Radiation Therapy for Extranodal Lymphomas

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Editors
Keisuke Sasai
Department of Radiation Oncology
Juntendo University Faculty of Medicine
Tokyo
Japan

Masahiko Oguchi
Department of Radiation Oncology
The Cancer Institute Hospital
Tokyo
Japan

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Preface

The paradigm in the treatment of malignant lymphomas has shifted dynamically with recent rapid advances in systemic pharmaceutical treatment. Previously, the utility of systemic therapy was severely limited because few effective chemotherapeutic agents were available. Therefore, radiation therapy played an important role in the treatment of malignant tumors. Today, many effective agents are available, including novel molecular targeted drugs such as rituximab. Consequently, malignant lymphomas can now be cured by systemic therapy.

Radiation therapy was previously very primitive. In the 1980s, tumors were usually treated using simple radiation fields. Because the tumor extent was unclear, the radiation fields had to be large. The standard treatment field for a malignant lymphoma was extremely large and the radiation doses were relatively high. Consequently, survivors developed unexpected complications, including secondary cancers and cardiovascular diseases. Therefore, many trials aimed to avoid radiation therapy for such disorders and currently few malignant lymphoma patients receive radiation therapy combined with standard chemotherapy. Hodgkin's lymphomas are usually treated with combination chemotherapy with or without very-low-dose radiation therapy. Nodal lymphomas are treated solely with combination chemotherapy. Only a few patients with very large mass lesions or those with mediastinal anaplastic large cell lymphomas receive radiation therapy combined with standard chemotherapy.

Today, highly sophisticated imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)/CT yield detailed data on tumors. Many advanced radiation modalities are available, including intensity-modulated radiation therapy, image-guided radiation therapy, and particle therapy. These advances can focus the radiation dose to the target volume precisely within a small margin. Therefore, radiation can be delivered only to tumors at the lowest effective dose to avoid adverse events. Involved-node radiation therapy (INRT), a new method, is now being used to treat malignant lymphomas and is effective as a large-field treatment. However, unsurprisingly, INRT is very difficult to deliver precisely. To overcome these problems, a larger treatment field has been proposed. This technique is called involved site radiation therapy (ISRT).

Historically, radiation therapy was the mainstay of malignant lymphoma treatment, as mentioned above. Specifically, the treatment of extranodal lymphomas was

in the hands of radiation oncologists. Extranodal lymphomas have specific characteristics involving their histopathology, lymphomagenesis, and clinical course, which are limited to the site from which the tumors arise. Many extranodal lymphomas are retained in the original organ and are radiosensitive or relatively radiosensitive. Diffuse large B-cell lymphomas that originate from the central nervous system (CNS) show a very different clinical course to that of histologically similar lymphomas arising from nodal regions. Lymphomas arising from one paired organ, such as mucosa-associated lymphoid tissue (MALT) lymphomas in the conjunctiva and testicular diffuse large B-cell lymphomas, tend to relapse in the opposing site. Testicular lymphomas also have a tendency to recur in the CNS.

Although such extranodal lymphomas are most often treated by hematological oncologists, radiation therapy still plays an important role. For example, MALT lymphoma arising from the conjunctiva is easily treated and can be cured by radiation therapy without any other treatment. Gastric MALT lymphomas and duodenal low-grade lymphomas can also be cured solely by radiation therapy. Furthermore, we radiation oncologists are highly experienced in the treatment of extranodal lymphomas. These diseases are relatively rare and thus our younger colleagues in radiation oncology and hematological oncology have little experience with respect to this treatment.

Because radiation is the single most effective agent for the treatment of malignant diseases, it is important to combine this treatment with chemotherapeutic agents. Therefore, new guidelines for the treatment of extranodal lymphomas using ISRT have been proposed by the International Lymphoma Radiation Oncology Group (ILROG). However, although these guidelines are very informative, some ambiguities remain.

The purpose of this book is to specify these issues and to transfer our legacy of knowledge regarding the treatment of extranodal lymphomas to younger investigators and physicians with less experience.

Although these diseases are rare, there are many patients in Japan with nasal natural-killer (NK)/T cell lymphomas, HIV-unrelated CNS lymphomas, and duodenal low-grade lymphomas. Specialists in the treatment of extranodal lymphoma produced this book, which provides substantial information on the treatment of these diseases. We also outline standard treatments for lymphomas arising from other extranodal organs. We believe that this book will help readers to learn more about extranodal lymphomas and to improve their treatment of these diseases.

Tokyo, Japan Keisuke Sasai
Tokyo, Japan Masahiko Oguchi

Contents

Primary Central Nervous System Lymphomas

1

Natsuo Oya

Abstract

Radiotherapy (RT) after systemic chemotherapy including high-dose (HD) methotrexate is widely accepted as the standard treatment for primary central nervous system lymphoma (PCNSL). Treatment must consider the blood brain barrier as it characterizes the clinical behavior of PCNSL. For consolidation RT in patients with complete remission (CR) after chemotherapy, 23.4–30 Gy of whole-brain radiotherapy (WBRT) is recommended. For salvage RT in patients with non-CR or recurrent disease (RD) after chemotherapy, 36–45 Gy of WBRT or 30 Gy of WBRT followed by 10–20 Gy of boost irradiation is recommended. The reported 5-year survival rate of PCNSL patients is 30–50%; it is worse than for patients with other extranodal lymphomas. Late neurological toxicity is a major problem in long survivors after HD methotrexate and WBRT. Chemotherapy alone may be considered in elderly PCNSL patients who are at high risk for radiation-induced neurocognitive dysfunction.

Keywords

Central nervous system lymphoma (PCNSL) • Whole-brain radiotherapy (WBRT) • Intraocular lymphoma • High-dose methotrexate • Neurocognitive dysfunction

N. Oya
Department of Radiation Oncology, Faculty of Life Sciences, Kumamoto University, 1-1-1, Honjo, Chuo-ku, Kumamoto, Japan
e-mail: n-oya@kumamoto-u.ac.jp

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1.1 Introduction

Primary central nervous system lymphoma (PCNSL) accounts for around 3% of all primary brain tumors; it is more frequent in adults 60 years or older. The most common treatment for PCNSL consists of chemotherapy with high-dose methotrexate (MTX) followed by radiotherapy (RT). Although the prognosis of PCNSL patients has improved by the establishment of regimens involving high-dose MTX, their 5-year survival rate is 30–50% and worse than for patients with other extranodal lymphomas [1, 2]. RT plays an important role in the treatment of PCNSL and is used for definitive-, consolidative-, salvage-, and palliative treatment.

1.2 Pathology

Most PCNSLs are diffuse large B-cell lymphomas (DLBCLs). AIDS-related PCNSL is less frequent in Japan than in Western countries. Usually, PCNSL presents with parenchymal infiltration with extensive brain edema and potential multicentricity. Autopsy studies of PCNSL patients demonstrated tumor cell infiltration far beyond T2 hyperintensity area in magnetic resonance imagings (MRI) [3]. The highly infiltrative and multicentric nature of PCNSL warrants the use of whole-brain radiotherapy (WBRT) for consolidation irrespective of the size, number, or location of the primary tumors observed on pre-chemotherapy MRI scans [4].

1.3 Pretreatment Evaluation

Most patients with PCNSL suffer neurological symptoms or convulsions. For diagnostic workup, computed tomography (CT)/MRI studies and surgical biopsy are usually performed. To differentiate PCNSL from metastatic disease from extracranial lymphomas, FDG-PET or whole-body CT studies are useful. The pretreatment tumor size, -number, and -location should be evaluated on MRI scans shortly before the start of treatment for an exact estimation of the response. Ophthalmologic examination to detect ocular involvement should be considered regardless of visual symptoms because approximately 10–25% of patients with PCNSL develop intraocular involvement [5].

1.4 Treatment Strategy

RT after systemic chemotherapy including high-dose (HD) MTX is widely accepted as the standard treatment for PCNSL. For patients intolerant of full chemotherapy due to a poor performance status, advanced age, or previous/coincidental disease, RT alone is a treatment option with curative intent [2]. The use of MTX concurrent with or after RT may be associated with an increased

risk of leukoencephalopathy. The intrathecal administration of MTX is not recommended as clinical practice because of the potential risk of leukoencephalopathy. Chemotherapy alone has been considered as an alternative approach in elderly PCNSL patients at high risk for radiation-induced neurocognitive dysfunction. The role of surgical intervention is limited to biopsy for a histopathological diagnosis [6].

1.5 Chemotherapy

Previously, treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP), the standard chemotherapy for most DLBCLs, was used to treat PCNSL. However, its effectiveness was unsatisfactory [7, 8]. Now the high efficacy of HD MTX has been widely recognized [1, 2] and its upfront use alone or in combination with other drugs, including rituximab, vincristine, and procarbazine, is recommended [9, 10]. The clinical benefit of adding temozolomide to HD MTX is under investigation [11]. The combination of systemic chemotherapy plus intraventricular chemotherapy with MTX (≥ 3.5 g/m^2), Cytarabine (Ara-C), and dexamethasone has been reported to prolong the response duration [12, 13].

1.6 Radiation Therapy (Indications)

1.6.1 Consolidation RT in Patients with CR After Chemotherapy

Consolidation RT is a traditional curative treatment option for nodal- and extranodal lymphoma patients who achieved CR after systemic chemotherapy. The omission or deferral of consolidation RT is now considered in patients with several lymphoid malignancies including PCNSL to avoid radiation-induced toxicity or a possible radiation-induced second malignancy.

Since the establishment of the HD MTX regimen, chemotherapy-alone approaches that omit consolidation RT in patients with CR have been attempted as a curative treatment option for PCNSL. The omission of RT was reported to result in a lower incidence of neurocognitive dysfunction; however, there was an increase in local or intracranial distant recurrence [12, 14–16]. Consequently, consolidation RT again plays a part in the initial treatment of PCNSL.

