39] after surgical intervention strongly plead for postoperative radiotherapy [13, 17, 19, 20, 22, 25, 27, 29, 30, 40–45] or even for exclusive radiotherapy following biopsy because of the inherent radiosensitivity of the MCC [8, 20, 21, 40, 42]. Differences of the recommended therapeutic procedures also depend on the location of the disease. Allen et al. [18], who reported retrospectively on 251 patients with presumably

exclusively nodal MCC, do not see any statistical advantage of additional radiotherapy after excision treatment; only 29% of their patients had the tumour located in the head and neck region. However, Gillenwater et al. [17] reported on 100% of head and neck MCC and they found that the use of postoperative radiation therapy was associated with a significant improvement in locoregional control. But they also stated that there was no detectable influence of the type of initial therapy on the rates of distant metastases or on survival.

Surgery

The recent publication of the department of surgery of the MSKCC brought some clarifications concerning the general and especially the surgical procedure in local and nodal treating of MCC [18]. A wide excision was attempted in all but 2 of 251 patients and the margins were negative in 94% out of 196 patients with determined status of the margins. The average width of the surgical margin was 1.1 cm. Local recurrences developed in 15 (8%) of the 185 patients who underwent a margin-negative excision and in 2 (18%) of the 11 patients with positive margins. Surgical margins of more than 1 cm were not associated with decreased local recurrence. Adjuvant irradiation was administered occasionally to 27/185 patients with negative margins and 3/11 patients with positive margins. It is surprising that only 2 of the 11 patients, who underwent a margin-positive excision of the primary tumour, had local recurrence.

Allen et al. [18] recommend that all patients presenting with localized MCC undergo pathologic nodal staging with sentinel lymph node biopsy. Since the formerly used elective lymph node dissection had been replaced by the sentinel biopsy 71% of MCC patients had undergone pathologic staging. In the current study, approximately 25% of patients with clinically negative nodes were found to have nodal disease after pathologic evaluation. Nodal recurrences developed in 15 (11%) of the 128 patients who presented with stage I–III and who underwent operative nodal staging and treatment and in 44 (44%) of the 102 patients who were clinically staged as node negative ($p > 0.001$). The reasons for the consequent staging strategies are 3-fold: pathologically staged categories, stage-specific survival and decreased regional nodal recurrence.

The use of adjuvant radiotherapy for the draining lymph nodes in this retrospective study was not associated with a statistically significant decrease of nodal recurrences, but radiotherapy was administered casually. Allen et al. [18] claim that the data demonstrate that nodal recurrence is low when pathologic staging has been performed. The 5-year disease-specific survival rate for all patients was 64%. Patients who were alive at the time of the last follow-up had an average follow-up of 46 months, 25% had died of disease.

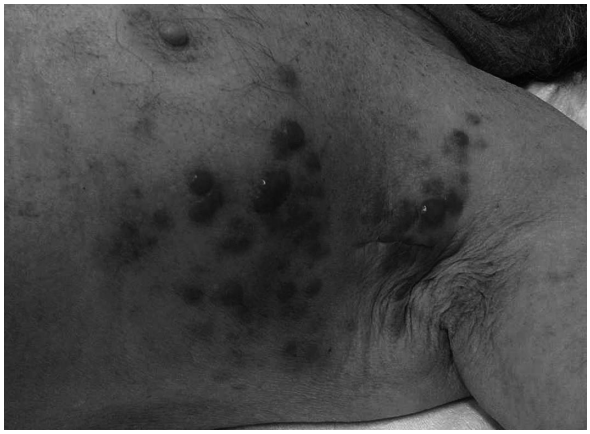

Fig. 4. Innumerable nodules of an MCC on the thoracic wall.

Radiotherapy

Even if this study gives good advice as regards surgical treatment and also excellent data as to the treatment results of surgery, there is not much information on the reasons for the difference in the local recurrence rates relative to published data, which have challenged radiotherapy to statistically significant successful postoperative or adjuvant treatment [13, 17, 23, 27, 29, 40, 45, 46]. When radiotherapy is used as postoperative measure, the controversy on how wide the margins should be is unnecessary because wide resection margins are not required provided radiotherapy is used [13, 40]. This aspect may be especially important for the head and neck tumours, where cosmetic points of view cannot be neglected and for the distal extremities, where there may be difficulties with plastic surgery. In these patients surgery and radiotherapy complement each other maintaining function and avoiding mutilation.

Presumably, Allen et al. [18] know the primary tumour only as a resectable nodule mainly at the trunk or only patients with resectable nodules have been referred, but the variety of the clinical features is immense (fig. 1–4) and the clinical reality concerning patients with MCC may in some oncological departments really differ from the patients who are presented by the authors. In such situations, an unresectable disease, an inoperable patient, or a refusal of surgery, radiotherapy can be used as the sole treatment modality with a high likelihood of achieving control of the primary site, especially for the treatment of the in-transit areas, which are often involved, and the draining lymph nodes [40]. Radiation is further well recommended for patients unable to have

complete excision or if complete histological margin control is unavailable [37]. Radiotherapy has to be considered for patients with large tumours and is the treatment of choice for locoregional recurrences after resection.

Surgery will remain the treatment of choice for solid nodal disease of the primary and the regional lymph nodes but radiotherapy is playing a more important role in the management of patients with MCC. Because of the wide variety of the clinical manifestation of the disease it is impossible to give advice as regards a standard procedure. The planning of the treatment and the application technique must always include a meticulous staging and a special attention to the in-transit areas. Target volume of the radiation are the primary region with an appropriate security margin, the in-transit area when indicated and the draining nodes, dependent on the histopathological result of the nodal staging. The biological efficacy of the performed radiotherapy technique should not be lower than a physical dose of 50 Gy given with 2 Gy per fraction; in the case of a palpable tumour or an R2 resection a regime of at least 60 Gy should be accomplished, even if we know about the intrinsic radiosensibility of the MCC.

Chemotherapy

The role of chemotherapy in the treatment of MCC would not be controversial, if the results of the currently mostly used substances were more convincing [18, 23, 31, 45]. A generally accepted statement is that chemotherapy has no primary role in the management of non-disseminated MCC. Chemotherapy should be considered in patients with advanced disease, when in good performance status [47]. The mostly used combinations of chemotherapy are cyclophosphamide, doxorubicin, vincristine and etoposide, cisplatin (or carboplatin) [25, 47]. These combinations can achieve good remission rates in more than 50%, but they are of short duration. Therefore, the role of chemotherapy still remains to be defined.

Poulsen et al. [28] have currently published their study on synchronous treatment of high-risk MCC with carboplatin/etoposid and radiation (TROG 96:07). The 53 eligible patients of this study had to have at least one of the following high-risk features: recurrence, involved nodes, primary tumour >1 cm, R2 resection or category T0 N+. Accrual time was from 1996 up to 2001. Sixty-two percent of the patients had positive lymph nodes. Every patient was treated with 50 Gy for the primary and for the nodal region. Chemotherapy was applied during 10 weeks. The major factor influencing survival was the presence of nodes in a multivariate analysis. The overall survival >3 years is 76%, the locoregional control is 75%, the distal control is 76%. The authors conclude

that high levels of locoregional control and survival have been achieved with the addition of chemotherapy to radiation treatment for high-risk MCC of the skin and that these results warrant further investigation.

The prognosis of MCC depends on the status of the patient at presentation. The metastatic disease is not dependent on the treatment techniques used for the primary tumour and the draining lymph nodes. It is all the more necessary to find substances for avoidance and successful treatment of the metastatic disease.

Conclusion

Treatment of MCC needs a multidisciplinary engagement to find the best procedure on an individual basis. The clinical features of this disease are extraordinarily different and so is the optimal strategy for every patient. This may be the reason for the statement that the best way to treat this disease has not yet been found. There is an urgent need for substances to treat the metastatic disease.

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Potential of Radiation Therapy in the Multimodal Management of Merkel Cell Carcinoma

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Merkel cell carcinoma (MCC) is the currently preferred term for a distinctive cutaneous malignancy originally described as trabecular carcinoma [38] and also known as neuroendocrine carcinoma of the skin. It is a rare but aggressive tumour which occurs mainly in adults and elderly individuals, but a few cases have been described in children. The most common locations are sun-exposed areas of head and neck (47%), especially the face and the extremities (40%), while truncal lesions are quite rare (8%) as has been analyzed in 875 cases [1]. The relationship between men and women is 1.5 to 1 [12].

MCC usually appears as an indolent, firm and dome-shaped reddish or violaceous nodular lesion of 1–3 cm in size often covered with intact epidermis. Macroscopically the tumours are homogenous and can be well delimitated. The clinical differential diagnosis includes leukaemia cutis, amelanotic melanoma, metastatic carcinoma, pyogenic granuloma, and squamous cell carcinoma [17].

MCC has at first been believed to be a relatively benign skin tumour with a protracted course [38], but nowadays it is recognized for its aggressive and potentially lethal behaviour. Regional nodal metastases are common, and distant metastases also occur, particularly to the lungs, liver and bones, but also to unusual sites such as the testis. Ten to 30% of the patients have lymph node metastases at the time of first diagnosis, increasing to 45–90% of all patients in the course of the disease [3, 41]. Local recurrence as well as the establishment of lymph node metastases are accompanied with a poor prognosis and seem to precede the cascade-like development of distant metastases [14]. The main factor significantly associated with overall survival is the stage of disease at presentation: median survival was 97 and 15 months for stage I and II (table 1), respectively ($p = 0.02$) [24].

Table 1. Stage-oriented treatment of MCC [modified after 9]

Stage I: primary tumour alone	Stage II: locoregional metastases	Stage III: distant metastases
Wide local excision with 2- to 3-cm safety margin or micrographic surgery	*In case of local recurrence* Extended excision and radiation of tumour region and regional lymph nodes	Reduction of tumour masses by excision or rather radiotherapy
Postoperative radiation of primary tumour region (field surrounds excision scar approximately 5 cm) and adjuvant radiotherapy of regional lymph nodes	*In case of lymphatic metastases* Complete lymph node dissection and postoperative radiation	*Polychemotherapy* Etoposide Doxorubicin Cyclophosphamide Methotrexate Cisplatin 5-Fluorouracil Vinca alkaloids

Diagnostics

Histology and Immunohistochemistry

Microscopically, the tumour is centred in the dermis or sometimes in the subcutaneous tissue, with the overlying epidermis usually being uninvolved.

Three histologic variants of MCC are described: trabecular, intermediate and small cell. The intermediate type appears to be the most prevalent and the small cell type to have the most unfavourable prognosis [26].

The diagnosis of MCC can be made on the basis of the cytologic features. The cytoplasm is scanty but visible, the nuclei are round and vesicular, with a typically fine granular ('dusty') chromatin and multiple nucleoli. Mitotic figures and fragmented nuclei are plentiful. The stroma may contain proliferated vessels with plump endothelial cells, a feature that these tumours share with many other malignant neoplasms having a primitive neural phenotype. MCC can be seen in association with in situ or invasive squamous cell carcinoma, with duct-like structures of the eccrine type, and with basal cell carcinoma-like areas, suggesting that it originates from a multipotential stem cell of ectodermal derivation [5].

Ultrastructure of the tumour cells reveal dense-core neurosecretory granules and tightly packed perinuclear intermediate filaments. Also filament-rich cytoplasmic spikes and paranuclear fibrous bodies can be observed.

Immunohistochemical markers for MCC include cytokeratins No. 20, 8, 18, 19 in the cytoskeleton or paranuclear areas, neurofilament proteins, and neuron-specific enolase. Some cases of MCC have shown focal reactivity for

chromogranin A and protein gene product 9.5 [26]. In recent studies abnormalities of various chromosomes have been shown [18].

Diagnostic Strategy

The clinical appearance of MCC is not very characteristic and the diagnosis is mostly confirmed by means of histology, immunohistochemistry and sometimes by electron microscopy. Especially the delimitation to metastases of small-cell lung cancers, lymphomas, carcinoids, sebaceous carcinomas, metastatic medullary thyroid cancers, Ewing sarcoma, neuroblastoma, but also to squamous cell carcinoma of the skin and to basaliomas have been reported as problematic [41].

Evaluation of a patient with histologically confirmed MCC must include full body skin examination and lymph node evaluation. A complete blood cell count and liver function tests should be performed as well; CT scanning of the chest, pelvis, and abdomen may be indicated to rule out the presence of small cell carcinoma of the lung. CT and MRT scanning of the head and neck may prove valuable in the detection of nodal disease. Unfavourable prognostic factors are a tumour size of more than 2 cm, angiolymphatic invasion, regional spread, localization in head and neck area and age under 60 years [12, 17].

Treatment

Management of MCC follows staging of patients according to local, regional, or metastatic disease (table 1). Current recommendations support wide local excision with lymph node dissection, adjuvant radiotherapy and chemotherapy, if indicated [6]. However, the most efficient therapeutic strategy is not yet defined due to low case numbers and missing prospective randomized trials. Adjuvant radiotherapy is recommended in addition to obligate surgery, as has been shown in a retrospective analysis of 1,024 cases [24].

Surgery

The initial treatment approach for MCC is the excision of the primary tumour including a 2- to 3-cm safety margin and therapeutic resection of pathologically involved regional lymph nodes. For facial lesions smaller safety margins and application of micrographic surgery may be appropriate [4]. Local recurrence rates after surgical treatment alone are high with 25–40% on average, occurring very fast in only 4–8 months (median). Eighty-five to 90% of all recurrences occur within 1 year, almost all within 2 years [7, 23, 25, 36]. Recurrences at the primary site, requiring multiple surgical excisions, are

common, and the failure to control the primary tumour is strongly correlated with distant and regional spread [35].

Considerable controversy exists on the management of clinically uninvolved regional lymph nodes. MCC is believed to spread in a manner similar to melanoma, with orderly progression to regional lymph nodes before distant spread, prompting many authors to recommend surgical evaluation or prophylactic treatment of regional nodes [34]. The technique of sentinel node identification by intraoperative lymphatic mapping using blue dye and radionuclide localization, first described for melanoma, has recently been applied to patients with MCC [13, 15, 16, 34]; however, the prognostic value is not clearly defined yet [12].

Radiation Therapy

The radiosensitivity of MCC is well documented [14, 28, 39], although the results with derivative clones of MCC suggest that some of them may develop resistance during clonogenic evolution [19]. The following analysis of retrospective data and prospective studies gives a clear profile of the role of radiotherapy in MCC. However, because of low patient numbers data from randomized studies are missing.

Indications

Primary radiotherapy is indicated in inoperable disease or patient refusal of surgery. Indications for adjuvant radiation therapy include tumour size >2 cm, positive resection margins or gross residual disease, angiolymphatic invasion and involved lymph nodes. Postoperative radiation therapy is recommended and may improve locoregional control up to 96% [3, 8, 23, 25, 27, 41]. Ott et al. [29] stress the need for adjuvant radiation therapy to the primary site for tumours of the face, where wide surgical margins are often difficult to obtain, and for truncal lesions which have shown a higher recurrence risk.

Because of the high incidence of lymph node metastases of up to 90% in the course of the disease [3, 41] the indications for radiotherapy of the regional lymph nodes are not only given after excision of involved lymph nodes, but also as prophylactic irradiation of regional lymph nodes as an alternative to surgical exploration [30]. Postoperative radiation should also be performed for clinically negative regional lymph nodes.

Radiotherapy Technique

Treatment fields are designed to encompass the original tumour bed and excision scar including a 5 cm margin of normal tissue. For patients with lesions on the head and neck, the ipsilateral cervical nodes are treated prophylactically,

and bilateral irradiation is recommended for midline lesions. Depending on the anatomic region irradiation can be done with superficial-quality X-rays or low-energy electrons and bolus. Lymph node areas should be treated with single or opposed photon portals.

For the head and neck area intensity-modulated radiotherapy has been applied in comparison to the conventional lateral photon-electron technique with three-dimensional treatment planning [20]. The clinical target volume included the entire scalp tissue volumes to the surface of underlying cranial bone, as well as superficial and deep neck nodes in the bilateral neck. The intensity-modulated radiotherapy plan resulted in a substantial dose to the lens, brain, and orbit, making it clinically unacceptable [20].

Doses

Typical treatment regimens deliver 45–50 Gy (1.8- to 2-Gy conventional fractionation) to the primary site for subclinical disease, with boost doses up to 60–70 Gy for microscopic or gross residual disease [35].

Morrison et al. [27] recommend postoperative radiation therapy in all cases of MCC, with wide fields covering the tumour (60 Gy), operative bed (56 Gy), and regional lymph nodes (46 Gy).

Results

Radiotherapy is an effective tool in the primary treatment strategy, if surgery is not available. In a comparison of stage I (without lymph node involvement) MCC patients treated with radiotherapy alone versus surgery followed by radiotherapy there was no statistical difference in overall and disease-free survival [28].

Adjuvant radiotherapy results in significant reduction of the risk of local recurrence ($p > 0.00001$), analyzed in a literature review of 1,024 cases [24]. Recurrence rates could be reduced from 100 to 30% and the median recurrence-free survival time could be significantly prolonged [11]. An immediate postoperative radiotherapy can achieve local control much better than irradiation after recurrence surgery [2]. In the biggest Australian study median disease-free survival for patients treated with surgery and adjuvant radiotherapy was 10.5 versus 4 months compared to those undergoing surgery alone. The 5-year overall and disease-free survival rates were 47 and 25%, respectively [39]. The Cologne group significantly improved the locoregional control and disease-free survival with postoperative radiotherapy ($p = 0.023$). Uni- and multivariate analysis revealed that head and neck location of the tumour and the lack of postoperative radiotherapy are unfavourable prognostic factors [7]. Those with head and neck disease had the highest risk of local recurrence, which

occurred in 62.5% at the Royal Marsden Hospital [33]. In another head and neck patient group distant disease developed in 36% of all patients regardless of therapy [10].

The effectiveness of synchronous carboplatin, etoposide, and radiation therapy was prospectively assessed in a group of 53 patients with high-risk MCC. The 3-year overall survival, locoregional control, and distant control were 76, 75 and 76% [31]. The protocol had acceptable toxicity and the treatment was delivered in a multi-institutional trial setting [32].

Sequelae

Lovett et al. [22] observed an overall complication rate of 5.3% in 339 patients that was directly related to primary lesion size. The complication rate was 0.9% for lesions up to 1 cm, 6.5% for lesions of 1–5 cm, and 13% for lesions of >5 cm. An excellent cosmetic result was achieved in 88% of patients and was related to treatment modality: superficial X-rays 95%, electrons 80%, mixed beams 76%, and photons 70%.

In the updated series of Locke et al. [21], the overall complication rate was 5.8%, with soft tissue necrosis being the most common problem. Cartilage necrosis occurred in only 1, bone necrosis in 3, and cataracts in 6 of 531 patients. In patients for whom cosmetic data were available, 92% overall had excellent to good cosmetic results, with fair to poor cosmetic results more likely in recurrent lesions or those treated with higher doses.

Chemotherapy

MCC is sensitive to both radiation [19] and chemotherapy [3], similar to small cell lung cancer. These treatments are frequently used in the palliative setting for nodal or distant metastases. Chemotherapy has been recommended against distant metastatic spread in spite of the inability to demonstrate a clear survival advantage with either approach.