In discussing the role of the consolidation radiotherapy, the blood–brain barrier (BBB), which may characterize the clinical behavior of PCNSL, must be considered. Both gadolinium (Gd) MRI contrast- and chemotherapeutic agents are blocked by the intact BBB. However, large PCNSL lesions with a disrupted BBB tend to be strongly enhanced on Gd-enhanced MRI scans. Such lesions are expected to be good chemoresponders because the chemotherapeutic agents can permeate into the lesion. On the other hand, extremely small PCNSL lesions that are too small to disrupt the BBB may be undetectable on Gd-enhanced MRI

scans. They may be unaffected by the chemotherapeutic agents and maintain their proliferative capacity even during chemotherapy. Thus, paradoxically, large visible lesions are chemoresponders while small undetected lesions are chemoresistant.

After chemotherapy alone, not a few PCNSL patients may suffer extremely early local recurrence, even after having been judged as CR on posttreatment Gd-enhanced MRI scans [12]. If the BBB recovers from disruption with shrinkage of the tumor and its recovery is complete before tumor cell annihilation, the previously chemoresponsive lesion may turn into a small, residual, chemoresistant lesion undetectable by MRI. It may be "more than microscopic" and consist of a cluster of a viable tumor cells. Regrowth of the post-chemotherapy residual lesion is clinically recognized as early local recurrence. Therefore, the significance of consolidation RT is different in PCNSL and other nodal or extranodal lymphomas because the determination of posttreatment CR is difficult on MRI scans of PCNSL.

As some PCNSLs are multicentric, even when an initial MRI-based diagnosis of solitary PCNSL, consolidation RT should be indicated considering the existence of small, undetectable, chemoresistant lesions beyond an intact BBB. After chemotherapy alone, some PCNSL patients may develop early intracranial distant recurrence. When only one of multiple PCNSL lesions is large enough to be detected on Gd-enhanced MRI scans, the diagnosis should be solitary PCNSL. If BBB disruption persists until total annihilation of the tumor cells by chemotherapy, true CR of this lesion can be achieved by chemotherapy alone. However, subsequently, other small lesions unaffected by chemotherapy may begin to grow, and in such cases the clinical diagnosis should be intracranial distant—without local recurrence. This reenforces the importance of consolidation RT in patients with PCNSL and may warrant the use of WBRT.

1.6.2 RT for Refractory or Recurrent PCNSL After Chemotherapy Alone

Depending on the chemotherapy regimen and patient background, the reported non-CR rate after MTX-based chemotherapy without RT is 22–71% [9, 15–18]. Among patients with CR, 50–81% developed intracranial relapse at the primary tumor site or at a distant site [15, 17, 18]. In patients with refractory or recurrent lesions, salvage treatment with RT or second-line chemotherapy should be considered. RT has been shown to be the most effective salvage treatment [15].

1.6.3 RT for Progressive Disease During Initial Chemotherapy

Approximately 10% of PCNSL patients experience tumor progression during initial MTX-based chemotherapy; their tumors are chemo-resistant and/or aggressively proliferating. In such cases RT should be started immediately to prevent symptomatic worsening.

1.6.4 Re-irradiation for Recurrence After Whole-Brain Radiotherapy

Intracranial relapse is seen in 30–50% of patients who received initial treatment with MTX-based chemotherapy and WBRT. While re-irradiation is a treatment option for the post-WBRT recurrence of PCNSL, repeat-WBRT with curative intent may be appropriate under limited conditions. As the TD5/5 to the whole brain is considered to be 45 Gy [19], re-WBRT after a prolonged interval may be safe if the cumulative dose does not exceed 50 Gy. Theoretically, a protocol with a reduced WBRT dose lower than 25 Gy could be repeated twice although it is unclear whether the second round of WBRT is safe. Since patients with recurrent PCNSL often have received or will receive several courses of salvage chemotherapy with or without MTX, it is difficult to estimate the possible neurotoxicity of re-WBRT. Therefore, partial brain- or local RT with palliative intent is often used for recurrent PCNSL after initial WBRT.

1.6.5 Palliative RT

RT is preferable as a palliative treatment in patients with symptomatic newly diagnosed or recurrent PCNSL because it results in prompt, safe, and long-lasting symptom relief. Partial brain- or local irradiation with a hypofractionated schedule and conventional WBRT is often used for palliative RT. In a subset of patients, single-dose or fractionated stereotactic irradiation may be a treatment option.

1.6.6 RT in Elderly Patients

Advanced age is a major adverse prognostic factor in PCNSL [20]. Among long-term survivors initially treated with WBRT, brain atrophy and neurocognitive dysfunction are more common in elderly than young patients [14, 21–24]. To decrease WBRT-induced neurotoxicity in the elderly with post-chemotherapy CR, consolidation RT can be omitted, the WBRT dose can be decreased, or partial-brain RT rather than WBRT can be administered [9, 25, 26]. However, it remains controversial whether the reduction in neurotoxicity achievable by RT omission or reduction is at the cost of an increase in intracranial recurrence. Not WBRT but also effective chemotherapy and disease progression may result in future neurocognitive dysfunction.

1.6.7 Radiotherapy for Intraocular Involvement by PCNSL

For patients who present with intraocular involvement at the time of a PCNSL diagnosis, the anterior edge of the WBRT field should be extended to include both eyes. In such patients, the intravitreal injection of MTX is often combined with systemic chemotherapy with high-dose MTX.

1.6.8 RT for Primary Intraocular Lymphoma

In patients with primary unilateral intraocular lymphoma without any evidence of intracranial diseases, RT to the involved eyeball, the ipsilateral optic nerve, and the chiasm, with or without intravitreal MTX injection, is recommended. Intraocular lymphoma has been documented to be a part of PCNSL, and it can be bilateral. Prophylactic WBRT or irradiation to the uninvolved eye may not be necessary. If the involved eye is treated appropriately with RT, the incidence of intracranial relapse is not sufficiently high to warrant routine prophylactic WBRT [27]. Patients with intracranial relapse after the treatment of primary intraocular lymphoma may respond well to chemotherapy and RT.

1.7 Radiation Therapy (Treatment Procedures)

A patient with multiple chemo-resistant PCNSL treated with WBRT and boost irradiation is presented in Figs. 1.1, 1.2, 1.3, and 1.4.

1.7.1 RT Planning

Three-dimensional (3D) CT imaging is usually performed in patients with PCNSL for the treatment planning with WBRT or partial-brain RT. Thin-slice CT images of the whole brain down to at least the third cervical vertebral level should be obtained with head fixation with a shell.

The fusion of CT and MR images on a radiation treatment planning (RTP) system is useful especially when partial brain RT is planned. The images to be fused, i.e., pre- and post-chemotherapy MRI scans, Gd-enhanced T1WI scans, and fluid-attenuated inversion recovery (FLAIR) images, should be chosen based on the gross tumor volume (GTV) or the clinical target volume (CTV) of the planned partial brain RT.

1.7.2 Whole-Brain Radiotherapy (Fig. 1.2)

With the exception of some patients requiring palliative RT, WBRT is the standard RT technique for PCNSL [4]. To obtain full coverage of brain tissues, adequate lens sparing, and radiation-dose homogeneity, CT-based 3D RT planning is recommended before the delivery of WBRT.

1.7.2.1 Target Volumes

The gross tumor volume (GTV) is identified on contrast-enhanced MRI scans performed before chemotherapy. It usually does not influence determination of the irradiation field for WBRT. However, superimposition of the GTV on planning CT images is helpful for avoiding unexpected under-dosing at GTV.

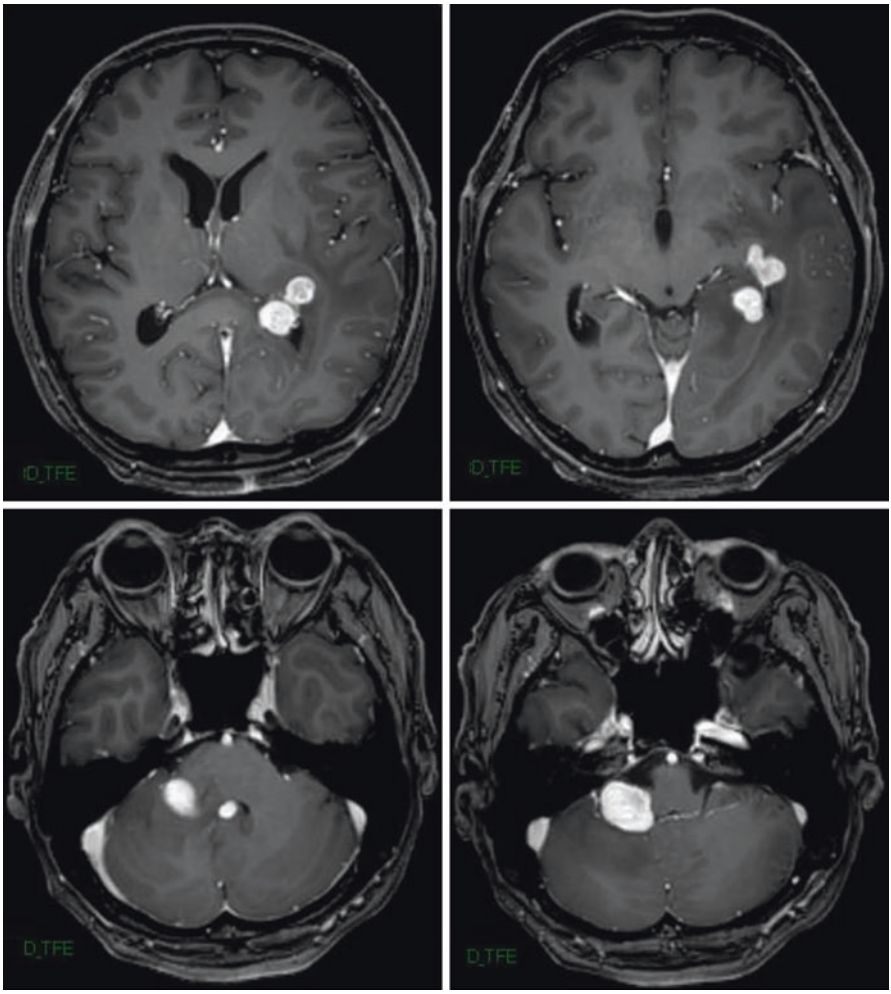

Fig. 1.1 Gadolinium-enhanced MR images of a 58-year-old male with multiple PCNSL presenting with right oculomotor nerve palsy. Two contiguous supratentorial lesions and two contiguous infratentorial lesions are observed. The patient showed symptomatic progression just after one course of high-dose MTX chemotherapy

The clinical target volume (CTV) includes the entire brain parenchyma, several centimeters of the contiguous cervical cord, and the posterior semispherical surface of the eyeballs.

The planning target volume (PTV) is determined by adding a margin ranging from a few millimeters to 1 cm to the CTV.

1.7.2.2 Radiation Field

Two laterally opposite fields are used. The anterior border of the field should include the posterior half of the bilateral eyeballs. The inferior border of the field is usually extended to include the second cervical vertebra. The posterior and superior borders

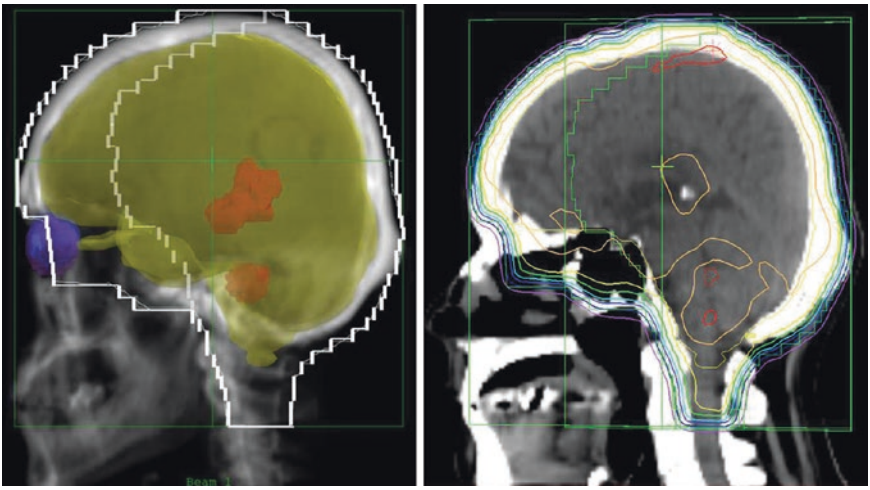

Fig. 1.2 Whole-brain radiotherapy. Two slightly angled laterally opposed 6 MV X-ray beams were used in the field-in-field technique. The GTV, a Gd-enhanced area (*red*), the brain parenchyma (*yellow*), eyeball (*violet*), and lens (*blue*) are superimposed on the beam's-eye-view (*left panel*). The *right panel* shows the dose distribution in a sagittal plane. Isodose (90%, 95%, 100%, and 105%) lines are drawn in *green*, *yellow*, *orange*, and *red*, respectively. In the course of 3 weeks, a total dose of 30 Gy was delivered in 15 fractions to the whole brain

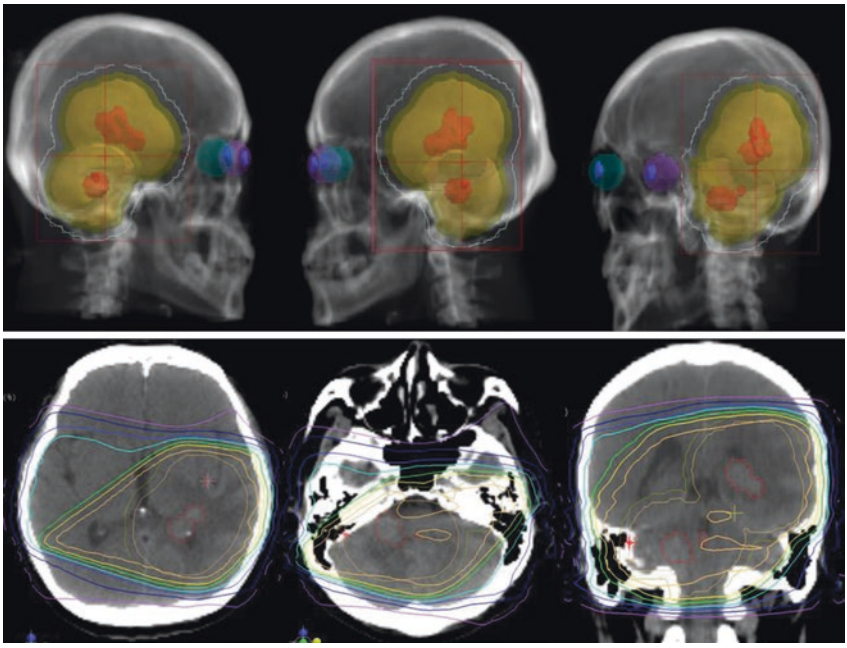

Fig. 1.3 Boost radiotherapy with 3D-CRT using three portal 15 MV X-ray beams. The GTV is displayed as a Gd-enhanced area (*red*). The CTV (*orange*) and PTV (*pale yellow*) are superimposed on the beam's-eye-views (*upper panels*). The *lower panels* show the distribution in the representative planes. A total dose of 10 Gy was delivered in five fractions over the course of 1 week

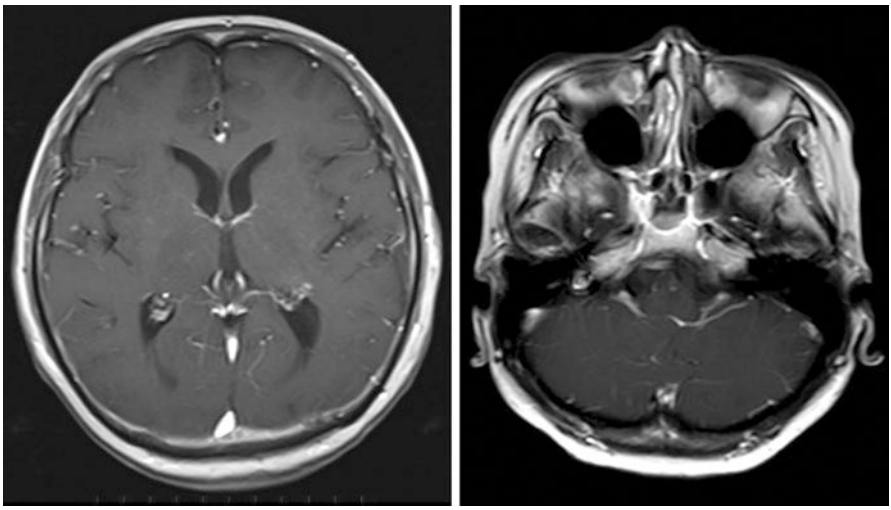

Fig. 1.4 Gd-enhanced MRI scans obtained on the day after the completion of radiotherapy

are set to cover the PTV with an adequate margin, usually a little beyond the outer surface of the skull.

Beam shaping with a multileaf collimator (MLC) is useful for achieving high conformity. The eye lenses are spared by placing the edge of the leaf a few millimeters behind the lenses. For the manual adjustment of the MLC, the leaf position must be selected carefully to minimize possible under-dosing at the tip of the temporal and frontal lobes.

To avoid divergence toward the contralateral eye lens, the beams are often angled so that the anterior beam edges are parallel. As beam angling may deliver an overdose exceeding 110% of the prescribed dose to the anterosuperior portion of the brain, the use of wedges combined with collimator rotation or the field-in-field technique may help to improve homogeneity of the radiation dose.

1.7.2.3 Beam Energy

High-energy photon beams, 6–10 MV X-rays, are used for WBRT.

1.7.2.4 Dose and Fractionation

The recommended WBRT dose for consolidation RT in patients with CR after MTX-based chemotherapy is 23.4–30 Gy; 24 Gy is the standard dose according to the most recent guidelines [4, 9, 10, 16].

Patients with non-CR after chemotherapy or with recurrence after chemotherapy alone are treated with a WBRT dose of 36–45 Gy [4]. The dose must consider the intensity of prior chemotherapy, the patient age, the time lapse since chemotherapy, and the aggressiveness of the tumor estimated from the clinical course.

In patients receiving RT alone as the primary treatment with curative intent, the delivery of at least 40 Gy of WBRT is necessary. Based on the tumor response, up

to 50 Gy of WBRT or 10 Gy of additional boost irradiation to the tumor site may be appropriate. For palliative RT 30 Gy of WBRT is usually effective.

The typical fraction size is 1.5–2 Gy for curative WBRT; 3 Gy or more per fraction are used for palliative or emergency WBRT. Considering the high alpha-beta ratio of lymphoma and the low alpha-beta ratio of the brain, PCNSL is theoretically a good candidate for a hyperfractionated radiation delivery schedule. The Radiation Therapy Oncology Group (RTOG) 9310 study used hyperfractionated WBRT of 1.2 Gy per fraction twice a day up to 36 Gy for consolidation RT [28]. This regimen, however, delayed but did not eliminate severe neurotoxicity.

1.7.3 Partial Brain RT (Fig. 1.3)

To manage PCNSL, partial brain RT is used in limited situations, such as boost irradiation after WBRT to non-CR or recurrent lesions, and as palliative RT for recurrence after initial treatment with WBRT. For the initial treatment of PCNSL, either for consolidation or salvage, partial brain RT is thought to be insufficient despite its potential advantage of reduced neurotoxicity [29]. Iwabuchi et al. [26] reported the results of the initial use of partial brain RT in patients with solitary PCNSL. They suggested that survival was acceptable when compared with patients who had undergone WBRT.

In clinical practice, a boost to the residual tumor is often delivered to improve local control, particularly in cases with incomplete chemotherapy, in patients treated with a reduced WBRT dose, and/or in cases with a solitary and large residual tumor. However, the benefits of adding a boost to WBRT remain controversial.

1.7.3.1 Target Volumes

GTV: For boost irradiation to the residual tumor, the GTV is the contrast-enhanced tumor(s) identified on MRI scans. For contouring the GTV, any MRI scans performed before or after chemotherapy, or after WBRT can be used.

CTV: The CTV adds an adequate margin to the GTV. The GTV-CTV margin can vary from a few millimeters to 3 cm; it is determined by the purpose of partial brain RT and institutional policies. Including the high-intensity areas on FLAIR images in the CTV is an acceptable option.

PTV: To obtain the PTV, a margin of a few millimeters is added to the CTV.

1.7.3.2 RT Technique

For 3D conformal RT (3D-CRT), multiple 6–15 MV and MLC-shaped X-ray beams from several directions are usually used.