Complete remissions have been achieved especially in manifest locoregional metastasis. The most common regimens use drugs active in small cell lung cancer [6]. Chemotherapy regimens with epirubicin, vincristine and prednisone or etoposide, and cisplatin show response rates of 75 or 60%, respectively, with complete remissions up to 36%, but short duration of remission [37]. In a review the overall response to first-line chemotherapy was 61%, with 57% response in metastatic disease and a 69% response in locally advanced disease. The 3-year survival rate was 17% in metastatic disease and 35% in locally advanced disease [40].

Conclusion

MCC is an aggressive skin cancer, with a high tendency for local recurrence and distant spread. Surgery and adjuvant radiotherapy markedly improve local control rates and should be considered the best practice. But there may be no detectable influence of the type of initial therapy on the rates of distant metastases or on survival. The role of chemotherapy as part of the initial treatment remains to be defined. Future therapeutic innovations should be directed toward controlling the development of distant metastases.

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Skin and Other Reactions to Radiotherapy – Clinical Presentation and Radiobiology of Skin Reactions

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The skin represented the dose-limiting organ in radiotherapy over long periods of time. In the first third of the 20th century, radiotherapy was associated with deposition of significant radiation doses in the superficial compartments of the skin. Therefore, all major radiobiological principles, such as effects of fractionation on radiation sensitivity or volume/area effects, were initially based on observations in epidermal radiation reactions.

The development of radiation sources producing mega-voltage X-rays resulted in translocation of dose maxima into the subcutaneous soft tissue. With this, and with the introduction of multiple-field irradiation techniques, severe radiation effects in the skin were almost completely prevented. However, skin reactions are still relevant to critical skin areas, such as intertriginous regions. Also, the treatment of skin tumours, which requires high skin doses, is associated with substantial skin effects. Combinations of radiotherapy, e.g. with chemotherapy or UV exposure, can significantly aggravate skin effects. Moreover, accidental radiation exposure is frequently associated with significant skin doses. Therefore, early and late reactions of the skin must still be considered clinically relevant.

Pathophysiology and Clinical Presentation of Skin Reactions

Radiation effects in skin represent an orchestrated response of all individual tissue components, i.e. epidermis, hair follicles, vasculature, glands,

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Management of Skin and Related Reactions to Radiotherapy

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The human skin has many unique functions and features: it is a barrier for fluid retention and diffusion and provides excellent protection against mechanical, physical and chemical stress. Other functions include thermal regulation, sensory function and secretion of different liquids and secretions. Ionizing radiation and cytotoxic drugs may disturb or damage several of these functions. While radiogenic skin reactions are easy to prove as they correspond to the radiation portal, cytotoxic drug-associated skin toxicity is much more difficult to detect. Early skin reactions are always a warning sign for a high individual sensitivity to ionizing radiation or chemotherapeutic drugs or may function as an indicator for other organ changes.

The radiogenic skin reactions are well known from long-term clinical experience, and related pathophysiological tissue changes are easier to examine than in other organ systems. They serve as an experimental model for the course of radiogenic reactions. Nevertheless, the 'standard of care of skin reactions' has remained a subject of controversy for decades.

Although there are abundant published data on the subject of acute skin care management after radiotherapy (RT), the standard of quality of the published studies is quite low and there is little empirical evidence on which to base a decision for *best clinical practice*. Thus, skin care varies widely between and even within different RT institutions. Clearly, there are few definitive guidelines, but much more contradictions in the care of skin altered by radiation and/or chemotherapeutic drugs. Methodological flaws are common in the skin care literature: lack of randomized studies, use of inconsistent toxicity grading scales, lack of information regarding the scoring process, lack of patient compliance with the skin care instructions and insufficient attendance

rate for patient reviews in long-term follow-up or other factors such as use of concomitant chemotherapy (ChT). Many reviews which claim to recommend guidelines are reproducing so-called already published 'facts', and are indeed most inconclusive. In many of these papers the summary conclusion is 'that it is recommended to develop clinical guidelines for skin care'. Thus, in this clinical chapter we will try to analyze current knowledge on skin care in oncology more cautiously.

Skin Anatomy and Pathophysiology

Anatomical Features

The human skin consists of several anatomical layers. The *epidermis* (30–300 μm thick) borders with its basal membrane to the stratum papillare of the *dermis.* On top of the basal membrane, the stratum basale (5–10 μm) consists of rapidly dividing basal cells, several layers of the metabolically very active stratum spinosum, the intermediate zone of the stratum granulosum and the stratum corneum directly on the skin surface, which contains no living cellular elements. The stratum corneum, the skin surface, has a variable thickness depending upon the body region and other factors like physical stress, e.g. on the palms of hands and soles of feet. Usually, the cell cycling time of the basal cells is about 50 h. Newly formed basal cells reach the intermediate zone within 2 weeks and require another 2 weeks to reach the skin surface, where the normal epilation process of the skin (desquamation) continuously takes place.

The *dermis* (1–3 mm) is situated below the basal membrane of the epidermis. Its uppermost layer, the stratum papillare, contains a dense network of small arterial and venous capillaries and some larger vessels which are responsible for the nutrition of the epidermis. Each papilla has a mean diameter of 30 μm and a mean length of 350 μm; it contains 15–20 vessels of about 5 μm in diameter. The vascular wall of the vessels consists of 10–20 linear endothelial cells. Each papilla and vascular network feeds about 120–150 basal cells which are regarded as the *functional subunit* of the skin; this subunit is most important for the pathophysiological alterations following RT and/or ChT [Archambeau et al., 1995]. Situated below the vascular network of the stratum papillare and subpapillare, the stratum reticulare contains only very few vessels, but a dense network of different collagen fibers connecting the vascular network of the stratum papillare with the subdermal vascular plexus of the subcutis.

The human hairs are a part of the skin and derive from the 2.5–3.5 mm deeply located hair roots. They are much more radio- and chemosensitive

during their anagenic growth period (M- and S-phase) than during the telogenic (G0) phase.

Pathophysiological Features

Pathophysiological skin changes after high single dose or fractionated RT are well known both experimentally and based on long-term clinical observation. After high single doses in the range of 16–22 Gy the number of proliferating basal cells of the *epidermis* is constantly reduced and reaches its lowest level at about 3 weeks after radiogenic exposure (linear decrement); afterwards, a rapid recovery leads to the original number of basal cells about 4 weeks after RT (exponential increment). The proliferative activity of basal cells increases only after 2 weeks, but reacts with very rapid cell cycle times of as low as 15 h. In animal models single doses of 45 Gy still lead to complete epidermal recovery within 6 weeks or less. A single surviving basal cell per square centimeter is sufficient for the induction of the repair process. Nevertheless, single doses as high as 25 Gy can cause secondary skin ulcerations and necrosis about 7–9 weeks after RT.

Up to 3 weeks after high single-dose RT no morphological damage of *endothelial cells* is observed in the vascular network of the stratum papillare; thereafter perivascular infiltrates of inflammatory cells, edema and erythema occur. Four weeks after RT the epidermis has recovered, but later the number of endothelial cells per papilla decreases rapidly, and the mean vascular diameters increase parallel to the rarefaction of vessels per papilla. Usually no new vessels are formed within the papillar microvasculature *(angio-neogenesis)* which has been observed in larger vessels [Archambeau et al., 1995]. In the long term, the number of papillar vessels decreases with increasing RT dose. The remaining vessels enlarge further in diameter and the papilla becomes shallower, until they disappear, and enlarged vessels become visible, a phenomenon which has been termed ‘teleangiectasia’. This papillar loss results in decreasing perfusion of the epidermis and increasing malnutrition leading finally to *skin atrophy*.

Fractionated RT concepts using 2-Gy single doses cause pathophysiological effects similar to those of high single-dose RT, but at a higher total RT dose level. About 3 weeks after RT the number of basal cells is reduced, reaching its lowest level at about 5 weeks, but at the end of the 6th week (at 60 Gy) normal levels of basal cells are achieved due to their rapid proliferation. The growth rate of basal cells increases at the 3rd week of fractionated RT and remains at an increased level for several weeks thereafter. At this early stage no morphological changes of the vascular network are detectable. The radiogenic *erythema* reflects perivascular infiltration of inflammatory cells and increased blood perfusion in enlarged skin vessels [Peter, 1996; Scholz, 1918]. In general, the

detectable morphological changes after fractionated RT correspond well to those observed after single-dose RT.

Functional Skin Unit

Late skin reactions are not related to the survival pattern of the basal cells and the reactive adaptation of endothelial cells. However, when considering the papilla as a relevant functional subunit of the skin including the basal cells and their associated vascular network, the observed radiogenic effects can be understood much better: late effects are more or less determined by the survival of the endothelial cells of the papillar vasculature. For long-term preservation of the skin a minimal number of functional subunits (papillae) is required [Archambeau et al., 1995]. When the number of subunits decreases below a critical level due to continuous vascular degeneration, the related basal cells are not sufficiently nourished, which leads to cell death and secondary skin atrophy. Further malnutrition induces long-term hypoxia and subsequent skin necrosis, which may appear even years or decades after a completed RT series. As endothelial cells within the papillar vascular network are replaced by repopulation to a very small extent, the 10–20 endothelial cells for each papilla are considered as the *critical structure* of the skin. Restoration of the proliferation rate of endothelial cells may require up to months or years [Archambeau et al., 1995]. Using conventional fractionated RT (with 1.8–2 Gy single dose) up to a total RT dose of 45–50 Gy only minor papillar remodeling takes place, but it becomes clinically evident at total doses of 50–60 Gy and leads to the development of telangiectasia and skin atrophy. With higher total RT doses these reactive skin changes are further accelerated and may result in skin necrosis usually at total RT doses beyond 60 Gy.

Besides the basal and endothelial cells within the dermis *fibroblast activity* plays an important role for the development of *subcutaneous fibrosis*. After radiation exposure the surviving fibroblasts differentiate increasingly to postmitotic fibrocytes, which deposit large amounts of free collagen into the tissue; this process induces loss of elasticity and hardening of the skin via contractile forces. Special tissue growth factors (TGF), e.g. TGF-β, play a key role in this process [Herskind et al., 1998].

Clinical Course of Radiogenic Changes

Acute skin reactions occur with various degrees of severity in most patients undergoing RT. Skin reactions are an unavoidable part of oncological treatments, thus, care should be directed toward the palliation of the skin symptoms. Typically, radiogenic skin changes occur only in the regions of the radiation beam entry and exit. They are mostly determined by the applied single and total RT doses and treatment time. Additionally, individual factors (age, comorbidity,

Table 1. Radiogenic skin changes depending on single and total dose

Radiogenic skin reaction	Single dose (Gy)	Fractionated 2-Gy dose (Gy)	Onset of symptoms days	Functional status	Histopathological features
Epilation	5–7	20	18	–	empty follicles; hair loss
Erythema	10–20	20–40	12–17	hyperemia	none/perivascular infiltrates
Erythema	20–30		2–6	hyperemia	none/perivascular infiltrates
Pigmentation	10–20	approx. 45		–	increased melanin deposition
Dry epitheliolysis	10–20	approx. 45	30–70	–	increased skin desquamation
Moist epitheliolysis	20–24	45–50	30–50	loss of serum	severely reduced cellular density
Moist epitheliolysis and not-healing ulceration, necrosis	>24	>60	at 30–50 d	loss of serum	severely reduced cellular density
Telangiectasia	17–24	45–50	at 6 months to years	–	skin atrophy, extended and rarified vessels
Nonhealing ulceration/ skin necrosis	>27 –	>60	at 6 months to years	complete loss of barrier function	–

skin condition) and medications (chemotherapy, radiosensitizer, radioprotectors) may influence the observed skin changes. Table 1 compiles typical radiogenic skin reactions depending upon the applied total RT dose (for 2 Gy single fractions).

Factors Influencing Skin Reactions

Acute skin reactions (≤90 days after RT) usually occur as *erythema* at the 3rd week of fractionated RT using single doses of 2 Gy. With time and increasing dose, *hyperpigmentation* of the skin becomes apparent which is followed by hair loss *(epilation)* and increased dry skin desquamation *(dry epitheliolysis)*. Beyond a total dose of 45 Gy moist skin desquamation *(moist epitheliolysis)* takes places with the risk of local complications due to infection; usually at the end of the RT series, all cutaneous changes heal rapidly and almost completely within 2–3 weeks. When total doses of 60 Gy are applied, moist skin

epitheliolysis may persist much longer. In case of incomplete healing about 7–8 weeks after the end of the RT course, *skin fibrosis and necrosis* of the skin may develop [Archambeau et al., 1995]. Thus, generally, long-term follow-up is required after any therapeutic exposure of ionizing radiation, to detect and appropriately treat possible radiogenic late effects. Those late reactions directly deriving from severe acute reactions are termed *'consequential late effects'*.

Acute skin reactions vary depending upon the anatomical site and thickness of the stratum corneum: the hand palms and foot soles react much less than the skin of the head and neck, the back of the trunk and the extensor side of limbs. Intermediate skin sensitivity is found on the chest and frontal part of the trunk and the flexor side of limbs. The frontal part of the neck, the inner part of the elbow and knee joint and the inguinal and anogenital regions are most radiosensitive, partially because of some additional physical reasons (loss of dose accumulation under the skin). Complete recovery and healing of the skin is possible with the exception of an altered skin pigmentation (hyper- and hypopigmentation), permanent hair loss (alopecia) within the RT portal(s) and permanent loss of function of the skin glands.

Chronic skin reactions (>90 days after RT) develop over months or years after completion of RT, but progress constantly. Total RT doses ≤40 Gy do not cause clinically detectable late skin effects; higher RT doses >40 Gy induce increased desquamation and skin atrophy, telangiectasias and subcutaneous fibrosis. With increasing skin atrophy secondary skin ulcerations and necrosis may develop which rarely heal spontaneously and will further progress over decades [Turreson and Thames, 1989; Thames et al., 1990]. Untreated subcutaneous fibrosis will induce an increasing loss of elasticity and hardening of the skin leading to further functional deficits especially around the joints. Fluid retention (edema) within the dermis and subcutis may cause a painful lymphedema of the arm (e.g. woman with breast cancer) or submental and neck regions (e.g. patients with head and neck tumors). In addition, the skin may become more sensitive to special infectious disorders, like erysipelas.

Hair loss (epilation) occurs after 3- to 5-Gy single doses and 4- to 8-Gy fractionated RT with 2 Gy as single dose. A tolerance dose for complete and permanent hair loss has not been established: in an animal model (pig skin) single doses of 7–8 Gy induce a measurable thinning of the hair, above 14.4 Gy hair loss is obvious and above 17.4 Gy, complete and irreversible [Malkinson and Keane, 1981]. Fractionated RT using 2-Gy single doses and total RT doses of 14–20 Gy induce measurable hair changes, and beyond 40–50 Gy complete and irreversible hair loss. The relevant α/β value is between 1.7 and 3.1 [Turreson and Thames, 1989].

Table 2. Impact of fractionation on radiogenic skin reactions [modified from Thames et al., 1990; Turesson and Thames, 1989]

Clinical effects	α/β value, Gy	95% percentile, 2-Gy fractionated doses
Acute skin reactions		
Erythema	7.5	5.4–10.9
Epitheliolysis	11.2	7.8–18.6
Chronic skin reactions		
Fibrosis	1.9	0.8–3.0
Telangiectasia	3.9	0.2–4.8

Modulation of the Radiogenic Effects

Impact of Fractionation

Acute and late skin reactions are depending upon single and total RT doses and the duration of the RT course *(fractionation effect)*. This clinical observation has led to the *tolerance dose concept* [Strandquist, 1944]. With increasing experimental studies and further clinical knowledge, the *nominal standard dose (NSD) concept* was developed [Cohen, 1949; Ellis, 1969; Fowler et al., 1965]. A better estimation of radiogenic late effects is possible with the *linear-quadratic model*, which assumes equal treatment times for acutely reacting tissues like the skin. Careful observation of the clinical RT course after total mastectomy and chest wall RT allowed the calculation of *α/β values* for acute and late radiogenic skin reactions: acute skin reactions have high α/β values that are not influenced by fractionation changes, while late skin reactions have low α/β values reflecting high sensitivity for different fractionation schemes [Turreson and Thames, 1989]. Table 2 summarizes the impact of fractionation on radiogenic skin reactions.

Impact of Treatment Volume/Treatment Area

The surface of the irradiated skin is important for the development of early and late skin reactions *(volume effect)*. A total skin dose of 70 Gy delivered to 100 cm^2 will lead to skin necrosis within 5 years in 50% of the treated humans. If the field size is reduced to 10 cm^2, the same RT dose will result in only 5% skin necrosis within 5 years (tolerance dose concept TD 5/5 and TD 50/5) [Emami et al., 1991]. Table 3 depicts the correlation of treatment volume and frequency of specific late cutaneous reactions. So far, no threshold dose has been found at which cutaneous side effects may be excluded. Telangietasias occur at a frequency of 3% or less at 45 Gy fractionated RT, skin necrosis at

Table 3. Impact of treatment volume on radiogenic skin reactions [modified from Emami et al., 1991]

Field size	TD 3/5, single dose (Gy)	TD 5/5, single dose (Gy)	TD 50/5, single dose (Gy)
Telangiectasia			
100 cm^2	50 Gy	59 Gy	65 Gy
Necrosis/ ulceration	TD 3/5, single dose, Gy	TD 5/5, 2-Gy fractionated dose, Gy	TD 50/5, 2-Gy fractionated dose, Gy
100 cm^2	51	55	70
30 cm^2	57	60	–
10 cm^2	69	70	–

50 Gy; for minor skin changes (skin atrophy, functional deficits) no valid RT dose data have been established.

Documentation of Treatment Sequelae

Acute Side Effects

For the documentation of acute skin reactions within an oncological treatment concept, three international classifications are available: both the World Health Organization (WHO) classification and the Common Toxicity Criteria (CTC criteria) are suitable for the scoring of chemotherapy-related systemic side effects on the skin as a whole, while the Radiation Therapy Oncology Group (RTOG) and European Organization on Research and Treatment of Cancer (EORTC) criteria are better suited for the documentation of localized radiogenic side effects at or around the treatment portal. There are minor differences between the three toxicity classifications: for example, the RTOG defines a (localized) moist desquamation as grade III, and only ulceration is regarded as grade IV toxicity; in contrast, the WHO and CTC classifications document (systemic) skin ulceration as grade III which allows no differentiation with moist skin desquamation.

Table 4 summarizes the three different classification systems for acute skin reactions.