1.7.3.3 Dose

The optimal dose for partial brain RT has not been established. PCNSL patients with non-CR or recurrence after chemotherapy alone are often treated with WBRT without boosting. In such cases, a WBRT dose of 36–45 Gy is recommended [4]. Shibamoto et al. [30] who performed a large-scale retrospective study suggested

that the optimal total dose is 40–49.9 Gy. Consequently, for the WBRT-plus-boost approach, the WBRT dose that does not compromise intracranial disease control should be 24–30 Gy, and the additional boost dose that does not compromise local control should be 10–20 Gy. One of the most practical schedules may be WBRT of 30 Gy in 15–20 fractions followed by partial brain RT with a boost of 10–20 Gy delivered in 5–10 fractions.

1.8 Outcomes

1.8.1 Survival

The 5-year survival rate and the median survival time of PCNSL patients treated with HD MTX and WBRT have been reported to be 30–50% and 36–63 months, respectively [28, 31–33].

1.8.2 Prognostic Factors

The patient age and Karnofsky performance status (KPS) are strong prognostic factors in PCNSL. Recursive partitioning analysis (RPA) incorporating only these two factors showed that the median survival time of class I (age = <50), class II (age > 50, KPS ≥ 70), and class III (Age > 50, KPS < 70) was 8.5-, 3.2-, and 1.1 years, respectively [34]. Other reported prognostic indicators are CR after chemotherapy [33], elevated lactate dehydrogenase- and cerebrospinal fluid protein levels, and tumors in deep regions of the brain [20, 30].

1.9 Toxicity

1.9.1 Acute Toxicity

Alopecia is a common finding in patients with acute WBRT toxicity. Nausea, vomiting, and anorexia tend to be limited to grades 1 and 2. Leukocytopenia may occur, but seldom forces treatment interruption.

1.9.2 Late Toxicity

As the survival of PCNSL patients improved, the incidence of late neurological toxicities, including neurocognitive dysfunction accompanied by leukoencephalopathy or brain atrophy, has become a major concern in patients treated by HD MTX and WBRT. Approaches to reduce late neurological toxicities have mainly focused on minimizing the adverse effects of RT by reducing the WBRT dose with or without boosting, by delivering smaller doses per fraction, by administering

partial brain RT instead of WBRT, and by omitting RT [9, 10, 26, 28]. Additional studies are needed to identify the optimal RT setting to preserve neurocognitive function without compromising intracranial control.

Ocular RT for primary intraocular lymphoma or PNSCL with intraocular involvement consisting of irradiation to the eye lens above 10 Gy often elicits cataracts. Xerophthalmia and dry eye syndrome may develop after the delivery of RT doses exceeding 30 Gy to the conjunctiva or lacrimal glands. Retinopathy and ophthalmic neuropathy are rarely seen at RT doses below 45 Gy [35].

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Ocular Adnexal Lymphoma

2

Yasuo Ejima

Abstract

Ocular adnexal lymphomas arise from the orbital structure, including the conjunctiva, eyelid, lacrimal gland, and retrobulbar region. The majority of ocular adnexal lymphomas are extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT lymphoma), which usually tend to remain localized for a long time and have an indolent natural history. Among various treatment options for localized ocular adnexal MALT lymphoma, such as chemotherapy, rituximab, antibiotic therapy, surgery, and watchful waiting, radiation therapy alone is the most promising modality as the definitive treatment. Moderate doses (24–30 Gy) of radiation therapy are safe and can achieve local control in greater than 95% of the patients. To avoid severe and incurable adverse events on the eyes, doses higher than 30 Gy should not be delivered for MALT lymphoma. Localized diffuse large B-cell lymphomas (DLBCL), which comprise a minority of primary ocular adnexal lymphomas, are commonly treated with a combined modality therapy consisting of chemotherapy with rituximab followed by radiation therapy. For DLBCL, a dose of 30 Gy is recommended for patients who had a complete response to immunochemotherapy. In the case of electron beam therapy for conjunctival lymphoma, lens shielding can effectively reduce the risk of cataract formation.

Keywords

Orbital lymphoma • Ocular adnexal lymphoma • Marginal zone lymphoma • MALT lymphoma • Diffuse large B-cell lymphoma

Y. Ejima
Division of Radiation Oncology, Kobe University Hospital,
7-5-2, Kusunoki-cho, Chuo-ku, Kobe, Hyogo, Japan
e-mail: ejimay@gmail.com

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2.1 Introduction

Approximately 8% of extranodal lymphomas are ocular adnexal lymphomas [1], and lymphoma is the most common malignant neoplasm of the retrobulbar region in adults [2]. The majority of ocular adnexal lymphomas are extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT lymphoma) [3, 4], which are characterized by an indolent natural history and good response to radiation therapy. In Japan and Korea, the proportion of MALT lymphoma among primary ocular adnexal lymphoma is approximately 75–90%, which is higher than the 35–80% rate in Western countries [2–4]. In the treatment of ocular adnexal lymphomas, it is important to protect against long-term toxicity; this is because the eye is a very sensitive organ, and the majority of patients with MALT lymphoma, which is usually curable, will survive for a long time. The appropriate radiation therapy should be the most effective and safe treatment modality for ocular adnexal MALT lymphomas.

Diffuse large B-cell lymphoma (DLBCL) comprises 2–7% of ocular adnexal lymphomas in Japan and Korea and 5–15% in Western countries [2–4]. Almost half of patients with ocular adnexal DLBCL present at an advanced stage or as a relapse of prior systemic lymphoma [5]. Ocular adnexal DLBCL is commonly treated with combined modality therapy.

Ocular adnexal lymphomas arise from the orbital structure, including the conjunctiva, eyelid, lacrimal gland, and retrobulbar region. Intraocular lymphoma, which is recognized as a manifestation of central nervous system lymphoma, is definitively distinguishable from ocular adnexal lymphoma.

2.2 Pathology, Immunophenotype, and Cytogenetic Abnormalities

2.2.1 MALT Lymphoma

MALT lymphomas are composed of morphologically heterogeneous cells, including cells most commonly resembling centrocytes, monocytoid cells, and small lymphocytes (Fig. 2.1). Centrocyte-like cells have small, cleaved nuclei resembling those of centrocytes, but with more abundant cytoplasm. Monocytoid cells have abundant pale-staining cytoplasm. The tumor cells infiltrate the marginal zones, extend into the interfollicular region, and sometimes specifically colonize the germinal centers of the reactive follicles [6]. The scarcity of lymphoepithelial lesions is the only feature that distinguishes ocular adnexal MALT lymphomas from those at other sites. Plasmacytic differentiation is frequently present, occurring in approximately 40% of cases of ocular adnexal MALT lymphoma [7]. In cases with marked plasmacytic differentiation, histopathological differential diagnosis between MALT lymphoma and plasmacytoid neoplasm may sometimes be difficult. In such cases, all clinical information should be comprehensively considered to decide the

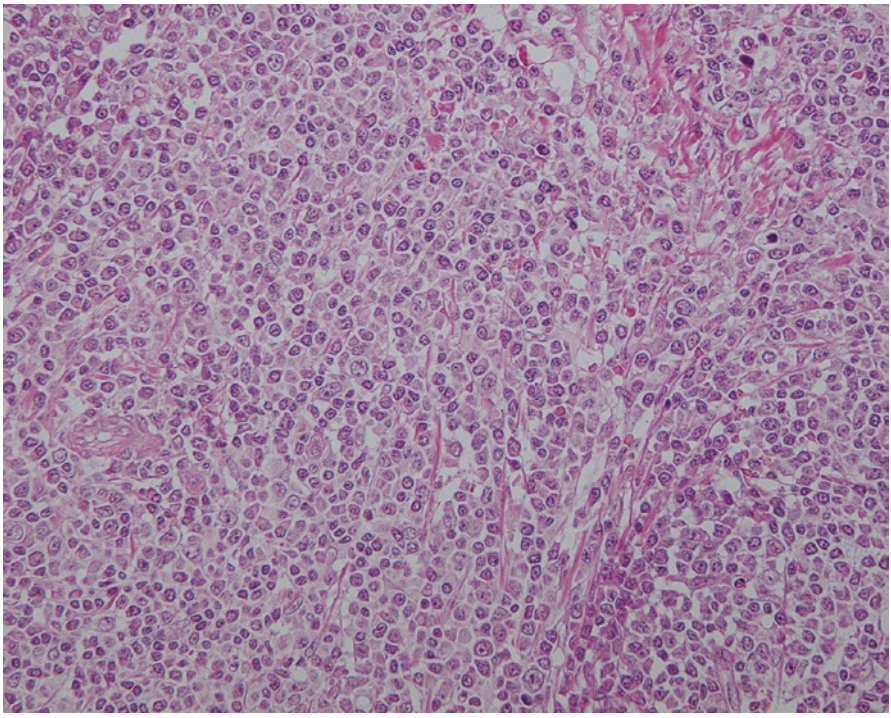

Fig. 2.1 Pathological presentation of a MALT lymphoma arising in the lacrimal gland. The tumor cells consisted of centrocyte-like cells with plasma cell differentiation and without blasts that infiltrated the connective tissue

treatment approach. Although MALT lymphomas are defined as being composed predominantly of small- or medium-sized cells, large cells resembling centroblasts or immunoblasts may be scattered. If solid or sheet-like proliferations of transformed large cells are present, the tumor should be diagnosed as DLBCL.

Tumor cells of MALT lymphoma are typically positive for surface immunoglobulin (sIg), CD20, and CD79a, and negative for CD5, CD10, and cyclin D1. The immunoglobulin light chain restriction is useful in the differential diagnosis with benign lymphoproliferative disease. Lack of CD5 is distinct from mantle cell lymphoma or small lymphocytic lymphoma, lack of cyclin D1 is distinct from mantle cell lymphoma, and lack of CD10 is distinct from follicular lymphoma [6]; thus, testing for the presence of these proteins is useful.

Although the most frequent chromosomal translocation in MALT lymphomas arising in the stomach is t(11;18)(q21;q21) involving the genes *API-2* and *MALT1*, it is rare in ocular adnexa. The most common chromosomal abnormalities in ocular adnexa are trisomies 3 and 18. The translocations t(14;18)(q32;q21), involving *IGH* and *MALT1*, and t(3;14)(p14;q32), involving *FOXP1* and *IGH*, are also common [6, 8].

2.3 Clinical Features

2.3.1 MALT Lymphoma

The majority of patients present with localized disease, with rare lymph node involvement in approximately 5% of patients and multiple extranodal site involvement in up to 25% [4, 9]. Bone marrow involvement is rarely observed, occurring in less than 10% of patients [3, 4, 10]. Bilateral involvement may simultaneously or metachronously occur in 5–20% of patients [4, 10, 11]. Ocular adnexal MALT lymphoma may frequently involve the conjunctiva or retrobulbar region, rather less commonly the lacrimal gland or eyelid, and rarely infiltrates the orbital osseous wall or extraorbital structures.

A common presentation of conjunctival lesions is called the salmon pink patch, and they usually present without pain or irritation (Fig. 2.2). Common symptoms of retrobulbar and lacrimal lesions include proptosis, ptosis, eyelid swelling, or a palpable rubbery firm mass. Diplopia occasionally occurs, but loss of visual acuity is rare. Few patients have B symptoms, a performance status greater than 1, or elevation of serum lactate dehydrogenase. Progression with transformation to DLBCL occurs in approximately 3% of patients [10, 12–15].

2.3.2 DLBCL

Ocular adnexal DLBCL most frequently involves the retrobulbar region and is rarely confined to the conjunctiva. Extraorbital invasion is observed in more than 10% of patients [5]. Tumor or swelling with globe displacement is the most

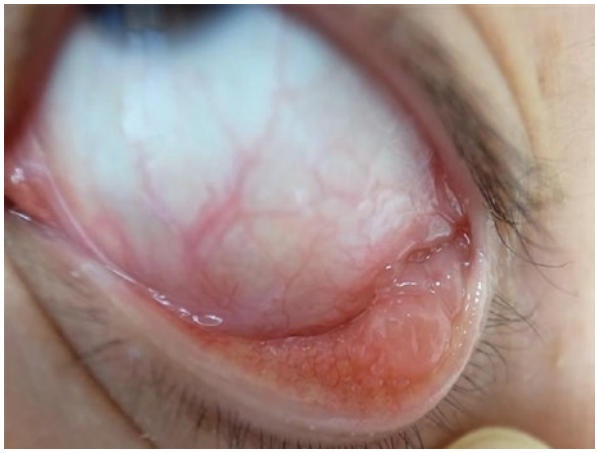

Fig. 2.2 Clinical presentation of conjunctival MALT lymphoma A case of a conjunctival MALT lymphoma appearing as a salmon pink patch with a smooth surface and a follicular form

common symptom and appears more prominent with rapid growth than that in MALT lymphomas (Fig. 2.3). In contrast to indolent lymphomas, decreased visual acuity due to tumor invasion to the optic nerve often occurs. In addition, the direct infiltration of intracranial structures and meningeal dissemination is occasionally observed in aggressive lymphomas [16, 17]. Approximately one-third of the patients present with advanced disease, and 20–40% of patients present with an ocular adnexal relapse of prior systemic lymphoma [5, 11]. Serum lactate dehydrogenase level is frequently elevated [5].

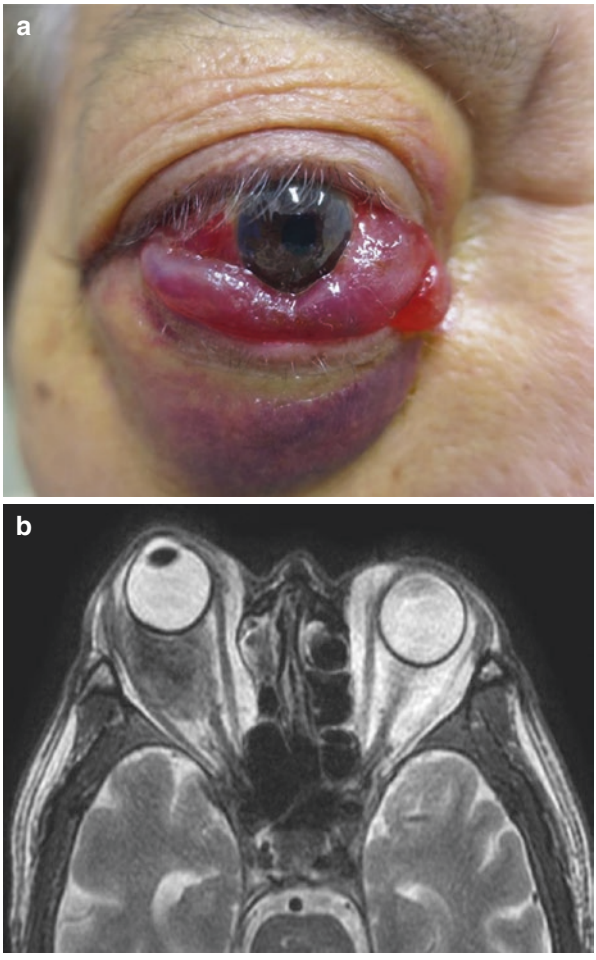

Fig. 2.3 Clinical and radiographic presentation of retrobulbar DLBCL. (**a**) The clinical appearance showing prominent exophthalmos and conjunctival edema with visual acuity loss. T2-weighted axial (**b**) and coronal (**c**) magnetic resonance imaging scans shows that the orbital mass causes proptosis

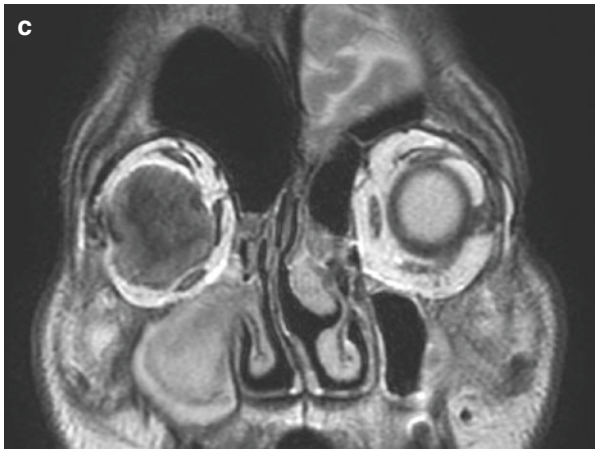

Fig. 2.3 (continued)

2.4 Pretreatment Evaluation and Staging

Recommended staging procedures include a history; physical and ophthalmologic examination; complete blood counts; serum lactate dehydrogenase; and computed tomography (CT) scan of the orbit, thorax, abdomen, and pelvis. Magnetic resonance imaging (MRI) is the gold standard of imaging for evaluation of ocular adnexal lymphomas. Moreover, although the value of bone marrow biopsy and positron emission tomography (PET) is still controversial in the initial evaluation for MALT lymphomas, PET-CT is the standard procedure for DLBCL [18, 19]. Brain MRI and cerebrospinal fluid evaluation should be considered in patients with DLBCL to estimate dissemination in the central nervous system.

2.5 Prognostic Factors

Data regarding prognostic factors are conflicting because they are derived from retrospective studies with a small number of patients. Distant relapse might be lower in patients with localized conjunctival disease than in those with lacrimal gland and retrobulbar disease [10, 14]. Although advanced disease stage, presence of B-symptoms, elevated serum lactate dehydrogenase levels, and higher International Prognostic Index score might also be associated with distant relapse [10, 12], these are minimal in MALT lymphomas. Other potential prognostic factors such as bilateral lesion [14, 20], CD5 expression, and plasmacytic differentiation have little impact on local control, distant relapse, or survival.

2.6 Treatment Strategy

2.6.1 MALT Lymphoma

Radiation therapy is the most extensively studied treatment in patients with limited stage ocular adnexal MALT lymphoma. Moderate doses of local radiation therapy, which achieves excellent disease control with minimal toxicity, are preferable as the first-line single-modality treatment for limited disease.

For asymptomatic disease or disseminated disease, careful observation is optional as the initial approach [13]. When treatment is required for patients with disseminated disease, rituximab plus chemotherapy may be indicated. Rituximab plus single agent chemotherapy, such as chlorambucil, cyclophosphamide, fludarabine, and cladribine, is frequently used. Anthracycline-containing chemotherapy regimens should be reserved for cases with transformation to DLBCL or those with rapid progression.

Several investigations have suggested that *Chlamydia psittaci* infection is associated with the development of ocular adnexal MALT lymphoma. However, there are marked geographic variations in the positive rates for *C. psittaci*, which are higher in Italy, Korea, the eastern USA, and Germany (30–80%), and virtually absent in Japan, Miami and New York in the USA, and France (0–6%) [21]. The efficacy of eradication therapy with doxycycline has been tested in those limited regions, but has not been universally effective.

2.6.2 Diffuse Large B-Cell Lymphoma

DLBCL of ocular adnexa is treated the same as for management of nodal DLBCL. Combined modality therapy is frequently used; this consists of rituximab-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP-like chemotherapy followed by external beam radiation therapy [5]. Because ocular adnexal DLBCL tends to grow rapidly and often causes an irreversible visual acuity loss, an immediate initiation of treatment is needed. In case of patients with involvement of the skull base or optic nerve, central nervous system prophylaxis should be considered [16, 17].