Chronic Side Effects

For the documentation of late or delayed skin reactions within an oncological treatment concept, the LENT-SOMA classification has been developed on

Table 4. Different classifications of acute side effects on skin/subcutaneous tissue [modified from Seegenschmiedt, 1998]

Toxicity/grade	Grade 1	Grade 2	Grade 3	Grade 4
WHO – acute				
(1) Total skin	Erythema	Dry desquamation, vesiculation, pruritis	Moist desquamation, ulceration	Exfoliative dermatitis; necrosis requiring surgical intervention
(2) Hair	Minimal hair loss	Moderate patchy alopecia	Complete, but reversible alopecia	Nonreversible alopecia
CTC – acute				
(1) Epidermis – local (e.g. after injection)	Minor pain and swelling	Moderate pain and swelling with inflammation or phlebitis	Severe pain and gross swelling, necrosis, ulceration	Plastic surgery required
(2) Epidermis – systemic (total skin related)	Scattered macular or papular eruption or erythema that is asymptomatic	Scattered macular or papular eruption or erythema with pruritus or other associated symptoms	Generalized symptomatic macular, papular, or vesicular eruption	Generalized exfoliative dermatitis or ulcerating dermatitis
(3) Allergy (systemic)	Transient rash, drug fever $<38°C/100.4°F$	Urticaria, drug fever $\geq 38°C/100.4°F$, mild bronchospasm	Serum sickness, bronchospasm, requiring parenteral medications	Anaphylaxis (anaphylactic shock)
RTOG – acute				
(1) Skin/subcutis local (within RT portal; from RTOG)	Follicular, faint erythema; epilation, dry desquamation, decreased sweating	Tender or bright erythema, patchy moist desquamation, moderate edema; local therapy required	Confluent, moist desquamation ($>50\%$), severe pitting skin edema; intensive local therapy required	Ulceration, hemorrhage, necrosis; surgical therapy required

the initiative of the National Cancer Institute (NCI) and many cooperating oncological working groups. It has been published in 1995 both by American and European scientific journals [Anonymous, 1995]. This classification system can differentiate between subjective (S) patient-related parameters, objective (O) examiner-related parameters and parameters related to the management (M) and analytic work-up (A) of radiogenic side effects; other oncological disciplines are invited to use this concept. For some specific questions it is meaningful to introduce, supplement or refine some of the criteria. Nevertheless, personal judgment and clinical experience are still required to use this concept and consistently evaluate the clinical outcome in patients.

Table 5 summarizes the criteria of the LENT-SOMA classification for the skin and subcutis.

Prophylactic Measures to Avoid Skin Reactions

Presently, no established measures are available to completely prevent known acute or late radiogenic skin reactions. However, there is evidence that administration of the *radioprotector amifostine (WR 2721)* protects the skin from radiation or exerts an influence on the repopulation of basal cells during fractionated RT. In animal models, *amifostine* increases the cutaneous resistance to the development of moist epitheliolysis by a factor of 1.1–2.3 after single dose and fractionated RT [Clement and Johnson, 1982; Rojas et al., 1986; Travis et al., 1982]; topical application of amifostine is similarly effective as long as the drug is able to diffuse through the stratum corneum; other experimental studies have not confirmed these results of radioprotection of the skin [Lamperti et al., 1990; Mc Chesney et al., 1986]. Thus, more valid clinical data have to be awaited including large randomized clinical studies.

Mechanical protection of the stratum corneum is important during the whole RT course. Local powders may increase the skin surface, absorb sweat and improve the thermal convection of the skin. Thus, many radiation therapists are convinced that the use of powder is the 'gold standard' of local skin prophylaxis and protection [Zimmermann et al., 1998]; however, so far no clear evidence for such an advantage has accumulated from clinical studies. The few comparative clinical studies provide no reported advantage for powder versus hydrophilic ointments (e.g. Linola®) at the stage of moist epitheliolysis (CTC grade 2); the application of powders on moist epitheliolysis at the skin surface is even contraindicated, as it may result in scurf formation and promote infections. In addition, washing with mild soaps has no negative impact on radiogenic skin reactions [Campbell and Illingsworth, 1992], as short-time exposure to water and mild soap will not cause or increase the desquamation of the stratum corneum; in contrast, short-term rinsing with normal water may improve the hygienic conditions in skin folds, e.g. the axilla or ano-genital

Table 5. LENT-SOMA classification of chronic side effects of skin/subcutaneous tissue [modified from Seegenschmiedt, 1998]

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective criteria				
(1) Scaliness/roughness	Present/asymptomatic	Symptomatic	Requires constant attention	
(2) Sensation	Hypersensitivity, pruritus	Intermittent pain	Persistent pain	Debilitating dysfunction
Objective criteria				
(1) Edema	Present/asymptomatic	Symptomatic	Secondary dysfunction	Total dysfunction
(2) Alopecia (scalp)	Thinning	Patchy, permanent	Complete, permanent	
(3) Pigmentation change	Transitory, slight	Permanent, marked		
(4) Ulcer/necrosis	Epidermal only	Dermal	Subcutaneous	Bone exposed
(5) Telangiectasia	Minor	Moderate <50% area	Gross >50% area	
(6) Fibrosis/scar	Present/asymptomatic	Symptomatic	Secondary dysfunction	Total dysfunction
(7) Atrophy/contraction (skin depression)	Present/asymptomatic	Symptomatic/<10%	Secondary dysfunction/ 10–30%	Total dysfunction/>30%
Management				
(1) Dryness			Medical intervention	
(2) Sensation		Intermittent medical intervention	Continuous medical intervention	
(3) Ulcer			Medical intervention	Surgery/amputation
(4) Edema			Medical intervention	Surgery/amputation
(5) Fibrosis/scar			Medical intervention	Surgery/amputation
Analytic measures				
(1) Color photographs	Assessment of changes in appearance			

Table 6. Randomized studies of prophylactic measures to avoid acute radiogenic skin reactions

Clinical study (author, year)	Cases n	Medication/drug A	Medication/drug B	Application	Clinical outcome
Gless et al., 1979	54	Hydrocortisone ointment	Clobetasone ointment	Prophylaxis starting at day 15 of RT	Clobetasone worse
Potera et al., 1982	19	Hydrocortisone ointment	Normal ointment without drugs	Prophylaxis starting at day 15 of RT	No difference
Maiche et al., 1991	50	Chamomile ointment	Almond extract ointment	Prophylaxis	No difference
Campbell and Illingworth, 1992	99	Water vs. water + soap	No measures	Prophylaxis	No difference
Halperin et al., 1993	65	Vitamin C lotion	Lotion-based	Prophylaxis	No difference
Maiche et al., 1994	50	Sucralfate creme	Creme-based	Prophylaxis	Sucralfate creme better
Lokkevik et al., 1996	86	Bepanthen ointment	No measures	Prophylaxis	No difference
Delaney et al., 1997	39	Sucralfate-sorbolene	Sorbolene	Treatment at moist epitheliolysis	No difference
Roy et al., 2001	64	Water vs. water + soap	No measures	Prophylaxis	Water better
Gujral et al., 2001	42	Hydrolytic enzymes	No measures	Prophylaxis	Hydrolytic enzymes better
Schmitt et al., (pers. data)	40	Neutral powder	Linola®	Prophylaxis	No difference

region, and avoid bacterial superinfection. Thus, it is neither recommended to avoid washing generally nor to do it extensively.

Measures which help to minimize mechanical stress, physical or chemical skin irritation are always helpful; thus, it is necessary to avoid tight clothing, frequent washing or extensive application of lotions, ointments or cremes on the skin, because they may soften the protective stratum corneum. Similarly, intensive sweating should be avoided. Thus, neutral powders are recommended for dry skin epitheliolysis (CTC 1°); however, they should not be applied more than two or three times daily. They may provide a ‘cooling effect’ similar to some hydrocolloid ointments.

Table 7. Prophylactic and therapeutic measures for acute radiogenic skin reactions (treatment recommendations of the Department of Radiation Oncology, Alfried Krupp Krankenhaus Essen)

Skin, general	Dry desquamation and skin erythema	Powder (e.g. talcum); Tannalbin (Tannolact® creme/powder/moist dressing) 2–3 times for 20 min; dry cooling (cool packs wrapped in soft linen on irritated skin regions) or moist cooling with gels (e.g. *Aloe vera* gels from pharmacies/drug stores) 2–3 times for 20 min;
	Pruritus	Dexpanthenol lotion or creme (Bepanthen®); isoprenaline sulfate (Ingelan powder or gel)
	Moist desquamation	Sulfadiazine silver (Flammazine® creme), Perubalsam dressing (Branolind® ointment compress)
	without infection	Hemodialysate gel (Actihaemyl®)
	with infection	Local H_2O_2 (peroxide) solution 1–2% spilling and PVP (iodine) solution, local plus possibly systemic antibiotics according to clinical judgment (most important skin infection with *Staphylococus aureus*) or after antibiogram testing (wide spectrum of antibiotics possible)
	Ulceration, necrosis	Tannalbin (Tannolact® creme/powder/moist dressing) 2–3 times for 20 min; sulfadiazine silver (Flammazine® creme), zinc sulfate creme dressing; possibly surgical debridement (for necrotic parts) and refreshing wound edges
Auditory canal	Otitis externa	ENT consultation; dexpanthenol lotion or creme (Bepanthen®)
Eye lids	Acute and dry conjunctivitis, without infection	Dexpanthenol ointment (Bepanthen® eye ointment); tetrazoline eye drops (Yxin®); carbomer gels (Thilo-Tears® Gel), hemodialysate gel (Actihaemyl®), 2–3 times for 20 min on sclera and conjunctiva; ophthalmologic consultation
	with infection	Gentamycin sulfate drops/creme (Refobacin® drops/creme) or antibiotics after antibiogram testing (wide spectrum of antibiotics possible); ophthalmologic consultation
Scrotum, vulva and anal region	Vulvitis, colpitis	Tannalbin (Tannolact® creme/powder/moist dressing 2–3 times for 20 min or sitz bath); dexpanthenol lotion or creme (Bepanthen®) external or internal by tampons; *Lactobacillus gasseri* capsules (Döderlein® capsules, in the evening vaginally)
	Prophylaxis of dryness and fibrosis of the vagina	Estradiol/prednisolone vaginal creme (Linoladiol®); physical dilatation of the vagina (e.g. with tampons soaked with dexpanthenol creme); early onset of sexual intercourse after full clearance of the acute skin and mucosal changes

The following results are known from comparative clinical studies: Skin care applying regular washing with mild soaps or powder is preferred and superior to no washing at all [evidence-based medicine (EBM) level II], especially in skin folds like the ano-genital region. There is no difference between the use of powder, ointments or cremes (EBM level V). Comparing cremes or lotions, there is a slight advantage for cremes containing either corticosteroids, sucralfat and hyaluronic acid versus cremes containing only the basic ingredients without a specific medical content (all EBM Level II). There is good proof for a positive effect of special enzymatic and hyaluronic ointments like Wobemugos© (EBM level II), while there is no advantage for the application of chamomile or vitamin C (EBM level II) [DEGRO Guidelines 'Supportive Care'/Feyer et al., 2004].

As most basal cells recover quickly from radiation exposure starting at around the 4th week of RT, some medical drugs may be able to induce an earlier onset of repair or an increased repopulation rate of the basal cells, respectively. Radioprotection of endothelial cells of the microvasculature of the stratum papillare or stimulation of surviving endothelial cells by application of intravenous amifostine may reduce *delayed skin atrophy* in vivo [Rojas et al., 1986].

Animal studies demonstrate that the decay of papillary vessels can be prevented by specific drugs without influencing cellular radiation sensitivity: Pentoxifylline increases radiation tolerance to secondary skin necrosis by a factor of 1.4 [Dion et al., 1989]; in addition, captopril can reduce late skin reactions [Ward et al., 1990]; a similar effect is achieved with unsaturated fatty acids [Hopewell et al., 1993] which increase the radiation tolerance dose by a factor of 1.14–1.51, but clinically no systematic exploration has been made so far.

In animal studies, amifostine reduces the development of fibrosis [Rojas et al., 1986; Thames et al., 1990], but convincing human studies are still missing. The role of the TGFβ and its signal cascade inducing, promoting and influencing tissue fibrosis is not clarified [Herskind et al., 1998]. Animal studies have shown that postradiogenic subcutaneous fibrosis can be significantly reduced by applying liposomal copper/zinc superoxide dismutase [Delanian et al., 1994].

Exposition to ultraviolet irradiation should be avoided until the acute skin reaction has completely resolved and thereafter, as exposition to ultraviolet irradiation may promote skin atrophy and other degenerative skin reactions [Leyden, 1990].

In addition, simple mechanical measures, such as adequate patient positioning, may reduce the occurrence of skin folds which are a major cause of acute skin reactions due to physical reasons, i.e. loss of the tissue repair effect within the RT portal (e.g. ano-genital region).

Therapy of Acute Radiation Effects of the Skin

Acute Erythema/Dry Epitheliolysis (RTOG Grade I–II)

The treatment of erythema and dry epitheliolysis follows the same principles as discussed for the prophylaxis of radiogenic skin reactions. Mechanical irritation and insufficient thermal regulation have to be generally avoided. Thus, it is not recommended to apply a thick layer of ointments on the skin surface, as this may compromise thermal conduction and regulation; powder and water-containing lotions should be preferred. Erythema and dry epitheliolysis may even be exposed to a short shower with lukewarm water.

Acute Moist Epitheliolysis (RTOG Grade II–III)

Moist epitheliolysis represents the excretion of body serum through the skin surface. Thus, full preservation or rapid repair of the damaged basal cell layer is of utmost importance. The exclusion of mechanical irritation and prevention of infectious disorders support the regrowth of the damaged basal cells, which is usually highly stimulated during the phase of moist epitheliolysis, which usually heals within 2 weeks after radiotherapy. In some cases surgical debridement and hydrocolloid dressing are useful to avoid secondary skin damages, protect the remaining basal cells and prevent fluid retention or dryness of the wound [Margolin et al., 1990]. Antiseptic dressings help to avoid superinfection.

Clinical studies for treatment of moist epitheliolysis have not yet revealed any specific benefit measure to be recommended [Zimmermann et al., 1998]. Nevertheless, antiseptic dressings are highly recommended to avoid secondary infections. To soften scurfs or hard wound edges non-steroidal cremes or lotions are available. Antiseptic liquids or 1% peroxide should be carefully applied to avoid additional damage to the exposed basal cell layer. Powder should not be applied at this stage as it may induce hard scurfs and wound edges which may endanger the healing process within the basal cell layer. The use of local corticosteroids is not recommended and may induce a local immune deficiency leading to a worsening of the local and systemic healing process [Potera et al., 1982].

Semipermeable dressings may lead to serum or liquid retention underneath the dressing which may contribute to some physical disadvantage and increase the RT dose to the basal cell layer. The daily change of the dressing should reduce the build-up effect within the skin. In addition, the daily removal of dressings prior to RT may also reduce the retention effect, but epidermal cells may also become attached to tapes and dressings which could interrupt the healing process. Generally, the success of these practical measures is very high,

but for the treatment of secondary moist epitheliolysis no specific measures exist so far.

Acute Skin Necrosis and Ulceration (RTOG Grade IV)

Skin ulcerations represent a deep tissue defect reaching beyond the basal cell layer of the stratum basale. It may even encompass the whole cutis and reach the subcutaneous tissue which can lead to the exposure of bones, vessels and muscles. These changes have been observed in earlier times when using lower voltage energy photons, i.e. 100 kV–1 MV: however, with megavoltage 6-to10-MV photons such side effects are rarely observed on the undamaged skin. Acute skin ulcerations may also be the result of tumor infiltration which should always be taken into account. The treatment goal is the prevention of local and systemic infections and encompasses all means and principles of surgical wound care [Chang et al., 1996]. If the granulation process is incomplete and does not provide long-term secondary healing of the wound, plastic surgery is recommended using uninvolved (non-irradiated) skin for coverage of the remaining lesion. Smaller defects may be treated postoperatively with hyperbaric oxygen to stimulate telangiectasia [Hartmann et al.,1996]. In some cases, full healing of the ulceration may be achieved, even in cases with LENT-SOMA grade III–IV treatment sequelae.

Treatment of Chronic Cutaneous Effects of Radiation

Chronic Late Effects (LENT-SOMA Grade I–II)

Late cutaneous lesions grade I–II (LENT-SOMA) represent a minor problem, e.g. dry skin, increased desquamation, formation of telangiectasias or itching. The persistence of local edema in the trunk or extremities may lead to cosmetic problems. Subcutaneous fibrosis may impair the mobility of the extremities. Physiotherapeutic measures and lymphatic drainage are the main treatment options for these sequelae. All other additional treatments are only symptom- and function-related measures.

Chronic Late Effects (LENT-SOMA Grade III–IV)

Chronic late effects are often associated with permanent loss of function and sometimes with considerable pain symptoms. Small ulcerations may heal with conservative wound management [Frank et al., 1998]. However, in the later course of sequelae, some recurrent ulcerations may occur which can only be managed with plastic surgery (skin flaps or free transplants). If surgery is not possible or leads to insufficient results, hyperbaric oxygen (HBO) may be

applied (HBO) [Hartmann et al., 1996]. This allows better healing of skin flaps in irradiated tissue.

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Malignant Melanoma – Markers for Progression and Prognosis in Malignant Melanoma

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Melanoma is the most serious of skin cancers and originates from melanocytes or nevus cells. The incidence of malignant melanoma is increasing throughout the world [1]. In 2004, cutaneous melanoma was diagnosed in about 55,000 individuals in the USA, and approximately 7,900 deaths occurred from metastatic disease [2]. Primary melanoma without evidence of metastasis includes AJCC stage I and II. Regional disease includes AJCC stage III with clinical, radiologic or immunohistologic evidence of regional metastases in lymphatic tissue or of satellite or in-transit metastases in the skin. In AJCC stage IV disease, there are metastases at any distant sites. Treatment remains essentially surgical in stage I and II melanoma with a high cure rate. When the primary site metastasizes locoregionally or distantly, however, the cure rates fall tremendously with a 10-year survival rate of 20–30% in stage III and less than 3% in stage IV [3]. Therefore, early detection and diagnosis of cutaneous malignant melanoma is the key to block progression and to improve prognosis. Targeting this aim, biochemical and molecular biological techniques have been introduced into the diagnosis and follow-up of malignant melanoma. They were applied for refinement of staging, in order to detect minimal residual or recurrent disease.

Serological Tumor Markers

Different serological tumor markers of melanoma are currently investigated, e.g. melanoma inhibitory activity (MIA), lipid-bound sialic acid, neuron

specific enolase, S-100β protein, 5-S-cysteinyldopa, tyrosinase, cytokines, metalloproteinases, lactate dehydrogenase (LDH). As serological tumor markers, LDH, protein S-100B, and MIA were evaluated successfully in melanoma patients. Thereby, LDH has been reported to be an independent prognostic factor in AJCC stage IV patients. However, it has a high specificity but low sensitivity, and is not useful in early stages. S-100B and MIA seem to be more promising as serological markers. Numerous reports confirm S-100B and MIA as prognostic factors in patients with metastatic melanoma. This marker was also shown to be useful in detecting recurrent disease in the follow-up of patients. It has been demonstrated that increased MIA values in melanoma patients mirror the degree of metastases. In a very recent comparison of several serum markers in high-risk melanoma patients, it was demonstrated that S-100B and MIA are more sensitive, specific and accurate in detecting recurrent disease than alkaline phosphatase and LDH. Therefore, S-100B and MIA are recommended as useful markers in the follow-up of disease-free stage II and III patients [4–8].

Tartrate-resistant acid phosphatase (TRAP) is a new marker for detecting bone metastases. Bone-resorbing osteoclasts contain high amounts of TRAP 5b which they release into the blood circulation. Circulating TRAP 5b activity is derived exclusively from osteoclasts. The diagnostic sensitivity and specificity of TRAP 5b as a marker of skeletal metastases in patients with breast cancer were 82 and 87%, respectively. In patients with prostate cancer, these values were 71 and 83%, respectively. First data from our group indicate that elevated serum TRAP values also reflect bone metastases in melanoma [9–11].

The changes of different proteins in the serum of tumor patients, as described above, indicate that a systematic analysis of serum of cancer patients may be useful. This analysis is called ‘proteomic oncology’. A novel technique, surface enhanced laser desorption/ionization (SELDI) mass spectrometric analysis was introduced to investigate sera from patients with prostate cancer. This serum finger printing coupled with a pattern-matching algorithm was able to distinguish between patients with prostate cancer, prostate hyperplasia and healthy men. Very recently, first data using this technique on sera of melanoma patients were published. It was shown that SELDI mass spectrometric analysis accurately identified patients who developed recurrences of melanoma after curative resection of primary melanoma [12–14].

Polymerase-Chain-Reaction-Based Techniques

Nucleic-acid-based molecular techniques have been introduced into the diagnosis of cancer. Since the seminal study of Smith et al. [15], many studies have assessed the presence of tyrosinase mRNA by the reverse

Table 1. Expression levels of different markers in circulating melanoma cells from stage I to stage IV patients

Marker	Stage I, %	Stage II, %	Stage III, %	Stage IV, %
Tyrosinase	16	18	19	39
MART-1	7	16	16	29
gp100	39	43	69	0
MUC18	57	50	75	67
TRP-2	0	0	0	0

Table 2. Stage-associated detection rates of circulating melanoma cells

	Detection rates, % stage I/II	stage IV
Brossart et al. [17] (1993)	10 (1/10)	100 (29/29)
Battayani et al. [18] (1995)	20 (2/10)	50 (16/32)
Melado et al. [19] (1996)	36 (14/39)	94 (32/35)
Reinhold et al. [20] (1997)	0 (0/31)	38 (5/13)
Farthmann et al. [21] (1998)	13 (6/46)	44 (16/36)
Schittek et al. [22] (1999)	18 (21/119)	36 (21/58)
Hanekom et al. [23] (1999)	7 (10/143)	0 (0/12)
Palmieri et al. [24] (1999)	34 (53/154)	75 (24/32)
Proebstle et al. [25] (2000)	14 (22/162)	67 (16/24)
Carrillo et al. [26] (2002)	14 (2/14)	87 (14/16)
Palmieri et al. [27] (2002)	42 (60/144)	65 (15/23)

transcriptase-polymerase chain reaction (RT-PCR) in peripheral blood from melanoma patients as a specific marker for circulating melanoma cells. There are also several other melanocyte-specific genetic markers, such as gp100, muc18, TRP-2 and Melan-A/MART-1, that can be used in this approach as a multivariate analysis. Table 1 shows the differing expression levels of these markers in melanoma patients from stage I to IV indicating a high phenotypic variance of circulating melanoma cells. Among these additional markers, MART-1 is probably the best evaluated one, whereas the others are still discussed. Whether multiple marker analysis may improve detection rates of circulating melanoma cells is not clarified yet. Although there are variations in the experimental protocols used, RT-PCR can detect a single melanoma cell in a background of 10^6–10^7 mononuclear blood cells [16]. Subsequent studies confirmed its ability to detect tyrosinase mRNA in the blood of melanoma patients and investigated its correlation to disease stage. Table 2 summarizes the results

of these studies. The data show a relatively high detection rate in primary melanoma patients (stage I/II), which may indicate that melanoma cells can circulate in the peripheral blood of patients without resulting in metastases. On the other hand, circulating melanoma cells of patients with progressive disease (stage III/IV) were not detected in all blood samples, which may be related to a discontinuous dissemination of tumor cells in the peripheral blood. The detection of circulating melanoma cells in peripheral blood may aid the clinician in assessing tumor progression, metastatic potential and response to therapy [28]. Using PCR techniques, several studies indicate that the quantity of circulating melanoma cells correlates with tumor burden and disease progression. On the other hand, molecular biological techniques may, as mentioned above, detect circulating melanoma cells more frequently than clinical manifestation of melanoma progression actually occurs. These findings may question the clinical significance of detecting a small amount of melanoma cells.

We investigated the prognostic value of detecting circulating tumor cells based on a long-term clinical follow-up for at least 3 years in a large group of patients with malignant melanoma ($n = 146$). In this group, circulating tumor cells were discovered in 44 cases (30%); i.e. 19% (4/21) in patients with thin primary tumor (stage I), 23% (7/31) in stage II patients with thick primary tumor, in 29% (13/45) in stage III patients with regional skin or lymph node metastasis and in 41% (20/49) in stage IV patients with distant metastasis. The minimal follow-up was 36 months after the first blood collection, with an overall median follow-up period of 45 months (range, 36–53 months). During the follow-up period of ≥36 months, clinical progression was registered in 56% of the patients (82/146). Statistically significant differences were found between patients testing positive and those testing negative: overall, the number of progressions was higher in the group of patients who had detectable circulating tumor cells in the initial examination as compared to the patients testing negative: 75% (33/44) vs. 48% (49/102) ($p < 0.001$). In stage I, none of the 17 negative patients but 1 out of 4 (25%) positive patients showed progressive disease ($p < 0.001$) with appearance of regional lymph node metastasis during the follow-up period. In stage II, progression occurred in 33% (8/24) of the patients testing negative vs. 57% (4/7) of those testing positive ($p < 0.01$). In stage III, progression occurred in 53% (17/32) of negative and in 69% (9/13) of positive patients ($p < 0.05$). Among stage IV melanoma patients 83% (24/29) in the negative and 95% (19/20) in the positive cohort died from malignant melanoma during the observation time.

These data clearly demonstrate that there are significant differences between melanoma patients found to be PCR-positive and those who were PCR-negative for circulating melanoma cells. According to the data, the progression rates were significantly lower in the negative groups, both in the total

collective as well as in the subgroups in different clinical stages of disease. This is most evident for stage I and II. Moreover, Kaplan-Meier analysis demonstrated that the difference in progression-free survival rate between positive and negative patients becomes evident only after 33 months for stage I, after 24 months for stages II and III, whereas in stage IV, significant variations are already obvious after 6 months of follow-up. It seems that the presence of circulating tumor cells is a reliable marker for a significantly higher risk of progression in all clinical stages of malignant melanoma. This is concordant with results recently published by Mocellin et al. [29]; these authors identified a subgroup of PCR-positive melanoma patients with a higher risk of disease recurrence clinically significantly in advance. Therefore, introduction of PCR in the clinical routine may contribute to predict the risk of progression. Further studies are necessary to define their diagnostic role in more detail.

In conclusion, the multiple molecular alterations underlying the neoplastic process and clinical characteristics of malignant melanoma are currently under intensive investigation. It has been demonstrated that serum levels of melanoma-associated proteins and circulating tumor cells can serve as new markers to predict disease outcome and therapy response. Similarly, gene expression analyses of melanomas can be surveyed simultaneously using DNA arrays, allowing molecular profiling of individual tumors, which gives the possibility of classifying melanomas based on their biological diversity. All these techniques led to development of a new, more precise melanoma staging and follow-up system, which emphasizes the biological characteristics of the primary disease.

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Malignant Melanoma – Sentinel Lymph Node Biopsy and Surgical Procedures

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Ongoing controversies in melanoma surgery involve the extent of excisions in primary tumors, but also the value of diagnostic or palliative procedures. As yet, surgical removal is regarded to be the most effective treatment for primary malignant melanomas, since it can cure the majority of patients with less advanced tumors and controls local disease. Despite the fact that the basic importance of surgery in managing these patients has always been beyond question, the discussion about its extent and the role of elective procedures in the care of stage I and II melanomas is still vivaciously sustained. However, a 'less is more' policy has become validated by several studies in particular with regard to the use of smaller excisions of only 1 cm in tumors up to 2 mm thickness and of 2–3 cm for thicker melanomas.

In critical anatomical sites of acral lentiginous types and lentigo maligna melanomas microscopically controlled surgery has almost replaced wide excisions in order to preserve tissue structure and function. Reduced safety margins enable us to cover most defects by primary closure or simple skin flap techniques.

The precise role of sentinel node biopsy (SNB) remains a further matter of debate in advanced primary tumors. Nevertheless, this technique rapidly developed over the past years as a widely accepted standard to identify patients at risk for early nodal spread more selectively, thereby avoiding the morbidity of earlier elective node dissections (ELND) for the majority of patients and possibly providing a method for local disease control in the remaining cases with positive nodes. Moreover, SNB was shown to be of predictive value for risk assessment of metastases and survival, particularly in patients with thicker primary tumors. However, a therapeutic value has not yet been proven and among other aspects, the need for subsequent removal of the entire nodal basin after positive sentinel involvement remains one of the current controversies.

Table 1. Techniques and indications in melanoma surgery

Procedures	Recommended indication(s)
Incisional biopsy	suspected lesions of critical size and/or in critical areas
Excisional biopsy	suspected lesions of appropriate size
Excisions with safety margins	
0.5 cm	MM in situ, Clark level I
1 cm	MM T1, T2a (stage I A,B)
2 cm	MM T3, T2b (stage II A)
2–3 cm	MM T4, T3b (stage II B,C)
Micrographic surgery	LMM, ALM
Sentinel node biopsy	MM ≥ 1 mm thickness
Radical lymphadenectomy	MM stage III, or positive sentinel node
Metastasectomy	MM stage IV with solitary metastasis

MM = Malignant melanoma; LMM = lentigo maligna melanoma; ALM = acral lentiginous melanoma.

Finally, in cases with distant spread, surgery can palliate certain patients or even remove solitary metastasis with improved prognosis in others.

Biopsies in Suspicious Lesions

Cutaneous melanoma can usually be detected by clinical inspection and dermatoscopy, though early melanoma or nodular, amelanotic and atypical variants may lack typical macromorphological criteria indicative of malignancy. Whenever possible, complete excision of suspicious tumors should be ensured, in order to preserve the architecture as well as the sometimes variable components of the entire lesion. Though yet no disadvantage with regard to disease prognosis could be demonstrated in patients following incisional biopsies [1], this procedure should therefore be considered only in those few cases were an excisional biopsy is not possible due to the size and/or unfavorable anatomical site (e.g. large pigmented lesion on the face). Shave biopsies, instead, might collect only incomplete superficial material and therefore result in inappropriate samples. Also electrosurgical procedures can severely interfere with proper tissue examination and must be avoided for this reason. In all uncertain cases, excisional biopsy is usually the first step in a two-stage procedure. If the lesion turns out to be histologically diagnosed as a melanoma, the second step would then be a wider local removal to the underlying fascia with an excisional radius depending on the specific tumor parameters (table 1).

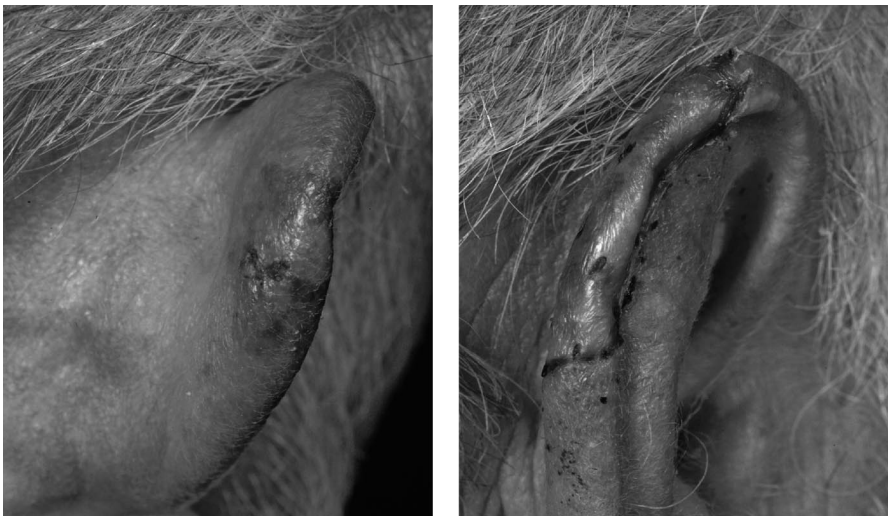

Fig. 1. Lentigo maligna of the ear. ***a*** Clinical appearance. ***b*** After tissue-sparing microscopically controlled excision, 7 days following grafting of the resulting defect.

Surgery in Lentigo Maligna and in situ Melanomas

Lentigo maligna (melanoma in situ), if left untreated, will progress to invasive tumor growth in approximately 30–50% of patients and then is thought to behave as aggressively as any other melanoma. In order to ensure the highest cure rates and to avoid recurrence, it should be treated preferentially by microscopically controlled excision, also detecting amelanotic areas, with the resulting facial defects being covered by local flaps or grafts depending on the localization and size of the wound bed [2–5]. However, in elderly patients at risk or those presenting with more extensive lesions, were surgery would result in disfiguring defects, radiation therapy is usually regarded as an alternative treatment option to surgery.

In micrographic surgery, residual tumor tissue is graphically mapped and extensions of lentigo maligna are managed with staged excisions until the entire lesion is removed. This technique best combines safety and sparing of adjacent tissue, especially when considering the sometimes ill-defined boundaries of lentigo maligna, the possibility of adjacent amelanotic areas, and the functional or esthetic requirements in cosmetic surgery units. By preserving a maximum of tumor-free skin, subsequent wound reconstruction can be optimized (fig. 1). The cure rate approximates 100% and in a long-term follow-up study by

Cohen et al. [6] no recurrences of lentigo maligna were seen. Basically all types of in situ melanoma can be treated in the same way, given that complete removal is ensured by histological control of the resection margins, though alternatively a 0.5- to1-cm-wide excision of the in situ lesions is generally recommended in these patients.

Surgery in Invasive Melanomas

Excisional removal with a therapeutic purpose is regarded as standard treatment in all primary tumors. Surgery consists of complete local excision including the subcutaneous fat and encircling an adjacent radius of normal-appearing skin. Theoretically, all patients in whom tumor cells are restricted solely to the resected volume of tissue are cured. Based on that assumption, and on an anecdotal report by Sir William Handley in the early 20th century, in which peripheral tumor involvement adjacent to the visible borders was detected in a single autopsy case, a wide 'safety margin' of 5 cm was considered necessary in order to achieve a complete elimination of tumor cells and has remained a dogma for many decades. However, the assumption that at the time of surgery tumor growth is a local event, is contradicted by practical experience, which has shown that radical surgery cannot always prevent tumor progression and that even after spontaneous regression of all primary tumor tissue, these patients might present with metastatic spread later on. Some researchers even suspect that surgical removal of a primary melanoma might on the contrary disinhibit metastatic growth and thus would result in more rapid progression of the disease [7]. For this purpose, the authors compared the risks of patients with thin melanomas of developing metastases within 1 year after removal to that of matched patients with thicker tumors to present metastasis at the time of diagnosis. Assuming a long tumor-doubling time, the removed tumors seemed to exhibit higher risks of metastases and even calculations with short doubling times did not prove to be superior for the surgically treated group. This outcome is not unexpected, since at the time of surgery metastatic spread from the primary site must have already occurred in all cases developing metastasis later on. In this context it is tempting to imagine surgical excision as a treatment of primary inoculation sites in infections, characterized by both local invasion and subsequent dissemination of the causative organism. Although the primary manifestation could be surgically removed, further disease development would depend on the interplay between the pathogen's virulence and the host immune surveillance. The disease would be cured neither after surgery nor after spontaneous regression of the primary site (such as in syphillis). Modern understanding of tumor progression and immune escape

mechanisms made obvious that especially in advanced primary tumors, excisions are in many cases at best palliative to achieve local disease control. The final success of surgical interventions seems to rely on the presence or absence of residual tumor cells in the body and their capacity to metastasize rather than on the initial extent of safety margins.

If distant spread has not occurred at the time of initial treatment, curative surgery of cutaneous melanomas is currently more extensive in the case of thicker tumors based on the hypothesis that potential micrometastases within the adjacent skin should be eliminated. Since we have got as yet no reliable parameters to predict the individual biologic behavior of melanoma cells in a given patient nor indicators of systemic micrometastases at the time of surgery, we still base our individual approach on known prognostic factors and on the evidence obtained from prospective clinical trials. In today's guidelines, tumor thickness and ulceration are generally considered as relevant factors predicting prognosis and determining the extent of required surgery. After Breslow and Macht [8] started to reduce safety margins considering the more favorable prognosis in thinner lesions, this concept has meanwhile been supported by several trials and has led to increasingly conservative excisional strategies with an ongoing debate on whether even a 1 cm margin or histologically verified in toto excisions would be appropriate for all melanomas irrespective of individual tumor parameters [9–11]. Nevertheless, in current clinical practice most experts follow a stepwise approach, where melanomas preferentially are grouped into thin (≤2 mm, T1,2), intermediate (2–4 mm, T3) or thick tumors (>4 mm, T4), in agreement with the latest version of the AJCC staging system [12]. Moreover, since ulceration hampers the estimation of thickness and has been shown to represent an independent prognostic variable for the risk of local recurrence by multifactorial analysis, this parameter can be considered in addition when designing an excisional approach (table 1).

For melanomas <2 mm thick, a 1-cm safety margin is considered adequate based on several observations confirming the safety of narrower margins in patients with thinner primary invasive melanoma [13, 14], published in various treatment recommendations [e.g. 15–20]. For thicker tumors instead, a 2-cm margin is regarded sufficient [21, 22]. Balch et al. [21] examined 486 patients with 1- to 4-mm-thick melanomas excised with 2 vs. 4 cm margins. The authors found no significant difference between the two groups with respect to local recurrence and survival and therefore concluded that 2 cm margins were adequate. Less radical resection has a major impact on wound management, morbidity, life quality, need for hospitalization and costs.

For high-risk tumors (>4 mm), some authors still recommend a wider safety margin based on the assumption that a better local control might be achieved, since these tumors have a particularly high recurrence rate [23–28].

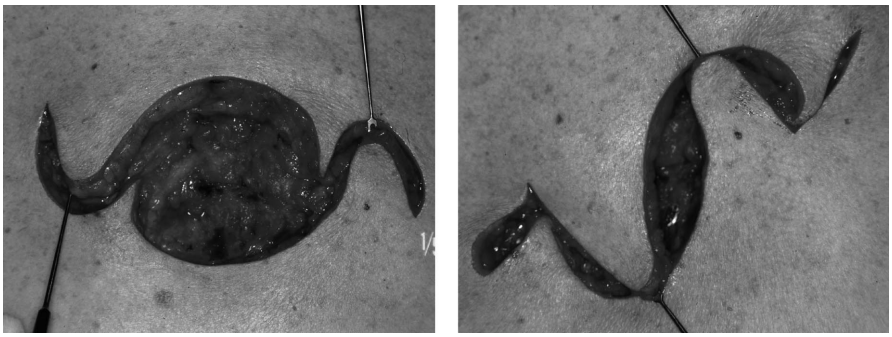

Fig. 2. Circular defect in the central back (***a***) area easily closed using a bilateral transpositional flap (***b***).

Nonetheless, with regard to a survival benefit, it remains to be shown whether a wider excision is of any benefit, given that the probability of systemic spread already having occurred is known to be high in this subgroup. Moreover, true local recurrences, that theoretically should only occur after residual tumor has been left following incomplete primary excision with subsequent regrowth, are in fact difficult to distinguish from metastatic spread to the scar area of the primary excision site and their real prognostic significance therefore remains controversial as well [29]. In clinical practice, any tumor regrowth after narrow excision might however pose serious legal problems, especially if a worsening of prognosis is supposed. Fortunately, patients with thicker tumors become more and more rare due to successful screening and improved public awareness. Though, randomized studies to analyze a potential benefit of wider margins on local recurrence or metastases would have to enroll large numbers of patients due to the expected low difference or no difference in outcome between the compared groups. Also, while formerly 5-cm margins had a major impact on further wound care, the decision between 2 or 3 cm in most instances does not really affect the surgical techniques required for defect repair at the present time. Indeed, reduced safety margins with a maximum of 2–3 cm enable us to cover most of the resulting wounds by simple skin flaps (fig. 2), even in patients with thicker tumors. The various methods of reconstruction are selected based on the size and extent of the wound left by the wider excision. Only in special anatomical sites, such as the distal extremities or the scalp, might skin grafting still become necessary.