2.7 Radiation Therapy

2.7.1 Clinical Target Volume

2.7.1.1 MALT Lymphoma and Other Indolent Lymphomas

For orbital or lacrimal gland lesions, the clinical target volume (CTV) should include the entire orbit, outlined by the inside of the orbital bony borders (Fig. 2.4a, b). In addition, care should be taken to ensure to encompass the extended lesions to

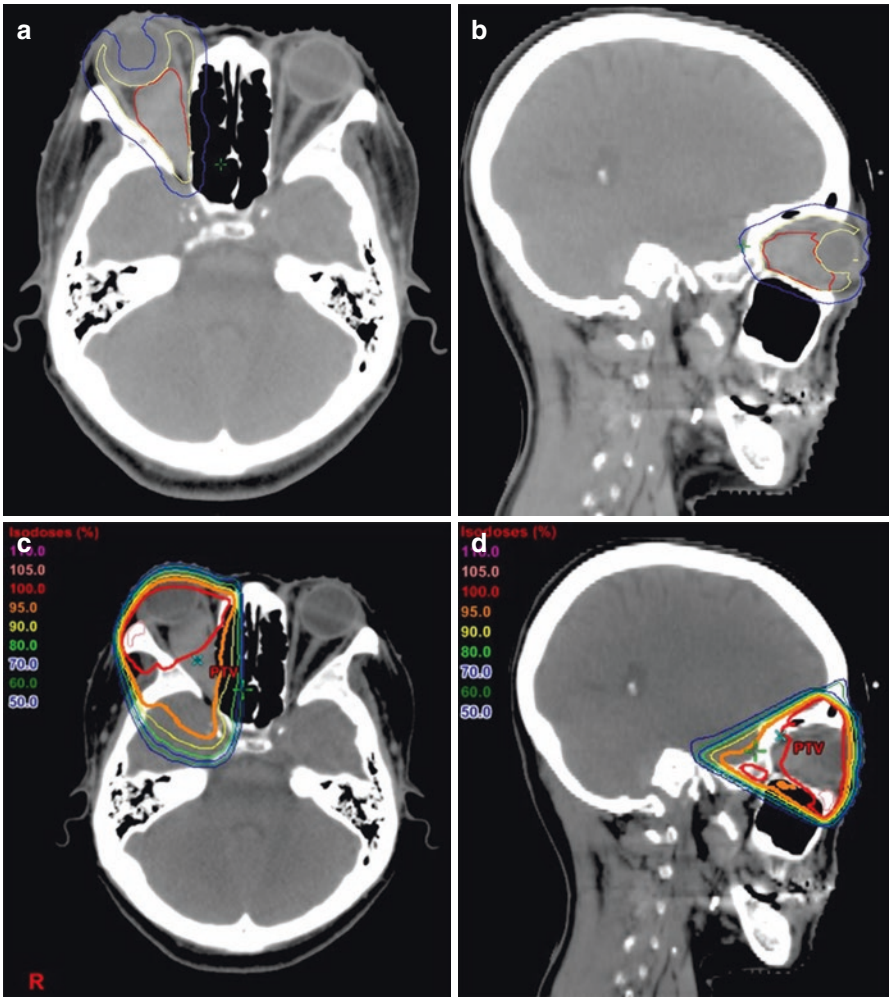

Fig. 2.4 Contouring (**a**, **b**) of the gross tumor volume (*red line*), clinical target volume (*yellow line*), and planning target volume (*blue line*) and dose distribution (**c**, **d**) in radiation therapy using a superior-inferior wedge pair technique for retrobulbar MALT lymphoma

the eyelids or conjunctiva, which are often invaded simultaneously. Partial orbital irradiation is not recommended as a standard method because it is associated with risk of marginal recurrences [20, 22, 23]. Intraocular invasion or extraorbital (bony or adjacent structure) extension is rare in MALT lymphoma.

For conjunctival lesions, the CTV should include the entire conjunctiva, which is composed of the palpebral conjunctiva (covers the posterior surface of the eyelids), bulbar conjunctiva (coats the anterior portion of the eyeball), and fornix (the transition portion). It need not include the entire orbit, but care should be taken if the tumor is limited to the conjunctiva.

2.7.1.2 DLBCL and Other Aggressive Lymphomas

The CTV is defined to the entire orbit, including the osseous wall in contact with the tumor and initial (pre-chemotherapy) tumor extension. In case of partial response (PR) after chemotherapy, the CTV for the boost dose should be confined to the residual tumor. When the tumor is confined to the lacrimal gland, the CTV for consolidation after chemotherapy may be limited to the lacrimal gland [23].

2.7.2 Dose

2.7.2.1 MALT Lymphoma and Other Indolent Lymphomas

A dose of 30 Gy in 1.5–2 Gy fractions is commonly used and is effective and safe. A high local control rate for MALT lymphoma is provided with a dose of 24–25 Gy [14, 24]. Published guidelines from the International Lymphoma Radiation Oncology Group also recommend 24–25 Gy [23]. To avoid severe and incurable adverse events on the eyes, a dose higher than 30 Gy should not be delivered for MALT lymphoma. Low-dose radiation therapy with 2 Gy × 2 is also effective with high response rates and durable local control and is optional in cases of advanced stage or re-irradiation [25, 26].

2.7.2.2 DLBCL

The recommended dose for consolidation in complete response (CR) after chemotherapy is 30 Gy. For residual disease (PR after chemotherapy) or for use of radiation therapy alone, 30–36 Gy to the whole orbit and a boost dose up to 40–45 Gy for the residual tumor are recommended [23].

2.7.3 Radiation Therapy Techniques

For disease cases showing deep invasion, a single anterior field or a wedged pair technique is usually used. In cases with tumor invasion to the conjunctiva, using a bolus is recommended. A superior-inferior wedge pair technique is useful for sparing the contralateral orbit in cases of metachronous contralateral disease, which might require subsequent radiation therapy (Fig. 2.4c, d).

An electron beam is used for treating conjunctival lesions. To prevent cataracts, lens shielding is often used. A lead lens shield is placed directly on the cornea after topical anesthesia (Fig. 2.5). Placing a disposable contact lens between the shield and cornea helps to avoid scratching the corneal surface. However, care must be taken to not shield part of the conjunctiva, because inadequate lens shielding may cause local recurrence [20, 27]. Therefore, lens shielding is contraindicated in cases in which the conjunctival tumor is too close to the limbus. In cases using lens shielding, a bolus is not applicable because the patients have to look directly at the shield shadow to keep it over the pupil.

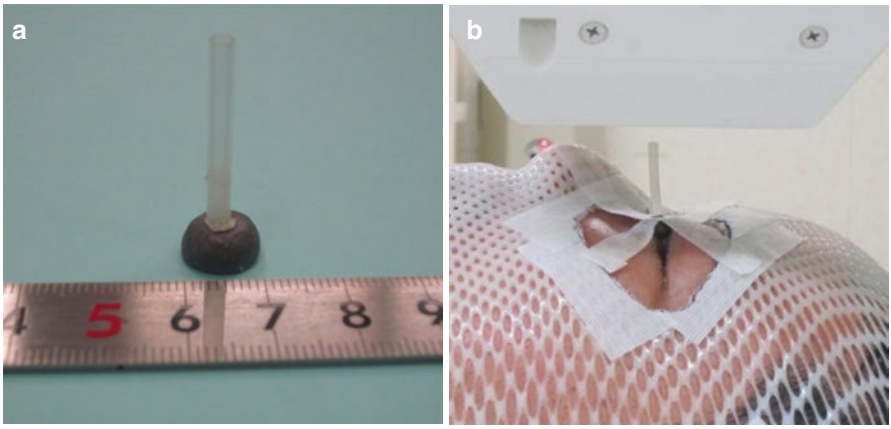

Fig. 2.5 (**a**) A lead lens shield for electron beam therapy. (**b**) The lead lens shield is placed directly on the cornea after topical anesthesia

2.8 Outcomes

2.8.1 MALT Lymphoma

2.8.1.1 Response

The response rate after radiation therapy for MALT lymphomas is almost 100%, and the CR rate is more than 80% [14, 20, 24, 27, 28]. MALT lymphomas sometime shrink gradually for months following radiation therapy, and can finally achieve local control [20, 27, 28]. For patients with advanced stage or for re-irradiation, low-dose radiation therapy with 2 Gy × 2 may achieve a high response rate and durable local control. Overall response rate is more than 90%; CR ranges from 60% to 85%, and PR from 10% to 30%. The median time to local progression reaches more than 2 years [25, 26].

2.8.1.2 Survival and Disease Progression

The 5-year overall survival, relapse-free survival, and local control rates after local radiation therapy are approximately 90% or higher, 70%, and 100%, respectively [10, 12, 14, 15, 24, 28, 29]. Most cases of local relapse may be caused by inadequate targeting or shielding [20, 22, 27]. Contralateral relapses may occur in approximately 5% of patients, and relapses in distant extranodal sites may occur in 5–15%. Lymphoma-related mortality is rare in localized MALT lymphoma after radiation therapy (Table 2.1). A large cohort study suggested that the use of radiation therapy might be associated with improved survival in ocular MALT lymphoma [30].

The combination of rituximab plus chlorambucil achieved a superior CR rate and better event-free survival compared with ether rituximab or chlorambucil as a single agent in a phase III study. However, there was no significant difference in overall survival [31]. Generally, there is no significant survival difference between various treatment modalities, including radiation therapy, surgery, chemotherapy, and antibiotic therapy with observation, in patients with MALT lymphomas [32].

Table 2.1 Outcomes of radiation therapy for ocular adnexal MALT lymphomas

Author	Year	*N*	Stage	Median dose	CR rate (%) (time of evaluation)	LC (%)	RFS (%)	OS (%)	CSS (%)	LRM (*N*)	Local relapse (*N*)	Contralateral relapse (*N*)	Distant relapse (*N*)	Histological transformation (*N*)
Le [29]	2002	31	IE	34	–	100 [10 y]	71	73	–	1	0	1	4	–
Uno [20]	2003	50	IE	36	52 (1 mo)	–	–	91 [5 y]	–	1	3	0	3	–
Ejima [28]	2006	42	IE	30.6	84 (12 mo)	100 [5 y]	77	97	100	0	0	4	4	–
Suh [27]	2006	48	IE-IV	30.6	88 (12 mo)	–	93 [10 y]	87	98	1	3	0	1	–
Goda [14]	2011	89	IE	25	99 (1 mo)	97 [7 y]	64	91	96	1	2	5	15	4
Tran [24]	2013	24	IE-IV	24	100	92 [5 y]	81	100	100	0	1	1	1	–
Harada [33]	2013	86	IE	30	–	98.7 [10 y]	–	93.5	100	0	1	6	3	–
Woolf [15]	2015	81	IE	30	–	100 [5 y]	95	100	100	0	0	1	3	1

N number, *CR* complete response, *LC* local control, *RFS* relapse-free survival, *OS* overall survival, *CSS* cause-specific survival, *LRM* lymphoma-related mortality, *mo* month, *y* year

2.8.2 Diffuse Large B-Cell Lymphoma

The largest report of ocular adnexal DLBCL was a retrospective international collaborative study that included 100 patients [5]. In this study, external beam radiation therapy was used in 31% of patients, and R-CHOP or R-CHOP-like chemotherapy with or without radiation therapy was used in 21% of patients. Of 57 patients with primary ocular adnexal DLBCL, 53 patients had Ann Arbor stage IE disease, and their median disease specific survival was 8.3 years.