Despite the fact that the majority of patients presenting with primary melanomas can be managed by leaving the recommended margins, there are few exceptions, in which a more individual approach has to consider special

anatomical or functional requirements. These cases comprise melanomas in acral areas, and those of the head and neck. In addition, in patients with lentigo maligna melanoma, it can be impossible to determine the exact margins along the entire lesional border, although Wood lamp examination or surface microscopy can help in some cases. Also here, Mohs' micrographic surgery has been suggested as an effective treatment alternative in order to minimize excisional margins and to conserve adjacent skin [30]. Even with this technique, the excisional margins required depended on initial tumor thickness and varied up to 2.5 cm [31]. In general, we prefer a multistep procedure in all larger or advanced tumors including microscopically controlled surgery of the entire process and closure of the defect not until all margins are free of disease. Whenever possible, at least an additional 1-cm safety radius is added around the final defect in all invasive tumors, since an excision width merely based on Mohs' surgery should still be considered as investigational. Cohen et al. [6] reported an overall long-term cure rate of 97% in these patients and observed only one recurrence in a 56-year-old woman after five prior recurrences.

Surgery in Clinically Uninvolved Draining Lymph Node Basins in Primary Melanomas

The role of surgery in clinically uninvolved locoregional lymph nodes of primary melanoma patients has been extensively debated in the context of staging, local disease control and prevention of tumor progression. The view that cutaneous melanoma predominantly metastasizes via the lymphatics and that consequently patients should have a better prognosis if their microscopic nodal involvement is removed by ELND does not necessarily conform with reality, and the utility of elective node removal to improve survival in patients with clinically localized primary melanoma has not been established convincingly. While several retrospective studies suggest a survival advantage for patients receiving ELND with intermediate thickness tumors, no such benefit has yet been demonstrated in prospective trials with the exception of a recently published trial that revealed longer survival only in patients with node metastases [32]. Within recent years, attempts have been made to better select patients with clinically occult metastases, who might benefit from lymph node resection while avoiding unnecessary ELND, morbidity and expenses. For this purpose, sentinel lymph node biopsy has been introduced by Morton et al. [33] in order to detect potential micrometastases in the first node(s) of the lymphatic basin that drains the primary cutaneous site at the time of melanoma surgery, restricting lymphadenectomy only to those patients with sentinel micrometastases. The technique originally involved the intradermal injection of a vital blue dye at the

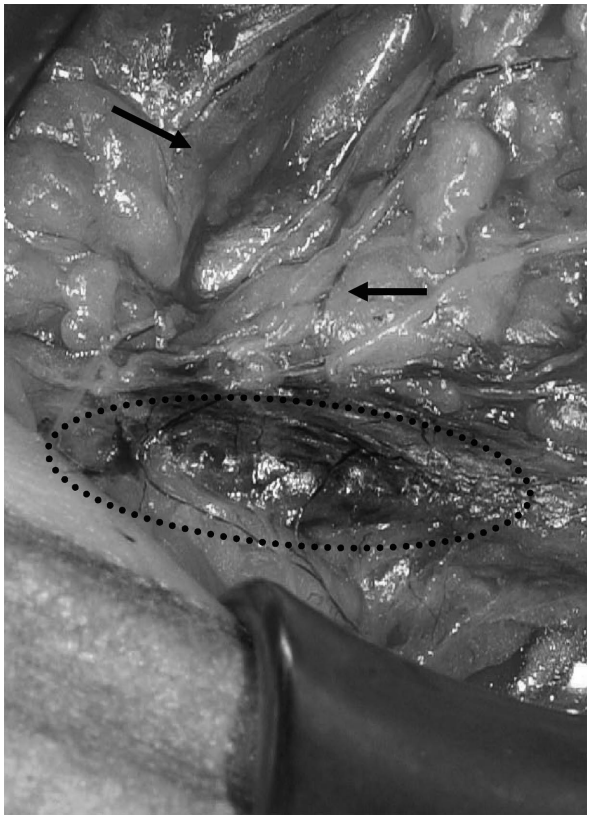

Fig. 3. Sentinel node biopsy as a diagnostic tool in staging of primary melanoma patients. In addition to gamma-probe-guided surgery, patent blue staining can easily identify both the node and the collecting lymphatic vessels.

melanoma site and was further developed by peritumoral intradermal injection of technetium-99m antimony trisulfide colloid with subsequent lymphoscintigraphy and gamma-ray probe detection. Meanwhile most investigators agree on using radiocolloids combined with radio-guided biopsy as a routine approach to locate the nodes and some feel that the additional injection of blue dyes might be helpful to identify nodes in critical sites or deeper locations more rapidly (fig. 3). The method was validated in a multicenter setting and standardized to a high level of accuracy successfully detecting up to 97% of sentinel nodes [34]. Also, sentinel node histology accurately reflects the histology of nodes in the lymphatic basin and 'skip metastases', defined as a negative sentinel node but positive lymphatic spread, seem to be rare for melanoma. It is mostly recommended to restrict sentinel node biopsy to patients with tumors thicker than

1 mm, where positive nodes can be expected in about 1 out of 5 cases. Among these, subsequent lymphadenectomy will also disclose another 15–20% of nodal metastases [35]. Sentinel node mapping and biopsy not only accurately stage the regional lymph node basin, but detection of positive sentinel nodes also correlates to prognosis and is therefore increasingly recognized as a valuable diagnostic tool in patients clinically presenting with primary melanomas [36]. Upgraded diagnostic techniques employing reverse transcription polymerase chain reactions with tyrosinase-specific primers have contributed to further improvement in micrometastasis detection rates. However, it remains to be seen whether this increase in sensitivity is of any biological relevance, i.e. whether these patients benefit from subsequent node dissection.

At present, lymphatic mapping, SNB followed by selective complete lymph node dissection in SNB-positive cases has become an increasingly used standard approach and has replaced ELND [37]. However, the therapeutic effect of lymphadenectomy following positive SNB, especially with regard to patient survival, has still to be accurately determined. Since in the majority of patients only the sentinel nodes are infiltrated by tumor cells while the draining nodes are not, this raises the question of whether therapeutic lymph node dissections are warranted in these patients and whether they improve their prognosis [38]. In the current debate, some experts argue against any useful role of this technique mainly due to the lack of any therapeutic benefit [39, 40]. In contrast, the many advocates of SNB among today's melanoma surgeons emphasize that even if SNB does not not yield any survival advantage, detection of nodal metastasis is such a strong prognostic factor that it would be difficult to imagine reverting to clinical staging of regional nodes and if nothing else SNB would at least provide excellent regional disease control [41–46]. Nonetheless, current trial efforts should be supported that further address the value of this technique, especially concerning the significance of subsequent lymphadenectomy following detection of micrometastatic involvement.

Surgery in Local Tumor Progression

True local recurrent melanoma, which theoretically only occurs after residual tumor has been left following incomplete primary excision, would be defined as melanoma bearing an in situ component that recurs contiguously to the scar of the primary excision. In fact most of these cases resemble satellite metastases with a poorer prognosis. But also true recurrent tumors seem to have a much worse prognosis than is expected with tumors of equal thickness. True local recurrent melanoma may require excisional margins of up to 2 cm, as calculated from Mohs' surgery by Brown and Zitelli [47]. Also satellites and

solitary in-transit metastases can be effectively removed by scalpel surgery in appropriate cases.

Surgery of Lymph Node Metastasis

Since removal of metastases to regional lymph nodes (stage III) might result in cure, the surgical excision of lymph nodes clinically positive for tumor is referred to as a therapeutic lymph node dissection. Controversies on regional lymph node dissection mainly concern the extent and nature of the lymphadenectomy, treatment of lymphatic metastases in unusual locations and the role of adjuvant radiotherapy. Current approaches with regard to modified neck dissection, axillary dissection and the appropriate management of groin involvement have been extensively reviewed by Mack and McKinnon [48]. In the neck area modified dissections do not seem to compromise regional control in appropriately selected cases. In the axilla, a level I, II or III dissection is most commonly performed. For clinically palpable disease, combined superficial and deep groin dissection is justified. Burden of disease, comorbidity, and Cloquet nodal status must be considered. Adjuvant radiation therapy is discussed in patients with a high risk of regional recurrence including bulky disease or extracapsular extension.

Surgery in Stage IV Metastatic Disease

In stage IV disease, surgical interventions are considered almost exclusively for palliation. This is especially the case in patients where circumscribed distant spread interferes with quality of life or might lead to severe complications, such as metastasis in the intestines or the brain [49, 50]. Metastasectomy should however always be considered as worthwhile, if an R0 resection of an entire solitary lesion is possible. Those patients might not only benefit from palliation but moreover might benefit from an improved prognosis in some cases. Therefore, patients with limited sites and numbers of metastases should be considered for curative resection regardless of the location of the disease [51, 52].

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The Role of Radiotherapy in the Management of Malignant Melanoma

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There are large differences in the use of radiation therapy in melanoma. Traditionally, many radiotherapists regard melanoma as a radioresistant disease. This led to the administration of hypofractionation, which might not be adequate in all clinical situations. The current guidelines in Europe, the United States and Australia diverge. Only a minority of the patients are treated in accordance to these guidelines: In 23% of all melanoma patients, radiotherapy may be indicated at some point in their illness, but the utilization rate is 1% according to SEER data [1].

The present paper reviews various clinical situations and therapeutic strategies based on the literature and actual guidelines.

Biology of Malignant Melanoma

Radiosensitivity

There is a controversy regarding the radiosensitivity of malignant melanoma. Traditionally, cutaneous malignant melanoma is regarded a radioresistant disease. But cell lines in vivo show characteristics of acutely- and late-responding normal tissue with a large range of α/β ratios from 1.0 to 48.7 Gy [2, 3]. Data from single and fractionated doses for uveal melanoma cell lines indicate large variations in radiosensitivity which are mainly dominated by intrinsic radiosensitivities. Single doses of 8 Gy in five fractions would be sufficient to eradicate 10^9 cells of the most radioresistant tumor cell lines, but

this schedule is an overkill for the radiosensitive tumor cell lines with a higher risk of developing late effects [4].

Rofstad [3] demonstrated the correlation between α/β ratios in vivo to survival fractions of the cell lines in vitro. Caution should be used in translating these in vitro data directly into clinical practice.

Cells with a low α/β ratio require large doses per fraction for effective tumor eradication. In this instance, little benefit in therapeutic ratio was seen, because the late-responding normal tissues also displayed low α/β ratios in the range of 1–5 Gy. For cells with α/β ratios >6 Gy, low single doses should provide an increased probability of tumor cell kill and sparing of normal tissues [4]. These conflicting data explain the large differences in radiation treatment schedules worldwide.

Dosage and Fractionation

The fact that the radiosensitivity of melanoma cells is mainly determined by their intrinsic radiosensitivity should lead to studies on morphologic and histologic tumor markers. Based on these morphologic markers, tumor classification would become possible and lead to more individualized dose fractionation schedules.

Although there are some authors who demonstrated a clinical benefit from hypofractionation [5–8], more recent data could not show any advantage in administering high single doses [9–11].

Overgaard [6] demonstrated that a high dose per fraction yielded a significantly better response for doses >4 Gy (59% complete responses; CR) versus 33% CR for doses per fraction ≤ 4 Gy.

In the 80s, the Radiation Therapy Oncology Group (RTOG) started a randomized trial evaluating the effectiveness of high-dose fractionated irradiation. One weekly single dose of 8 Gy (32 Gy total dose) was compared to 5 weekly single doses of 2.5 Gy up to a total dose of 50 Gy in the treatment of measurable lesions of malignant melanoma. No advantage concerning complete or partial response rates could be shown for the high dose per fraction arm [10].

Fenig et al. [11] examined the role of radiotherapy in the adjuvant and palliative situations in malignant melanoma. Reported response rates of 52% using 3-Gy single doses were significantly superior compared with 35% response rate using higher single doses. There was no significant difference in duration of the response.

Data concerning dose and fractionation suggest great inhomogeneity in the material (primary and metastatic site, number, size and thickness of the lesion, single dose, fractionation, total dose). Treatment time has no demonstrable

influence on tumor control probability in melanoma [5, 6]. In contrast to earlier series, recent publications state that conventional fractionation schedules are equally effective in tumor control [10, 11]. Conventional fractionation is safer than hypofractionation because it minimizes set-up errors due to multiple low single doses, decreases the incidence and duration of severe acute and late reactions, especially in the case of head and neck and brain irradiation.

Cutaneous Malignant Melanoma

Definitive Management of Cutaneous Malignant Melanoma

The standard treatment of malignant melanoma is local excision in stages I and II. Radiotherapy is rarely indicated as a definitive management of primary malignant melanoma. Exceptions to this rule are inoperable tumors, contraindications to excision and/or large facial lentigo maligna melanoma [12], Breslow thickness >4 mm, and satellites and/or ulceration, where excision would lead to a poor cosmetic outcome and may require extensive reconstruction [13].

Harwood [14] reported on a series of 35 irradiated patients. Tumor control was achieved in 23 patients (92%). The median time to complete regression of the lesion was 8 months. This requires an adequate follow-up and compliance of the patients. Response to treatment of malignant melanoma is stage dependent. Patients with stages IIB, III and IV showed an overall response rate of 100, 77 and 49%, respectively [15]. Concurrent therapy with interferon-α2b may influence treatment response and side effects [16].

Adjuvant Radiotherapy in Malignant Melanoma

Adequate surgery remains the mainstay of melanoma treatment. The use of adjuvant radiation has been hindered by the unsubstantiated belief that melanoma cells are radioresistant. Based on retrospective evidence, adjuvant radiotherapy of melanoma should be used in those patients with clinicopathologic features that indicate a high risk for local relapse. The potential benefit must be weighted against the morbidity. Different clinical situations have been addressed by several authors.

Ballo et al. [17] reviewed 89 patients with axillary lymph node metastases from malignant melanoma. All patients underwent axillary dissection and postoperative radiation to a median dose of 30 Gy at 6 Gy/fraction delivered twice weekly. Axillary disease >6 cm in size, unknown location of primary, axillary failure within 18 months from diagnosis of the primary or Breslow thickness

>4 mm were identified as poor prognostic factors. Five-year-axillary control rate after adjuvant radiotherapy was 87% versus 50–70% to control rate achieved with surgery alone.

The role of adjuvant radiotherapy in head and neck melanoma has been addressed by Ang et al. [18]. High-risk patients (group 1: AJCC stage II/IIIA after wide excision, group 2: AJCC stage IIIB after wide excision and limited neck dissection, group 3: locoregional relapse and after neck dissection) with a projected locoregional recurrence rate of 35–50% underwent hypofractionated radiotherapy with single doses of 6 Gy, two fractions per week to a total dose of 30 Gy. Actuarial locoregional control after 5 years was 88% for all patients, after a median follow-up of 35 months, 101/174 patients were alive without any evidence of disease, 2 patients had a nodal relapse, 3 patients a dermal relapse, 1 patient presented a dermal and nodal recurrence. Fifty-eight patients were shown to have distant metastases, 9 of them in combination with dermal and/or nodal relapse. Radiotherapy was well tolerated.

These impressive results could demonstrate a benefit of adjunctive therapy in high-risk patients. American and Australian guidelines took this into account and recommend postoperative adjunctive irradiation in melanoma >4 mm thickness (head and neck), Stage IIIB, IIIC and N3, respectively [13, 19, 20].

Cooper et al. [21] reported an actuarial 5-year locoregional control of 84% in patients in high-risk situations (close margins, extracapsular spread, multiple node involvement, deep invasion) after hypofractionated irradiation with 30–36 Gy total dose. Without radiotherapy locoregional failure rates of 30–50% have been reported for those patients.

Desmoplastic malignant melanoma (DMM) is a rare variant of malignant melanoma with a high local recurrence rate after surgical excision. The local recurrence rate of DMM after surgery could be dramatically reduced by adjuvant radiation therapy. Adjuvant postoperative radiation therapy is recommended as a part of the treatment of DMM [22].

Acute reactions to irradiation of locoregional lymph nodes were moist desquamation, (patchy) mucositis and pain. Using hypofractionation, lymphedema was the most significant late effect following surgery and irradiation. Nineteen percent of the treated patients experienced grade 2 arm edema [17]. Stevens et al. [23] reported 58% symptomatic lymph edema in those patients who survived for 2 years without recurrence. These high rates may be reduced by conventional fractionation schedules.

Although data in the literature remain sparse, evidence also indicates that elective irradiation is effective in eradicating subclinical nodal metastases after removal of the primary melanoma. Consequently, radiotherapy should be integrated into the multimodality treatment of patients at high risk of subclinical nodal disease, particularly those with an involved sentinel lymph node [24, 25].

The impact of adjuvant radiotherapy on the incidence of distant metastasis and overall survival has yet to be determined, however [24].

The target volume for malignant melanoma patients with stage I–III includes the tumor (tumor bed) with margins of at least 2 cm and the entire ipsilateral neck nodes down to the clavicle. Photons or electrons of appropriate energy are used to cover the target. Immobilization devices help to ensure daily reproducibility, even for hypofractionation [26].

Brain Metastases

After breast and lung cancer, melanoma represents the third most common cause for CNS metastases [27]. Metastases to the CNS develop in nearly half of patients with advanced melanoma. In 15–20% of the patients, CNS is the first site of recurrence. In the majority of patients, multiple lesions are present, in up to 50% with intratumoral hemorrhage [28–30]. In addition, the incidence of CNS metastases as first site of relapse may be increasing due to the better control of extracranial disease by interferon and new chemotherapeutic approaches. Systemic therapy induces response rates of 15–50%, but the available drugs do not penetrate very well into the brain [31].

The therapeutic goal of whole brain radiotherapy (WBRT) is local disease control, stabilization or improvement of neurologic function and survival.

In a retrospective analysis on 1,292 patients, Broadbent et al. [32] could show that patients with treated brain metastases from melanoma had no significantly different survival compared to those patients with other entities with a median survival of 5.5 months.

The clinical benefit from radiotherapy depends on several prognostic factors. Lagerwaard et al. [33] identified age, sex, performance status, response to steroids, systemic tumor activity and serum LDH as independent prognostic factors with the strongest impact on survival. Based on pooled data from RTOG trials between 1979 and 1993, three classes of patients were derived, based on four prognostic factors: Karnofsky Performance Score (KPS), primary tumor status, age and presence of extracranial disease. Class I is age <65, KPS ≥ 70, controlled primary, no extracranial disease; class III with KPS <70, class II includes patients that are neither class I nor III [34]. The recursive partitioning analysis (RPA) classification scheme likely has prognostic value for patients with brain metastases from malignant melanoma [35, 36]. It should help selecting those patients who will benefit from treatment [37, 38].

Depending on the RPA classes, size, number and localization, conventional WBRT, stereotactic radiosurgery (SRS), surgery, or combinations of

surgery and WBRT or WBRT and SRS are treatment options. In the case of edema, corticosteroids might be given additionally.

WBRT is usually done with two lateral fields including the whole brain with photons and standard fractionation with 5 weekly single doses of 3–30 Gy total dose.

The question of the optimal fractionation schedule remains unresolved. Concerning WBRT total dose and response to irradiation, Isokangas et al. [39] pointed out that patients with favorable prognostic factors benefit from a higher total dose. They reported median survival rates of 9.6 months and 2.1 months for patients treated with >30 and ≤ 30 Gy, respectively. But higher total dose implies a higher rate of side effects and neurologic dysfunctions, although the prognosis of these patients is poor.