2.9 Toxicity

The common acute reactions of radiation therapy are mild and transient dermatitis, focal hair loss, conjunctivitis, periorbital edema, and/or keratitis. The typical late reactions are cataract and dry eye. Eyelid ptosis occurs in some cases with tumor invasion of the eyelid. Lens shielding can effectively reduce the risk of cataract formation [14, 15, 28, 33]. The 5-year incidence rates of grade 3 cataract with and without lens shielding are approximately 10–15% and more than 30%, respectively [14, 28]. Although some patients may develop cataracts, visual acuity of those patients will be well preserved by cataract extraction with intraocular lens implantation [28, 34].

The risk of developing retinopathy depends on total radiation dose and fraction size, and vascular risk factors such as diabetes mellitus may also increase the risk. A total dose of less than 30 Gy and a daily dose of 1.8 Gy may reduce the risk of retinopathy to less than 5% [35]. Thus, the standard dose of 24–30 Gy in 1.5–2.0 Gy fractions radiation therapy is usually well tolerated, and no serious toxicity is observed.

2.10 Summary

MALT lymphomas, which comprise the majority of ocular adnexal lymphomas, are curable. For localized MALT lymphomas, moderate-dose radiation therapy is the most promising and safe treatment modality. However, inadequate radiation therapy may cause late ocular toxicity. Moreover, because of the indolent nature of MALT lymphomas, care should also be taken to avoid overtreatment. For DLBCL, which shows rapid and aggressive progression, a prompt diagnosis and initiation of treatment is needed. Especially, in cases with decreased visual acuity, immediate radiation therapy should be considered even if the diagnosis has not been confirmed.

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Extranodal NK/T Cell Lymphoma, Nasal Type

3

Masahiko Oguchi

Abstract

The extended involved site radiation therapy (ISRT) is incorporated into the treatment of patients with stage I and contiguous stage II extranodal natural killer/T cell lymphoma. It is suggested combined modality therapy with radiation and chemotherapy. The extended ISRT should be given concurrently with chemotherapy, but if the patient's performance status and comorbidities do not allow concurrent therapy, radiation should be administered prior to chemotherapy.

Keywords

Nasal cavity • Extranodal natural killer/T cell lymphoma • Nasal type • Extended involved site radiation therapy (extended ISRT) • Epstein-Barr virus (EBV)

3.1 Introduction

Extranodal natural killer/T cell lymphoma, nasal type (nasal ENKL) is a rare subtype of lymphoproliferative disorders and more common in East Asia and South America than Western countries. It accounts for 5–10% of all non-Hodgkin lymphoma [1]. The median age at presentation is around 50 years old. A male predominance with 2:1 male-to-female ratio is reported. It used to be known as "lethal midline granuloma."

The standard treatment has not been established yet, although new regimen therapy has been investigated intensively with East Asian oncologists.

M. Oguchi, M.D., Ph.D.
Radiation Oncology Department, The Cancer Institute Hospital Japanese Foundation for Cancer Research, 3-8-31, Ariake, Kouto-ku, Tokyo, Japan
e-mail: oguchi@jfcr.or.jp

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3.2 Pathology

The nasal ENKL is characterized with positivity for Epstein-Barr virus (EBV) and variety of morphologic spectrum, frequent necrosis, and angio-invasion. According to the gene rearrangement studies, most cases are originated in a natural killer cell, and a small minority is derived from cytotoxic T cells. The monoclonal episomal EBV DNA, detectable EBV encoded small nuclear RNAs (EBERs), and EBV latent membrane protein-1 (LMP-1) by immunohistochemistry have been described [2].

3.3 Pretreatment Evaluation and Prognostic factors

The standard approaches to the diagnostic workup and staging of lymphoma, including bone marrow biopsy and FDG-positron emission tomography (PET)/CT, are recommended. Most of the cases are FDG-avid [3]. The magnetic resonance imaging (MRI) provides more detail on radiological information to identify real gross tumor volume (GTV) from secondary inflammatory changes than computed tomography (CT). Also physical examination and flexible fiber-optic endoscope should be included to the diagnostic workup to assess not only nasal cavity but also oral cavity and all pharynxes which have high incidence of EBV infection. The primary tumor invasion (PTI) is reported as an important prognostic factor; however, the usefulness of PTI depends on results and quality of imaging studies such as CT, MRI, and PET. The strict evaluation of subclinical tumor extension of ENKL is difficult.

The disease-specific prognostic models have been reported to predict survival of ENKL such as international prognostic index (IPI), NK/T-cell lymphoma prognostic index (NK-PI), and prognostic model for NK/T-cell lymphoma (PINK) [4–8]. The PINK is validated in the all staged ENKL population, however not in those with localized ENKL, in Japanese retrospective study [9]. In this analysis, the elevated soluble interleukin-2 receptor is reported to be an independent predictive factor for worse overall survival (OS) and progression-free survival (PFS) [9].

3.4 Treatment Strategy

The standard treatment has not been confirmed yet for early stage ENKT with phase III studies, although the new generation therapies for ENKL have been investigated intensively. Since early 2000s, clinical trials have been conducted to evaluate efficacy and toxicity of concurrent chemoradiotherapy for localized ENKL. In Japan, concurrent chemoradiotherapy with radiotherapy (RT) and dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC) chemotherapy (RT-DeVIC) was the most common first-line therapy in patients with localized ENKL [9–11]. In Korea, phase II trials of concurrent RT and weekly cisplatin followed by etoposide, ifosfamide, cisplatin, and dexamethasone (VIPD) or etoposide, ifosfamide, dexamethasone, and L-asparaginase (VIDL) chemotherapy are reported [12, 13]. In China, based on their

prognostic models using nomogram, RT alone for patients with localized low risk ENKL provided excellent local control [7, 8, 14].

In 2013, based on the mature results of JCOG0211 study, Japanese Society of Hematology published the guidelines in Japan [11]. RT-DeVIC, only 9 weeks to complete this regimen, can be applicable for any patients classified into all risk groups.

For patients with advanced ENKL, L-asparaginase-containing chemotherapy including steroid, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) is the most selected treatment. The RT has limited role on the management of advanced ENKL [15].

3.5 Chemotherapy

The results of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like chemotherapy for localized nasal NKTCL are unsatisfactory due to presence of *p*-glycoprotein which is related with multidrug resistance. Etoposide/Platinum/L-asparaginase containing chemotherapy such as DeVIC, VIPD, VIDL, and SMILE have been reported in the phase II trial setting resulting improving survivals (Tables 3.1 and 3.2) [9, 15].

Table 3.1 DeVIC chemotherapy regimen (two-thirds DeVIC)

Agent	Dose/day/route	Days
Dexamethasone	40 mg/d intravenously	1 2 3
Etoposide	67 mg/m^2 intravenously over 2 h	1 2 3
Ifosfamide	1000 mg/m^2 intravenously over 3 h	1 2 3
Carboplatin	200 mg/m^2 intravenously over 30 min	1

Chemotherapy was planned to repeat every 3 weeks. Three courses of chemotherapy were planned

Table 3.2 SMILE chemotherapy regimen

Agent	Dose/day/route	Days
Methotrexate	2 g/m^2/d intravenously over 6 h	1
Leucovorin	15 mg × 4 intravenously	2 3 4
Ifosfamide	1500 mg/m^2 intravenously over 3 h	2 3 4
Mesna	300 mg/m^2 × 3 intravenously	2 3 4
Dexamethasone	40 mg/d intravenously	2 3 4
Etoposide	100 mg/m^2 intravenously	2 3 4
L-Asparaginase	6000 U/m^2 intravenously	8 10 12 14 16 18 20

SMILE steroid (dexamethasone), methotrexate, ifosfamide, L-asparaginase, and etoposide
Granulocyte-colony stimulating factor SC or IV Day 6 to WBC >5000/μL
Cycles were repeated every 28 days. Two courses were planned as the protocol treatment

3.6 Radiation Therapy (Indications)

Patients with stage I or contiguous stage II nasal ENKL are treated with radiation therapy (RT) with or without consolidation chemotherapy [16]. Upfront or early administration of RT is recommended prior to chemotherapy or concurrently with chemotherapy. If the patient's performance status and comorbidities do not allow combined modality therapy, RT should be administered immediately.

3.7 Radiation Therapy (Treatment Procedures)

3.7.1 RT Planning

The RT planning CT should be obtained with intravenous contrast media. The image fusion with FDG-PET/CT and MRI is strongly recommended, which provide the precise information of tumor invasiveness. The FDG-PET/CT and MRI are useful to distinguish between gross tumor volume (GTV) and secondary inflammatory changes such as edema and fluid collection.

3.7.2 Extended Involved Site Radiation Therapy and Target volumes

The involved site radiation therapy (ISRT) should encompass the GTV with a sufficient margin and also entire nasal cavity which has been estimated as EBV infection site [16]. It is termed the extended ISRT, although small differences of target volume delineation are recognized among institutions and or radiation oncologists.

In the JCOG0211 study, the GTV had been defined as soft tissue density mass on CT and MRI images [10, 17, 18]. Recently it is suggested that the GTV should be delineated based on the information of FDG PET/CT. In the three-dimensional conformal RT protocol of JCOG0211, the clinical target volume (CTV) had a 2 cm margin to and also encompassing nasal cavities and nasopharynx, to reduce geographic miss. The entire nasal cavity and nasopharynx should be included in the CTV (Fig. 3.1). And also the endoscopic lesion and skin involvement, which could not be identified on CT images, were included in the CTV. The CTV could be shaved according to the organs at risks surrounded with the anatomical barriers such as eye balls, chiasma, and brain/cord.