SRS provides high-dose, single (or multiple) session irradiation to 1–6 single metastases without treating the whole brain [40]. As for patients with WBRT, the absence of active systemic disease and a single brain metastasis contributed independently to increased survival [41]. The efficacy of SRS has been evaluated in patients with single and multiple brain metastases. After SRS, RPA class I patients showed a significantly improved survival compared with those with RPA class II and III. Only 12% of these patients suffered local recurrences, but more than 50% had distant brain failure (DBF). Additional WBRT could decrease the DBF from 64 to 17% after 6 months [42]. Data from the randomized trial RTOG 9508 showed improved DBF and overall survival for patients with one single unresectable metastasis after combination of WBRT and SRS boost which should thus also be considered for those with 1–3 brain metastases [43]. Shehata et al. [44] supported these conclusions. They treated 160 patients with 468 brain metastases ≤ 2 cm. Those who underwent combined treatment achieved significantly superior local control rates compared with SRS alone. SRS dose escalation >20 Gy did not improve local control, but resulted in a higher rate of grade III and IV neurotoxicity.

Retrospective data have shown improved median survival rates and CNS control rates for those patients treated with combined radiosurgery and WBRT compared with WBRT alone [31, 45].

Conclusion

Radiotherapy is useful in patients with inoperable large primary cutaneous malignant melanomas, for large inoperable primaries, Breslow thickness >4 mm, and satellites and/or ulceration and in patients with local recurrences.

Postoperative radiotherapy improves local control and is recommended for patients at high risk of local recurrence: >4 mm tumor thickness (head and

neck), close margins, extracapsular spread, multiple node involvement, deep invasion), Stage IIIB, IIIC and N3, and for DMM malignant melanoma, respectively. The impact of adjuvant radiotherapy on the incidence of distant metastasis and overall survival has yet to be determined. The importance of local control to reduce local morbidity, however, should not be underestimated, and future research goals should include randomized clinical trials to further define the role of adjuvant irradiation alone or in combination with chemotherapy.

Patients with treated brain metastases from melanoma had no significant different survival compared to those with brain metastases from different entities. The therapeutic goal of WBRT is local disease control, stabilization or improvement of neurologic function and survival. The clinical benefit from radiotherapy depends on several prognostic factors. Patients with RPA classes I/II and inoperable single lesions should be offered WBRT in combination with SRS boost; this combination should also be considered for those with 1–3 brain metastases.

Data concerning radiation fractionation, single and total doses are inconsistent and do not allow general recommendations. Although more recent data confirm the effectiveness of conventional fractionation, radiation therapy should be adapted to the individual clinical situation and take into account the disease site, the size of the lesion and the patients' general condition.

Disadvantages of hypofractionation include the impact on dose heterogeneity, resulting in large changes in normal tissue responses and a higher risk for late effects. This requires close attention and quality assurance in order to minimize set up errors, which are clinically more significant when using hypofractionation.

Chemotherapy may be gaining a role with newer agents that penetrate the blood-brain barrier. Combined modality therapy appears to be the future direction of treatment of multiple metastases. Further prospective studies are urgently needed. Significant improvements in the prognosis of melanoma patients will require better systemic disease control.

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Malignant Melanoma: Classification and Staging of Malignant Melanoma

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Seventy-nine percent of skin-cancer-related deaths are caused by cutaneous malignant melanoma [1]. During the last decades, the incidence of malignant melanoma has raised in all developed countries independently of sex [2]. In 2005, the American Cancer Society estimated that there were 59,580 new cases of melanoma in the USA [1].

The prognosis of cutaneous malignant melanoma strongly depends on the stage of detection [3]. Whereas the prognosis is excellent for thin melanoma diagnosed early and treated with adequate surgical excision [4], the 5-year overall survival declines to 60% for patients with lymph node metastases [5]. The overall survival of patients with advanced malignant melanoma is most unfavorable with a 5-year survival rate of 5–14% [5, 6]. Fortunately, about 82% of all cutaneous melanomas are detected at a localized stage of the disease [5].

During the last decades, the importance of prognostic indicators played a central role in scientific reports on malignant melanoma. Numerous analyses led to continuous modification of the American Joint Committee on Cancer (AJCC) classification of cutaneous melanoma [7].

Screening

Most of the patients detect a suspicious pigmented lesion on their own. Only few patients, e.g. those with a dysplastic nevus syndrome, are regularly screened by dermatologists. Pigmented lesions are reliably analyzed and documented by digital dermatoscopy. Often diagnostic clues are exclusively detectable using this technique (fig. 1). Experts achieve a 20% increase in diagnostic sensitivity in contrast to conventional clinical observation. They achieve

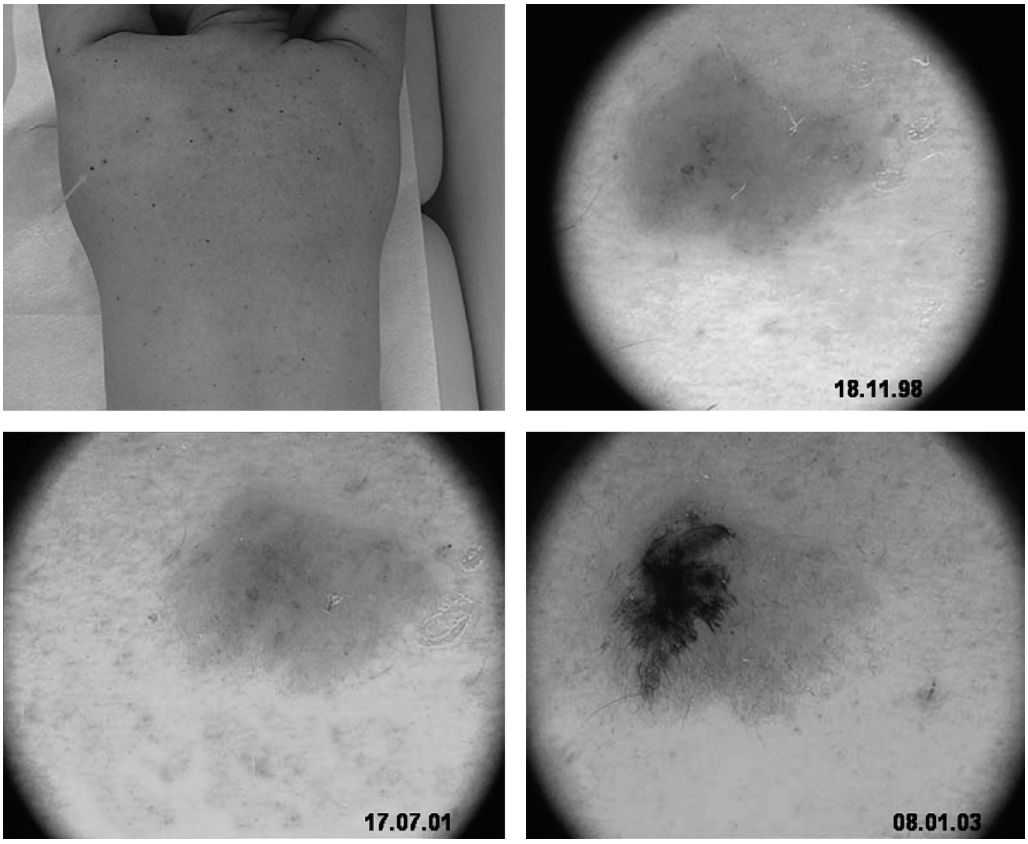

Fig. 1. Computer-aided dermatoscopy: Follow-up of an atypical melanocytic nevus, which developed to a melanoma in situ.

a sensitivity of about 90% and a specificity of approximately 80%. Up-to-date systems are computer based and include automated diagnostic algorithms.

The Novel 2001 AJCC Classification of Cutaneous Melanoma

The AJCC classification bases on the UICC T(umor)N(ode)M(etastases) system. It was renewed in 2001 and is currently used in the daily routine [7]. Prognostic factors for overall survival were analyzed based on a database of 17,000 melanoma patients. Additionally, the validity of the clinical classification was reviewed [8].

Table 1. Staging of the primary tumor (T-category) according to the AJCC classification (2001) Tumor thickness (according to Breslow) and ulceration are the two most important prognostic factors. Clark's level of invasion is only considered in thin (<1 mm) melanoma

Clinical stage	T	Tumor thickness, mm	Ulceration/level
IA	T1A	<1	no ulceration
IB	T1B	<1	ulceration/level IV/V
	T2A	1–2	no ulceration
IIA	T2B	1–2	ulceration
	T3A	2–4	no ulceration
IIB	T3B	2–4	ulceration
	T4A	>4	no ulceration
IIC	T4B	>4	ulceration

Tumor thickness (according to Breslow) and ulceration are the two most important prognostic factors. Clark's level of invasion is only considered in thin (<1 mm) melanoma.

T Category (table 1)

The old T category [9] used tumor thickness (according to Breslow) and Clark's level of invasion as criteria for the T category. However, as multiple studies indicate, not Clark's level of invasion but the absolute tumor thickness and ulceration are the two most important prognostic factors [10, 11].

Tumor Thickness

In the new AJCC classification the cut-off values for tumor thickness were redefined to integer values (1, 2 and 4 mm) in contrast to the old values (0.75, 1.5 and 4 mm). Thereby the pT1–pT3 categories were redefined (pT1: ≤1.00 mm; pT2: 1.01–2.00 mm, pT3: ≥2.01–4.00 mm) whereas the pT4 category (pT4: >4.00 mm) did not change. Patients with an in situ melanoma should be classified as Tis. If a primary melanoma is not evaluable (e.g. because of a curettage) it should be classified as Tx. The same applies for occult melanoma. In contrast to the old classification, Clark's level of invasion is only considered in the new T category in case of thin melanoma (pT1: ≤1.00 mm).

Definition of new cut-off values simplifies the T category significantly. However, the impact on prognosis of Clark's level of invasion remains doubtful even in thin melanoma. A multivariate analysis (Cox regression model) of the German Central Malignant Melanoma Registry did not find any prognostic significance for Clark's level of invasion in thin melanoma [10]. Also the further subclassification for thin melanoma is not adequately represented in the current

AJCC classification. A more detailed differentiation of Breslow's tumor thickness seems to be useful (≤0.5 mm, 0.51–0.75 mm, 0.76–1.00 mm) [10].

Ulceration

Ulceration of the primary melanoma was introduced into the new classification as a relevant prognostic factor. It is represented by distinct subgroups (T1b, T2b, T3b, T4b). Under two circumstances, the histopathological detection of ulceration leads to an upgrading of the clinical stage (T1a/b: IA to IB; T3a/b: IIa to IIb): in one case, ulceration results even in an upgrading in the main category (T2a/b: IB to IIA). Additionally, a new subgroup (T4b; clinical stage IIc) was introduced for ulcerated, thick melanoma (>4.00 mm). The introduction of ulceration as prognostic marker leads to an upgrading in the AJCC staging in about 25% of the patients.

The potential prognostic impact of ulceration is controversial. In a meta-analysis, Vollmer [12] recognized a significant prognostic impact in 20 studies, but no evidence of prognostic relevance in 25 clinical trials. In the current AJCC classification, ulceration of the primary melanoma is defined as 'absence of an intact epidermis overlying a major portion of the primary cutaneous melanoma based on microscopic examination of the histologic sections'. However, the missing epidermis could also artificially result from scratching by the patient, or could imply previous traumatic surgery. Thus, the pathologist is left with the difficult task of distinguishing between trauma-induced, artificial, or T-related ulceration. The present definition of ulceration does not seem to guarantee either precise diagnosis or high interobserver reproducibility. In a recent analysis of German Central Malignant Melanoma Registry a significant impact of ulceration could only be confirmed for pT2 and pT3 melanoma [13].

A dilemma exists for patients with a thick melanoma (>4.00 mm) and ulceration but without evidence of lymph node metastases (clinical stage IIc). These patients have a worse prognosis than patients with lymph node metastases (clinical stage IIIA). Therefore, in the former classification such patients were classified as stage III. In the current classification there is now a broad overlap of the prognostic outcome between patients in stages II and III with partly a worse prognosis for patients in stage II than patients in stage III. This confusion of the staging classification complicates its application in clinical practice.

N Category (table 2)

The N category of the current AJCC classification was totally revised. In contrast to the former classification, which focused on the maximum diameter

Table 2. Staging of lymph node metastases as well as satellite and/or in-transit metastases (N-category) according to the AJCC classification (2001)

Clinical stage	Primary tumor (pT)	Regional lymph node metastases (N)
IIIA	Any tumor thickness, no ulceration	Micrometastases
IIIB	Any tumor thickness, with ulceration	Micrometastases
	Any tumor thickness, no ulceration	Up to three macrometastases
	Any tumor thickness, ± ulceration	None but satellite and/or in-transit metastases
IIIC	Any tumor thickness, with ulceration	Up to three macrometastases
	Any tumor thickness, ± ulceration	Four or more macrometastases, or lymph node involvement extending beyond the capsule, or satellite and/or in-transit-metastases with lymph node involvement

Number of involved nodes and type of metastases (micro- vs. macrometastases) are considered. The N-classification also takes into account ulceration of the primary tumor.

of the lymph node metastases, the current classification considers the number of metastatic lymph nodes. The extent of metastases (micro- vs. macrometastasis) was introduced into the new classification as well. In the new staging system, diagnostic finding of sentinel node biopsy, which is suggested to be a standard procedure nowadays, or of elective lymph dissection is considered for N classification. However, metastasis of single tumor cells detected with molecular methods only is not mentioned in the current AJCC classification. Hermanek et al. [14] suggested to classify single tumor cells as pN0(i+) for solely immunohistological detection or as pN0(mol+) for solely molecular detection [14]. Until now only small collectives have been evaluated with regard to a potential prognostic impact of these two detection methods. Some reports suggest a possible correlation of the size of clusters of metastases in the lymph node and overall survival.

Satellite and In-Transit Metastases

According to the former AJCC classification, satellite metastases within 2 cm around the primary melanoma were staged as T4b, in-transit metastases were classified as N2b. However, both manifestations express a lymphogenic metastasis prior to the draining lymph node basin. The overall survival prognosis does not differ between satellite and in-transit metastases. Thus satellite and

Table 3. Staging in case of distant metastases (M-category) according to the AJCC classification (2001)

M-classification	Type of distant metastasis	LDH
M1A	Skin, subcutaneous tissue or lymph nodes	Normal
M1B	Lungs	Normal
M1C	All other distant metastases	Normal
	All distant metastases	Elevated

Consideration of the type of distant metastasis and LDH level as marker of tumor burden.

in-transit metastases are now classified as N2c in the new AJCC classification. Patients with an additional involvement of the lymph nodes are staged as N3.

Ulceration

Patients with lymph node metastases and additional ulceration of the primary melanoma are considered in the current AJCC classification to have a worse outcome than patients with lymph node metastases without ulceration of the primary melanoma. Patients with ulceration of the primary melanoma are suggested to be upstaged by one subgroup in the histopathological staging. However, in an analysis of the German Central Malignant Melanoma Registry, the potentially unfavorable impact of ulceration in patients with lymph node metastases could not be confirmed [13].

Clinical versus Histopathological Staging

In contrast to the histopathological staging, patients with lymph node and/or in-transit metastases are clinically grouped as stage III. By definition, clinical staging should be used after excision of the primary melanoma and subsequent clinical examinations of the lymph nodes. Histopathological staging of the lymph nodes should not be attempted until the diagnostic findings of the sentinel node and the complete lymph node dissection (in case of detection of tumor spread into the sentinel node) are available.

M Category (table 3)

In the current M category three subunits may be distinguished (M1a–M1c). On the one hand they rely on the localization of the distant

metastases on the other hand they depend on the lactate dehydrogenase (LDH) level as an indicator of tumor burden. Patient with solely metastases of the skin, subcutis and distant lymph nodes should be classified as M1a. Those patients with single metastases of the lungs should be categorized as stage M1b. All other patients, e.g. those with metastases in other visceral organs are stage M1c. Independently of the localization of the metastases, patients with an elevated LDH value are classified as M1c. Clinically, all patients (M1a–M1c) are classified as stage IV.

For the first time a serum parameter (LDH) as marker of the tumor burden was introduced in the current AJCC classification. However, as LDH is an unspecific marker, the evaluation of more a specific marker like soluble S100-protein would possibly improve the classification.

Critical Evaluation of the New AJCC Staging System for Cutaneous Melanoma

On the one hand, the current AJCC classification simplifies the staging of primary melanoma and introduces the possibility to differentiate between micro- and macrometastases of the lymph nodes (including the sentinel lymph node). On the other hand, the introduction of the factor 'ulceration' and the consideration of the LDH value complicate the application of the classification in the daily routine. Therefore a simplification is mandatory. However, clinical studies should use the current AJCC classification to allow comparability.

Follow-Up Schedule in Cutaneous Melanoma Patients (table 4)

The follow-up strategy for cutaneous melanoma is prognosis and stage related [15]. The majority of metastases in stage I of disease are discovered by clinical examination, and almost half of these are categorized as late discoveries (fig. 2). Thus, the use of certain technical examinations for metastasis screening in stage I of disease is of little benefit [15]. Lymph node sonography detects approximately one fifth of stage II recurrences at an early stage. Additional technical examinations ought to be confined to further clarification of suspicious symptoms or elevated blood tumor markers [15]. Follow-up of patients in stage III should be carried out with an intensification of technical examinations during the first 3 years. Clinical examination, lymph node sonography, and blood tests, including protein S100β, should be carried out at

Table 4. The clinical follow-up is stage dependant and lasts 10 years

Clinical stage and tumor thickness	Physical examination years 1–5	Physical examination years 6–10	Ultrasound of the lymph nodes years 1–5	Laboratory values[2] years 1–5	Radiology[1] years 1–5
I, ≤1 mm	every 6 months	yearly	none	none	none[3]
I + II, >1 mm	every 3 months	every 6–12 months	every 6 months	every 6 months	none
III[4]	every 3 months	every 6 months	every 3–6 months	every 3–6 months	every 6 months
IV	individually				

[1] Ultrasound of the abdomen, chest X-ray, or CT/MRT/PET.
[2] LDH, alkaline phosphatase, protein S100β.
[3] In case of adjuvant clinical trials, every 6–12 months.
[4] Stage IIC should be treated like stage III because of comparable prognoses.

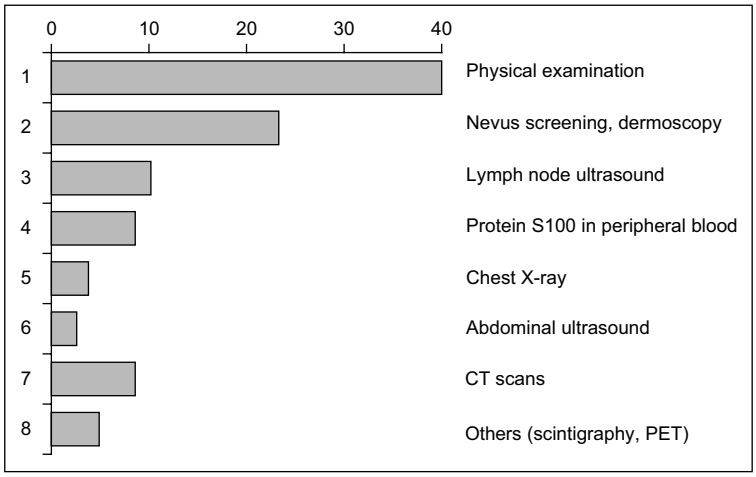

Fig. 2. Detection of recurrences (in percent) in stage I–III of disease achieved with various techniques.

three-monthly intervals, and technical examinations should be performed every 6 months [15]. This strategy may result in an increase in the detection rate of metastasis at an early phase of development. For each patient with stage IV disease, an individual follow-up strategy according to the patient requirements has to be established [15].

Recent Developments in Imaging Techniques

The continuous improvements in radiological methods led to a more sensitive recognition of tumor spread. Even small metastases are detectable with modern CT or MRT scans. The introduction of 'whole-body' MRTs [16] enables the definite detection of brain, liver, spleen, lymph nodes, bone marrow, muscle, and subcutaneous fat tissue metastases from head to toe in one single examination. Also the performance of a whole body dual-modality PET/CT provides information of the metabolism of suspicious lesions, which are not definitely evaluable in normal CT scans. Both, whole-body MRI and PET/CT enable the early identification of patients who may benefit from surgery.

Conclusions

Classification and staging of melanoma have been influenced by new diagnostic techniques and new staging rules. Diagnosis of primary melanoma has been greatly improved by dermoscopic techniques and by digital dermoscopy. These techniques facilitate screening of high-risk patients and early recognition of cutaneous melanoma. The introduction of the new AJCC staging system focuses on the role of Breslow's tumor thickness and ulceration in primary melanoma and improves the classification of regional and lymph node metastasis. However, this classification should be further improved and better adapted to the needs of medical practice. Follow-up examinations of melanoma patients should be planned according to the risk of recurrences and aim at early detection of recurrences. A 10-year period for scheduled follow-up with emphasis on clinical examination, lymph node ultrasound and determination of the blood tumor marker protein S100 is suggested. Finally, there is a significant improvement of imaging techniques by introduction of whole body MRT and PET-CT. These imaging techniques enable reliable identification of the extent of metastasis and guide the therapeutic decisions particularly for the indication of surgical metastectomy.

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Malignant Melanoma: PET/CT as a Staging Procedure

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Prognosis and treatment strategies in patients with malignant melanoma are determined by the stage of the disease [1]. Patients with a small number of metastases limited to a few sites, for instance, may benefit from surgery [2]; therefore, accurate staging is of great importance for disease management. In the following, we will explore the role of positron emission tomography (PET) with the radiopharmaceutical [^{18}F]2-fluoro-deoxyglucose (FDG) in staging malignant melanoma.

Positron Emission Tomography

Although in clinical parlance 'PET' frequently refers to PET imaging with FDG, PET more generally describes imaging of positron-emitting radioisotopes. The great success of PET in biomedical research and – more recently – in clinical routine applications rests on two advantages it has over conventional nuclear imaging systems for single-photon-emitting radioisotopes.

The first one is the wealth of physiological tracers. Typical examples of positron-emitting radionuclides are ^{11}C (T1/2 = 20.3 min), ^{13}N (T1/2 = 10.0 min), ^{15}O (T1/2 = 2.07 min), ^{18}F (T1/2 = 109 min), i.e., elements which abound in many biomolecules, allowing the synthesis of chemically unaltered labeled substrates, ligands, or therapeutic agents (radiopharmaceuticals). Only small tracer quantities of a radiopharmaceutical, which do not alter biological processes, are applied (10^{-12} to 10^{-9} moles). This makes PET imaging suitable for molecular imaging.

The second advantage of PET lies in the physical characteristics of the PET scanner [3, 4], which offers substantial physical advantages over conventional nuclear-imaging devices. In current tomographs, the patient is surrounded by rings containing thousands of small scintillation detectors. Coincidence circuitry monitors all events which are detected simultaneously. A positron emitted by the decay of a positron-emitting isotope travels within the body over a short distance, and, after it has come to rest, it interacts with an electron. The mass of both particles is transformed into two photons with an energy of 511 keV each which fly apart with an angle of approximately 180°. In the absence of photon scattering, the positron-electron annihilation must have occurred on a line connecting the two detectors where the photons were detected. The resulting coincidence lines map out a fan beam or cone beam geometry suitable for tomographic reconstruction similar to X-ray CT. This electronic collimation by coincidence detection in PET results in vastly higher detection efficiency at better resolution than obtainable with gamma cameras for single-photon imaging.

Several physical effects, which deteriorate imaging performance, have to be corrected (e.g., scatter attenuation, random coincidences). One of the corrections of immediate practical interest is attenuation correction. On their path from the positron-electron interaction to the detectors, photons may be lost due to scattering or absorption in the tissue. Attenuation correction is typically accomplished using measured attenuation data from a transmission scan, a procedure similar to transmission CT, which takes about 30% of the total imaging time.

Only fully corrected PET images allow quantitative in vivo assessment of the distribution of radiopharmaceuticals. The high resolution (little partial volume effects or improved recovery) and good efficiency (low image noise) of PET results in better detectability of anomalies and better precision in follow-up measurements than with conventional single photon imaging.

Because of the high costs of the detectors, the axial field of view covered by a typical PET tomograph is currently limited to 10–16 cm. Whole-body imaging is accomplished by moving the patient bed through the scanner in several steps. The total acquisition time is determined by the number of bed positions necessary to cover the volume of interest and the acquisition time per bed.

[^{18}F]2-Fluoro-Deoxyglucose

Even before the introduction of PET, ^{14}C-labeled 2-deoxyglucose was used with an autoradiographic technique for measuring the regional metabolic rate of glucose consumption [5]. This model was later applied to PET using

[^{18}F]2-fluorodeoxy-*D*-glucose [6, 7]. FDG is transported into the cells via glucose transporters phosphorylated to FDG-6-phosphate, but – unlike glucose – it does not enter the glycolytic pathway. Since dephosphorylation is negligible under many conditions, FDG-6-phosphate is effectively trapped in the tissue. Transport and phosphorylation are different for the tracer FDG and the natural substrate glucose. Sokoloff introduced the 'lumped constant' to describe these differences. The 'lumped constant' is tissue dependent and different in pathological tissues. Although the trapped amount of FDG is related to glucose metabolism, it is not universally proportional, particularly in tumors, and must not be regarded a quantitative measure of the metabolic rate of glucose [8]. Regardless of whether it reflects an elevated glucose metabolism or an increased lumped constant, the high FDG metabolism seen in many tumors makes FDG the most important PET radiopharmaceutical for applications in oncology.

An important aspect of the clinical success rests on the half-life of the label, ^{18}F (110 min), which is long enough to distribute this radiopharmaceutical to PET installations without own radiochemical production facilities. Due to the superior physical imaging characteristics of PET, the broad availability of FDG, and its favorable biological properties in many tumors, FDG PET imaging has become an established diagnostic modality for diagnosis, staging, and therapy monitoring for many tumors [9–11] and for the evaluation of patients with cardiac and neurological diseases [12, 13].

For clinical applications, the 'standardized uptake value' (SUV) has been introduced as a semiquantitative measure of FDG metabolism, despite the fact that many determinants of uptake variations are not accounted for [14]. Given fully corrected FDG PET images from a calibrated PET scanner, the SUV can be calculated as the ratio of the measured activity concentration in the lesion divided by the expected concentration when the injected activity is distributed evenly throughout the body, i.e., SUV = tissue concentration/(injected activity/body weight).

PET/CT

Combined PET/CT scanners were recently introduced that allow the acquisition of near-simultaneous coaxial PET and CT data [15], thus minimizing spatial misalignment. This novel technique promises to resolve diagnostic problems like ambiguous anatomic identification of PET findings in normal and especially altered anatomy. PET/CT also has logistic advantages over PET. The CT data, which are acquired in seconds, are also used for PET attenuation correction, obviating the need for a transmission scan, thus resulting in shorter

scan times and higher patient throughput. The combination of separate investigations into one furthermore simplifies and reduces the time for patient workup [16]. In addition to diagnostic advantages [17–19], PET/CT promises the integration of functional information into the treatment planning process in conformal radiotherapy [20], stereotactic and robot-assisted surgery, and minimally invasive percutaneous interventions.

Positron Emission Tomography as a Staging Procedure in Melanoma

Staging of the Primary Tumor

The stage of the primary tumor is determined by its thickness, presence of ulcerations, and depth of invasion and is an important prognostic determinant for the risk of locoregional or metastatic involvement [21]. Due to insufficient spatial resolution, PET cannot be expected to contribute pertinent diagnostic information. Consequently, data on the usefulness of PET for T staging are not available and there is no evidence supporting a role for PET in the initial diagnosis of malignant melanoma.

Assessment of Initial Nodal Involvement

Two situations must be distinguished in nodal staging, the search for subclinical lymph node involvement in the context of initial lymph node staging and the assessment of clinically or radiologically suspect lymph nodes.

Since the status of metastatic involvement of regional lymph nodes, even on a microscopic scale, is the most important predictor for recurrence and is closely correlated with survival, sentinel lymph node biopsy (SNLB) has become a mainstay initial staging and prognostic tool for melanomas exceeding 1 mm in thickness. FDG PET imaging is no alternative to SNLB for the detection of occult lymph node metastases. In a carefully designed prospective study, Wagner et al. [22] compared FDG PET imaging to SNLB as the gold standard in a series of 70 patients with a prevalence of 25% for subclinical lymph node metastases and a median aggregate tumor volume of 4.3 mm^3 in the involved lymph node basins. The sensitivity of FDG PET imaging was 17% and the specificity 96%. In a second study, the same group investigated the sensitivity of PET imaging as a function of tumor volume in 45 patients [23]. In this patient population, the median volume was 28.3 mm^3 and the overall sensitivity for PET 49%. A sensitivity of 90% was not achieved unless the tumor volume

Table 1. Sensitivity and specificity of FDG PET imaging compared to sentinel lymph node biopsy (SNLB) for initial staging of regional node status in low-risk melanoma

	Year	n	PET sensitivity	PET specificity	SNLB sensitivity	SNLB specificity
Wagner et al. [22]	1999	74	17	96	94	100
Acland et al. [25]	2001	50	28	n.r.	100	n.r.
Belhocine et al. [26]	2002	21	14	93	86	100
Havenga et al. [27]	2003	55	15	53	100	n.r.
Longo et al. [28]	2003	25	22	n.r.	100	n.r.
Fink et al. [29]	2004	48	13	100	n.r.	n.r.

n.r = not reported

reached approximately 80 mm^3, corresponding to ~5.3 mm in diameter. Tumor volume and PET sensitivity were significantly correlated with the AJCC stage, reflecting the observation that lymph node metastases in low-stage disease are very small, e.g., 65% of lymph node metastases in clinical stage I melanoma have tumor volumes less than 10 mm^3 [23, 24].

These data, which were subsequently confirmed by other studies (table 1), led to the decision to exclude initial nodal staging from reimbursement for FDG PET by Medicare in the US and the recommendation by the 3rd German Interdisciplinary Consensus Conference Onko-PET III in Germany, the AETMIS in Quebec, and the MSAC in Australia not to include initial nodal staging into the catalog of indications for FDG PET in malignant melanoma.

Furthermore, these data imply that PET or other current imaging modalities are not suitable when the clinical question demands the exclusion of metastatic lymph node involvement. For the same reason microscopic or very small distant metastases cannot be ruled out conclusively.

PET is more sensitive in advanced melanoma (stage III and IV) where the tumor burden is more commensurate with the typical resolution of current generation PET scanners [30–34]. Lymph node metastases with diameters greater than 5 mm are detectable by FDG PET with a sensitivity of 83–90% [23, 35]. This implies that PET is able to detect metastatic involvement in nonenlarged lymph nodes, i.e. earlier than e.g., CT or ultrasound [36].

Staging and Restaging of Melanoma

Similar to its role in many other malignancies, where FDG-PET imaging often leads to the discovery of unexpected tumor manifestations [e.g., 9, 10, 33],

Table 2. Sensitivity and specificity of FDG PET imaging compared to conventional diagnostics

	Year	n	PET sensitivity	PET specificity	Conventional imaging sensitivity	Conventional imaging specificity
Gritters et al. [38]	1993	12	100 L	100 L		
Boni et al. [39]	1995	15	91 L	67 L		
Blessing et al. [40]	1995	20	74 L	93 L		
Damian et al. [41]	1996	100	93 L	n.r.		
Steinert et al. [42]	1995	33	92 L	77 L		
Hsueh et al. [43]	1998	87	72 L	91 L		
Macfarlane et al. [30]	1998	23	85 L	91 L		
Gulec et al. [44]	2003	49	>1 cm: 100 L	75 L		
			≤1cm: 13 L	33 L		
Holder et al. [45]	1998	76	94 P	83 P	55 P	84 P
Rinne et al. [31]	1998	100	100 P (92 L)	96 P (94L)	85 P (58 L)	68 P (45 L)
	lung		70 L	100 L	87 L	100 L
Eigtved et al. [46]	2000	38	97 L	56 L	62 L	22 L
Stas et al. [47]	2002	84	85 L	81 L	90 L	87 L
	lung		91 L	97 L	82 L	91 L
Swetter et al. [36]	2000	104	84 L	97 L	58 L	70 L
Fuster et al. [48]	2004	156	74 L	86 L	58 L	45 L
	lung		57 L	92 L	93 L	70 L

Lesion-based analysis is labeled L and patient-based analysis by P. This table excludes the data on subclinical disease presented in table 1

PET has high sensitivity and specificity for the detection of lymph node as well as distant metastases from malignant melanoma (table 2). PET was found to be superior to conventional imaging (X-ray, CT, MRI, ultrasound) in the majority of studies. Furthermore, since PET is a whole-body imaging modality, body areas not covered by conventional imaging are investigated, leading to an additional advantage for PET [36].

Detection of pulmonary and cerebral metastases appear to be exceptions to the general superiority of PET for staging melanoma. Due to respiratory motion during the several minute acquisition of the PET image, small lesions are blurred and the image contrast may be reduced to below detectability, a phenomenon well understood in the context of differentiating pulmonary lesions with PET [37]. There is also a general consensus that brain metastases of malignant tumors are often missed by FDG PET because the high glucose metabolism in the brain severely impairs detectability. Therefore, very few studies have analyzed and reported data on brain metastases from malignant melanoma and

in only a small number of patients, e.g. [36]. Because of this low sensitivity, PET should not be used to assess brain metastases in melanoma patients.

Although the accuracy of FDG PET imaging is high, false-negative and false-positive scans may be obtained. Given the very high FDG uptake in melanoma, the main determinant for false-negative PET findings is small lesion size. Although no data comparable to the work of Wagner et al. [23] on lymph node staging of melanoma relating the sensitivity for detecting distant metastases to tumor volume are available, several studies distinguish sensitivities for lesions below and above 0.5 or 1 cm in diameter, leading to the conclusion that small distant melanoma metastases may be missed by FDG PET [33, 34, 38, 44, 45].

The majority of studies report a high specificity for FDG PET imaging in melanoma. The main sources of false-positive PET findings are benign lesions such as, e.g., healing after recent surgery, inflammation, granuloma, or sarcoidosis, and secondary malignancies unrelated to melanoma [33, 34, 45, 47]. False-positive findings may be reduced by taking into account the patient's history and all clinical findings [33, 34, 42, 45], leading to improved specificity under clinical conditions compared to a blinded reading of the PET scans which is commonly employed in the setting of clinical studies.

Change in Patient Management

Improved sensitivity and specificity only become clinically relevant if they result in improved patient management. No data have been reported as yet on improved outcome due to PET imaging in melanoma; however, initial observations with the impact of PET on therapeutic decisions have been published. Table 3 summarizes changes in patient management due to FDG PET imaging, as reported in several studies. While a few studies only show the total percentage of change, others allow an assessment of the way PET affects treatment. There are two possible scenarios, namely the detection of unexpected tumor manifestations due to the superior sensitivity of PET and the characterization of suspected metastases as benign due to its better specificity. This is particularly important in the context of surgical excision of melanoma metastases. Patients with a small number of metastases limited to a few sites may benefit from surgery [2]. Therefore, the potential for a more accurate determination of the extent of metastatic involvement by PET is important for proper treatment stratification. PET was able to detect candidates for surgery with resectable metastases among high-risk patients ('upstaging to surgery' in table 3). Likewise, PET detected patients with unsuspected disseminated disease who were unlikely to benefit from surgery

Table 3. Change of patient management due to FDG PET imaging in percent of patients reported

	Year	n	Overall change	Down-staging from surgery	Down-staging from CTX	Upstaging to surgery	Upstaging to CTX	Upstaging to RTX
Gritters et al. [38]	1993	49	37			12	25	
Steinert et al. [42]	1995	33	14			14		
Valk	1996	45	37	16		7	11	
Damien et al. [41]	1996	100	22		5	12	4	1
Hsueh et al. [43]	1998	87	9			9		
Rinne et al. [31]	1998	100	8				8	
Eigtved et al. [46]	2000	38	34					
Tyler et al. [33]	2000	95	16			1	15	
Stas et al. [47]	2002	100	26	9	10	3	4	
Gulec et al. [44]	2003	49	49			12	37	
Fuster et al. [48]	2004	156	36					

and were more suitable for systemic therapy ('upstaging to CTX' in table 3). On the other hand, patients with suspected resectable metastases may be diagnosed with benign disease by PET and do not have to undergo surgery or the extent of the resection can be reduced ('downstaging from surgery'). The characterization of suspected disseminated metastases as benign by PET may result in patients with a limited number of resectable tumor manifestations becoming eligible for resection or patients without metastases continuing follow-up without therapy ('downstaging from CTX'). In this context false-negative PET scans due to very small metastases do not lead to a detriment for the patient because there is no evidence that early treatment of microscopic disease improves patient outcome.

PET/CT in Melanoma

Unfortunately, no studies have been published on the clinical benefits of using fused PET/CT images in melanoma patients. A recent paper suggested a complementary role for PET and CT or MRI [34]. CT or MRI were read with the clinical history while PET was assessed under blinded conditions. In this setting PET and CT/MRI had a similar sensitivity and specificity (PET: sensitivity 79%, specificity 87% and CT/MRI: 76% and 87%) but the joint reading of PET and CT/MRI was found to be superior (sensitivity 88%, specificity 91%). Whenever both PET and conventional imaging are clinically indicated,

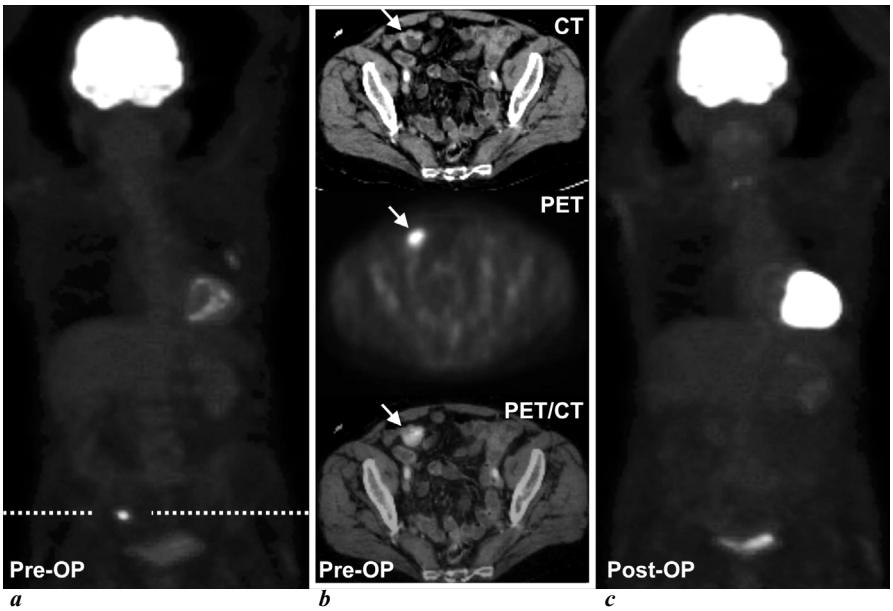

Fig. 1. The figure shows the anterior maximum intensity projections of the FDG-PET scan before (***a***) and after surgical resection (***c***) of a solitary melanoma metastasis to the small intestine. ***b*** Intrinsically coregistered preoperative PET and CT images from the PET/CT. The bowel lesion, which is readily seen on the PET image, is easily missed on CT. The fused image at the bottom provides the clear anatomical correlate of the FDG focus. Note the less intense FDG focus in the chest wall on the preoperative scan, which coincided with the location of a recent biopsy. This lesion, though not treated, was no longer present on the postoperative scan.

logistic and cost benefits are evident when patients are scheduled for a single PET/CT study rather than separate CT studies and a PET scan. Furthermore, recent studies in patients with other malignancies found that PET/CT had diagnostic advantages compared with separate PET and CT imaging [17–19]. These benefits resulted from the unambiguous correlation of suspicious FDG foci with physiological (e.g., urinary tract, brown fat, muscular structures, degenerative changes) or pathological structures (e.g., lymph nodes, masses, osteolytic lesions). Furthermore, involved lymph node stations or mass lesions could be defined anatomically, leading to greater confidence of the clinicians, especially surgeons. Reading the fused images also facilitated the identification of lesions which had been previously missed either on the PET or CT images alone (fig. 1). Finally, since PET and CT are assessed by diagnosticians with expertise in both modalities, a single synoptic PET/CT report is generated

which integrates all pathological findings. Thus the clinician is not burdened with having to weight potentially conflicting findings in separate PET and CT reports to reach a conclusion. Until clinical studies on PET/CT in melanoma patients better define its specific role in patient workup and management, these considerations suggest that PET/CT may be useful in staging melanoma.

Recommendations for using Positron Emission Tomography in Melanoma

The literature presented strongly suggests that FDG PET imaging is the most accurate imaging modality available today for detecting locoregional or distant melanoma manifestations in high-risk melanoma patients; however, like all other diagnostic modalities, it is not suitable to rule out very small or even microscopic disease. Therefore, FDG PET currently appears to be best suited for high-risk patients who are likely to benefit from local surgery or systemic therapies if metastases are detected. Future studies are necessary to show whether the resulting change of treatment strategies will lead to improved outcome.

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Malignant Melanoma – Clinical Development of Peptide-Based Melanoma Vaccines

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Background

The surface of tumor cells presents specific peptide epitopes in the context of HLA class I molecules, which can be selectively detected by the T cell receptor (TcR) of CD 8+ T lymphocytes. After recognition, activated CD8+ T cells can exhibit cytotoxic effector function, leading to the destruction of tumor cells. The first description more than a decade ago of the tumor-associated antigen (TAA) MAGE-1 recognized by CD8+ T cells was a groundbreaking step in cancer immunology [1]. In recent years, effective strategies to identify TAA recognized by specific T cells were developed and led to the characterization of various families of TAA, including the differentiation antigens, overexpressed antigens, cancer germline antigens, mutated antigens and viral antigens [reviewed in ref. 2]. These TAA have facilitated the analysis of T cell responses to tumors and the development of immunotherapeutic approaches. The characterization of numerous MHC-class-I- binding epitopes of the TAA recognized by CD8+ T cells simplified the development of synthetic vaccines. MHC-class-I-binding epitopes consisting of 9–12 amino acids can directly be injected for patient immunization. More recently, epitopes derived from various TAA presented in association with MHC class II and recognized by CD4+ T cells have been identified as well.

Sensitive T cell assays allowing direct analysis of single antigen-specific T cells, without the need for prior in vitro expansion, are available now. These functional T cell assays, such as the ELISPOT assay and intracellular cytokine

Table 1. Clinical studies of peptide vaccination in patients with metastatic melanoma

Antigen	Adjuvant	Patients	Tumor response	T cell response (type of assay)	Ref.
MAGE-3	None	39	7 CR/PR of 25	0/4 (Cr)	6
Tyrosinase + MART-1 + gp100	GM-CSF	3	3 CR/PR	3/3 (Cr)	7
MART-1	IFA	18	none	12/18 (Cr)	8
Gp100	IFA	11	3 M × R	10/11 (ELISA)	9
	IFA + IL-2	19	8 CR/PR, 3 M × R, 3 SD	3/19	
Tyrosinase	QS21	9	none	2/9 (ELISPOT)	10
Tyrosinase	GM-CSF	18	1 MxR, 2 SD	4/15 (ELISPOT)	11
Gp100	IFA + Anti-CTLA-4	14	2 CR, 1PR	11/11 (Cr) 0/11 (ELISPOT)	31

CR/PR = Complete/partial remission; MxR = mixed response; SD = stable disease; Cr = chromium-release assay following in vitro sensitization; ELISA = cytokine-release assay following in vitro sensitization.

flow cytometry, use antigen-specific induction of cytokines to detect specific T cells at a single cell level [3, 4]. Multimerized HLA class I molecules carrying a peptide epitope and labeled with a fluorescent marker bind to the specific TcR and allow direct ex vivo staining of specific T cells, but they do not provide data on T cell function [5].

Clinical Vaccination Trials in Metastatic Melanoma

First trials studying the immunogenicity and toxicity of peptide vaccination have been performed in patients with metastatic melanoma [6–11, 31, summarized in table 1]. In general, objective tumor remissions were seen only occasionally and were usually restricted to melanoma patients with limited disease. For instance, in a MAGE-3 peptide trial reporting a 30% response rate the 7 patients showing an objective tumor remission all had metastatic disease limited to soft tissue or lymph nodes and 14 patients who were not included in the response evaluation had early progressive disease during vaccination [6]. Antigens tested in clinical studies were mostly cancer germline antigens or melanocyte differentiation antigens, either alone or combined with various adjuvants, as outlined below. Routes of administration (mostly intradermally or subcutaneously), dosages usually ranging from 0.1 to 1 mg of peptide and vaccination intervals ranging from 1 to 3 weeks varied and none of these variations was clinically or immunologically clearly superior. The results from the vaccine peptide trials in metastatic melanoma are also reviewed in detail in references 12 and 13.

Association of T Cell Responses with Tumor Regression

The reported success rate in inducing specific T cell responses was rather heterogeneous in the vaccination studies performed in patients with metastatic melanoma. In a series of vaccination studies using peptides derived from the MAGE antigens without adjuvants, either no or very low frequency T cell responses were detectable in spite of objective tumor responses in several patients [6]. In contrast, vaccination with gp100, MART-1 or tyrosinase peptides, usually emulsified in incomplete Freund's Adjuvant (IFA), resulted in the induction of specific T cell responses in the majority of patients, but few patients had evidence of clinical efficacy [8, 9]. Various reasons for the lack of efficacy of vaccine-induced T cells may be discussed and are potentially related to quantitative or functional limits of the T cell responses, limited accessibility of solid tumors by vaccine-induced T cells, or tumor escape mechanisms and tumor-specific immunosuppression occurring in patients with a large tumor burden. Since most T cell response analyses in these earlier trials were performed with in vitro stimulation assays, no conclusions can be drawn concerning the in vivo functionality of these T cells. One explanation for the failure to detect a vaccine-specific T cell response in some patients despite tumor regression is that the initial attack of the tumor cells by vaccine-specific T cells may induce subsequent T effector cells with other specificities. This phenomenon called 'epitope spreading' has been shown in several vaccination studies [14]. Similarly, the enhancement of preexisting immunity to antigens not used for immunization, as observed in a patient following vaccination with peptides, may mediate the observed tumor regression [15].

A major problem in correlating T cell responses with clinical responses is that most phase II vaccination studies reported so far had an objective response rate of less than 10% on an intent to treat basis, making such a correlation difficult. There is some evidence now from more recent vaccination trials, including peptide-loaded dendritic cell trials, that there is a relation between the detection of vaccine-induced T cells and clinical effects. Of 18 melanoma patients vaccinated with peptide-pulsed dendritic cells, 10 developed a specific T cell response to >2 peptide antigens, which was correlated with a favorable clinical outcome [16]. A study in which melanoma patients were vaccinated with autologous heat shock protein vaccine also showed a close correlation between clinical response and specific T cell response monitored by an ELISPOT assay [17]. In stage IV melanoma patients vaccinated with tyrosinase peptides in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), induction of specific T cell responses was observed in 4 out of 15 patients that was associated with tumor regression, stabilization or long-term freedom from relapse [11, 18]. While initial studies failed to demonstrate the

Table 2. Clinical studies of peptide vaccination in patients with resected melanoma

Antigen	Adjuvant	Patients	T cell response	Ref.
MAGE-3	IFA+PADRE	18	5/14 (Cr)	21
MART-1	IFA	25	12/20 (ELISPOT)	22
Tyrosinase+gp100	QS21	9	4/9 (ELISPOT)	23
	IFA	9	0/9	
	GM-CSF	8	4/8	
Tyrosinase	none	9	3/9 (ELISPOT)	24
	GM-CSF	9	4/9	
	KLH	10	0/10	
	GM-CSF+KLH	9	5/9	
Gp100	IFA or QS21+/− tetanus toxoid	22	3/21 (ELISPOT)	25
Tyrosinase+gp100	IFA+/−IL-12	48	33/38 (ELISA) 37/42 (tetramer)	26
Tyrosinase+gp100	IFA+/−GM-CSF	48	34/39 (ELISA) 37/42 (tetramer)	14
gp100	IFA	30	28/29 (tetramer)	27

Cr = Chromium-release assay.

induction of MAGE-3 vaccine peptide specific T cells in melanoma patients despite objective tumor regressions [6], a more recent report showed very low frequency T cell responses in 4 of 9 responding but only 1 of 14 progressing patients [19].

A recent report suggests that epitope spreading may be associated with a clinical response. Spreading of the T cell response to other melanoma antigens was found in a patient with a complete response to vaccination with peptide-loaded dendritic cells, while nonresponders did not display reactivity to epitopes other than those used for vaccination [20].

Clinical Trials in Patients following Tumor Resection

Adjuvant vaccination of high-risk tumor patients following resection of the primary tumor or metastases or successful systemic therapy may have a much greater immunologic and therapeutic potential. There are several clinical phase I and II trials in patients with resected melanoma [ref. 14, 21–27, summarized in table 2]. In recent studies, induction of specific T cells has been demonstrated

in the majority of tumor-free patients by prolonged vaccination (8–13 cycles) with gp100 peptides emulsified in IFA using direct tetramer staining [14, 26, 27]. In a randomized trial no differences in the frequency of peptide-specific T cells was observed between patients vaccinated every 2 weeks or every 3 weeks [27]. Prolonged disease-free and overall survival of melanoma patients receiving peptide vaccination was observed compared to historical controls [14, 22, 25, 26]. Tyrosinase peptide vaccination resulted in long-term freedom from recurrence in several high-risk melanoma patients who had multiple cutaneous relapses prior to vaccination [18, 28]. However, no formal proof of the efficacy of adjuvant antigen-specific vaccination has been provided in clinical phase III studies in melanoma patients so far. The Eastern Cooperative Oncology Group (ECOG) is currently performing a large multicenter study evaluating the effect of peptide vaccination and the role of GM-CSF in a randomized phase III trial in relapsed stage III and stage IV patients after resection of metastases.

Role of Immunological Vaccine Adjuvants

Following intradermal injection, TAA-derived peptides are thought to bind to empty MHC class I molecules on dendritic cells, which then migrate to the draining lymph nodes where specific T cell activation occurs. Vaccination with TAA-derived peptides alone may be suboptimal to charge and activate dendritic cells, and elicit specific T cell responses. Therefore, much attention is being focused on the identification of immunological adjuvants that can enhance T cell responses to TAA-derived peptides in the vaccinationsetting. GM-CSF has been used in various vaccination protocols, despite limited data supporting its usefulness in MHC class I peptide vaccination. GM-CSF promotes local recruitment and migration of dendritic cells and was shown to enhance induction of specific T cell responses against self-proteins and MHC-class-II-binding epitopes in animal models. Enhanced induction of CD8+ peptide-specific T cells and objective tumor responses had initially been reported in 3 melanoma patients following the addition of GM-CSF to a multipeptide vaccine [7]. In two consecutive small phase I trials performed in tumor-free melanoma patients, no difference in the induction or frequency of peptide-induced T cell responses analyzed by an ELISPOT assay was observed if tyrosinase peptides were administered alone or in combination with GM-CSF [24]. Weber et al. who vaccinated stage III patients after resection with gp100 and tyrosinase peptides emulsified in IFA with or without GM-CSF observed a trend of GM-CSF to moderately increase the frequency of specific T cells detected by tetramers [14]. A small trial was reported comparing the potency of the three adjuvants GM-CSF, QS21 and IFA in melanoma patients immunized with tyrosinase

368–376(370D) peptide [23]. While half of the patients immunized with peptide with either GM-CSF or QS-21 developed a T cell response detected by an ex vivo IFN-γ-ELISPOT assay, no T cell response induction was seen in the IFA group. Although used in most peptide vaccination trials nowadays, the adjuvant effect of IFA has not been comparatively evaluated in any other trial. The vaccination of resected stage III patients with gp100 and tyrosinase peptides emulsified in IFA without or with the T-cell-stimulating cytokine IL-12 resulted in the induction of specific T cell responses in the majority of patients with significantly higher levels of cytokine-releasing T cells and a trend towards an increase in the frequency of specific T cells detected by tetramers in patients receiving IL-12 [26].

In several trials reported by Rosenberg et al. [29], a decrease in the precursor frequency of peptide-specific T cells by vaccination with gp100 peptide in IFA in combination with the T cell cytokines IL-2, IL-12 or GM-CSF was observed. Following vaccination with gp100 peptide together with IFA without cytokines, specific T cells could be expanded from peripheral blood in the majority of patients, while in patients receiving peptide together with GM-CSF, IL-2 or IL-12 expansion of specific T cells was possible in fewer patients and in lower frequencies. In one of these studies, the decrease in specific T cells in peripheral blood was, however, associated with higher clinical efficacy, since administration of peptide together with IL-2 resulted in tumor regression in 40% of the patients while no tumor responses were seen in patients receiving peptide alone [9]. Similarly, we observed a transient decrease in specific T cell responses detected by the ELISPOT assay in patients vaccinated with tyrosinase peptides, GM-CSF and keyhole limpet hemocyanin (KLH) [24]. The decrease in specific T cells seen in these studies may be a compartment phenomenon (especially in the case of IL-2), but could also be similar to the so-called ‘antigen stunning’ observed during acute viral infections, a transient loss of function perhaps associated with overexposure to antigen [30].

Another strategy to enhance T cell responses to MHC class I epitopes is the use of T helper antigens. Animal models show that the induction of CD8+ T cell responses may require the presence of CD4+ T helper cells, which stimulate dendritic cells and cytokines. CD4+ T helper cell responses may also be of importance for the long-term maintenance of CD8+ T cells. Simultaneous induction of CD8+ and CD4+ T cell responses was either achieved using specific MHC class II epitopes or unspecific T-helper antigens like a pan-class II epitope (PADRE) [21] or (KLH) [24]. In a series of small phase I trials vaccinating high-risk melanoma patients with tyrosinase peptides, the combined administration of GM-CSF and KLH was associated with earlier induction of T cell responses as compared with patients receiving either GM-CSF or KLH alone [24].

Another study by Rosenberg et al. [31] evaluated a new promising strategy to enhance T cell responses to tumor peptides. CTLA-4 (cytotoxic-T-lymphocyte-associated antigen 4), which mediates downregulation of T cell activation, was blocked by a specific antibody followed by vaccination with gp100 peptide resulting in one partial and two complete responses in 14 melanoma patients. However, 6 of the 14 patients, including the 3 responders, developed severe grade III/IV autoimmune manifestations.

Future Development of Peptide Vaccines

Future perspectives focus on more potent vaccination strategies. This may be achieved using more potent immunological adjuvants. As outlined above, results from first comparative clinical phase I/II studies suggest that certain cytokine adjuvants, including IL-2, IL-12, or GM-CSF together with KLH, can enhance the immunogenicity of peptide vaccines. Other promising adjuvants, e.g. CpG oligonucleotides, are currently tested in phase I trials. Further, the need of T helper antigens for the induction and maintenance of CD8+ T cell responses needs to be clarified. Most antigens that have been tested so far in clinical studies are not tumor-specific and the use of these self-antigens for vaccination may be suboptimal. High-avidity precursor T cells to self-antigens may have been deleted or anergized, and induction of autoimmunity is always of concern if low-level expression of vaccine antigens is also found on normal cells. Ideal tumor antigens should not only be expressed exclusively by the tumor cells but their expression should also be essential for tumor cell survival and growth.

Systematic development of vaccination strategies is urgently warranted, since so far its role in the adjuvant and therapeutic setting as well as its implementation in multimodal therapies remains undefined. The most promising approach is the vaccination of patients with minimal residual disease in whom vaccines will most likely have a much greater immunologic and therapeutic potential as in patients with progressive metastatic disease. However, the evaluation of clinical efficacy is difficult in this patient group. A logical approach would be to establish immunogenic vaccination protocols in phase I/II studies that lead to a rapid and sustained induction of tumor-specific T cells in the majority of patients. The potency of vaccine preparations and vaccination schedules should be compared with direct T cell assays requiring no in vitro expansion. Phase II trials in patients with limited disease or with resected metastases with a high risk for recurrence would allow the subsequent assessment of clinical efficacy prior to definite randomized phase III trials. In patients with advanced disease, it is unlikely that high clinical efficacy will be achieved by peptide vaccination. In this setting, combined modality treatments need to

be developed. The in vivo induction of tumor-specific T cells by vaccination followed by large-scale ex vivo expansion and adoptive T cell retransfer may also be a promising strategy in patients with metastatic disease.

An effective vaccine should elicit an effector T cell response able to mediate the destruction of tumor cells as well as memory T cells providing long-term immunity. Therefore not only the quantitation but also the characterization of differentiation subsets of specific T cells is of great interest. A detailed phenotypic analysis of specific T cells is possible by flow cytometric methods. The currently most frequently used classification is the one proposed by Sallusto et al. [32] based on the expression of the lymph-node-homing chemokine CCR7 and CD45RA-classifying CD45RA+CCR7+ naive T cells, CD45RA-CCR7+ central memory T cells, CD45RA-CCR7 effector memory T cells and CD45RA+CCR7 effector T cells. A similar distinction of T cell subsets can be made using CD27/CD28 [33]. These classifications are a very helpful tool to further characterize the type and function of TAA-specific T cell responses, and induction of memory as well as effector T cells by peptide vaccination was shown in first studies [34–36]. In addition, a number of further characteristics of tumor-specific T cells may be important for their efficacy in attacking disseminated tumor cells. These include the avidity of the TcR-antigen binding, the presence of cytotoxic granules and the type of cytokine released in response to antigen exposure, the proliferative capacity, and the expression of functional adhesion and chemokine receptors driving T cells specifically into distinct peripheral tissues.

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