3.7.3 Radiation Delivery

The three-dimensional conformal RT (3DCRT) (Fig. 3.2) had been widely used for many years, resulting in some cases with late toxicity. The intensity modulated

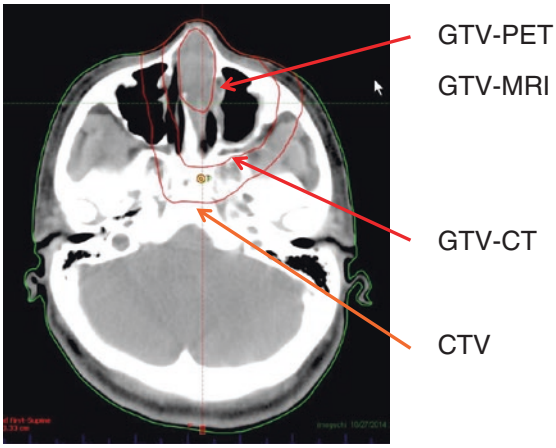

Fig 3.1 Delineation of target volumes. The example of delineation of gross tumor volume and clinical/planning target volumes for stage I extranodal NK/T cell lymphoma

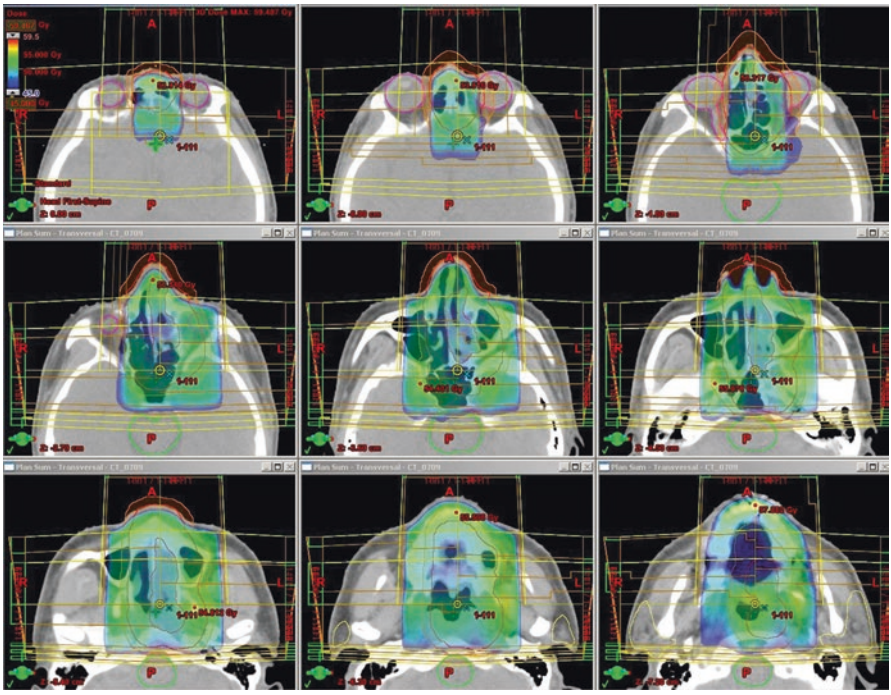

Fig 3.2 3-D conformal radiation therapy. The example of three-dimensional conformal radiation therapy for stage I extranodal NK/T cell lymphoma

radiation therapy (IMRT) or volumetric modulated ark therapy (VMAT) (Fig. 3.3) is the standard approach at present time, which provide better dose coverage to the target volume and lower dose to organs at risks than 3DCRT [7, 19].

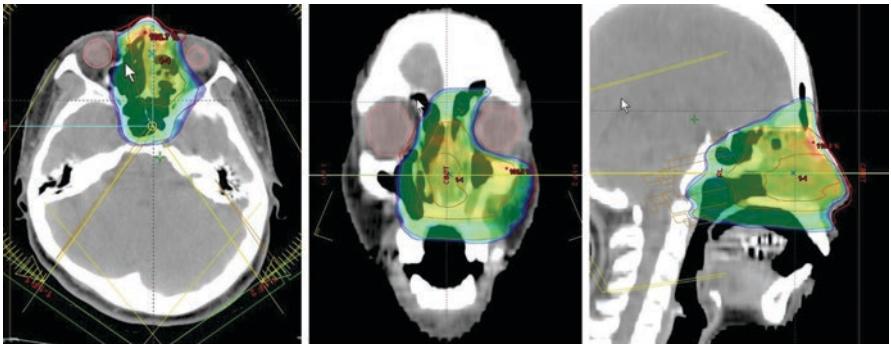

Fig 3.3 Intensity modulated radiation therapy, volumetric modulated arch therapy. The example of volumetric modulated arch therapy for stage I extranodal NK/T cell lymphoma

3.7.4 Dose and Fractionation

Data regarding an appropriate radiation dose are limited; however, the Japanese retrospective analyses have reported 50 Gy or more [9–11, 17, 18]. A choice of radiation dose must balance efficacy with toxicity. The 50–54 Gy dose of IMRT will be tested prospectively.

3.8 Outcomes

3.8.1 Survival

The 5-year OS and progression-free survival at 5 years of patients in the JCOG0211 who received RT-DeVIC were 73% and 67%, respectively (Fig. 3.4) [9, 10]. The retrospective study has validated the results of the JCOG0211 trial in terms of 5-year OS (72%), 5-year PFS (61%) and CR rate (82%) [11]. The Latent membrane protein 1 (LMP1)-positive patients showed a better overall survival (OS) than the LMP1-negative patients (Table 3.3).

3.8.2 Failure Patterns

Although the local control rates were reported high, we have some patients who developed local failure in the nasal cavity and adjacent organs such as nasopharynx, orbital wall, and sinus after 50 Gy dose of definitive RT. The CR rate of RT-DeVIC in clinical trial and practice was 75% and 82%, respectively. Some patients experienced early rapid systemic progression and hemophagocytic syndrome-associated ENKL were reported [20].

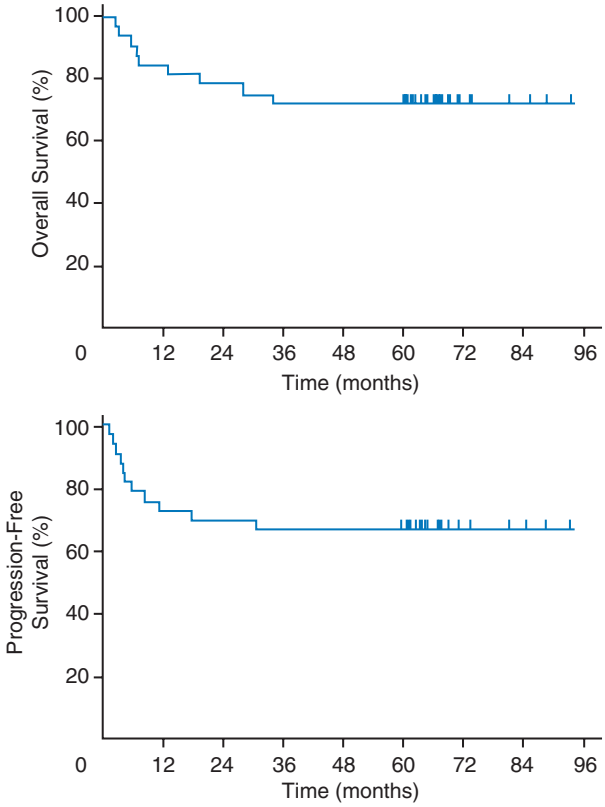

Fig 3.4 Survival curves of JCOG0211study [9, 10]. Overall survival and progression-free survival of 33 patients treated with radiotherapy and dexamethasone, etoposide, ifosfamide, and carboplatin. Overall survival and progression-free survival rates of 33 patients treated with RT-DeVIC: radiotherapy and dexamethasone, etoposide, ifosfamide, and carboplatin in the JCOG-0211 study

Table 3.3 Survivals of extranodal natural killer/T cell lymphoma, nasal type stage I/II

	Regimen	*n*	PFS (%)	Ref.
Japan (JCOG0211)	RT DeVIC	33	67 (5-year)	[9, 10]
(NKEA)	RT DeVIC	169	61 (5-year)	[11]
Korea	RT VIPD	30	85 (3-year)	[12]
	DI-CHOP RT		62 (3-year)	
	RT VIDL	30	73	[13]
China	RT alone RT ± CT Chemotherapy alone	253 1103 170	56.3 45.9 21.7	[7]

3.9 Toxicity

3.9.1 Acute Toxicity

Almost half of patients treated with RT-DeVIC experienced acute non-hematologic toxicity grade 3 or greater, mostly mucositis (38%) followed by infection (22%) in Japanese clinical practice [9]. All toxicities were transient and resolved with supportive care.

3.9.2 Late Toxicity

The late toxicity was chronic dryness of mucous membranes on the head and neck. The potential secondary malignancies were observed 5% [9].

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Thyroid Lymphoma

4

Masatoshi Hasegawa and Nobuhide Wakai

Abstract

Primary thyroid lymphoma is relatively rare, accounting for approximately 1–2% of all lymphomas, and it is often associated with thyroid diseases such as Hashimoto's thyroiditis. The majority of the tumors consist of diffuse large B-cell lymphoma (DLBCL) or extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). Localized aggressive lymphomas such as DLBCL are usually treated with immune/chemotherapy (R-CHOP) with or without radiation therapy. Doses of 30–40 Gy of involved site radiation therapy (ISRT) are recommended for localized aggressive lymphomas following combined immune/chemotherapy (R-CHOP). Localized indolent lymphomas such as MALT and follicular lymphomas are usually treated with radiation therapy alone following biopsy. A dose of 24–30 Gy of ISRT is recommended for indolent lymphomas. Other treatment modalities are performed in some cases. The histopathological subtype, stage, age, and treatment (radiation or surgery) have been suggested to be important prognostic factors. More disease-specific approaches using large cohorts are required to confirm the treatment strategies because the number of patients is limited.

Keywords

Thyroid lymphoma • Hashimoto's thyroiditis • ISRT • DLBCL • MALT

M. Hasegawa (✉) • N. Wakai
Department of Radiation Oncology, Nara Medical University,
840 Shijo-cho, Kashihara, Nara 634-8522, Japan
e-mail: hasegawa@naramed-u.ac.jp

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4.1 Introduction

Primary thyroid lymphomas are rare, accounting for approximately 1–2% of all lymphomas, and they are often associated with autoimmune or inflammatory thyroid diseases such as Hashimoto's thyroiditis or chronic lymphocytic thyroiditis. Patients with thyroid lymphoma may show a mass or swelling in the anterior neck. Hoarseness and dysphagia may also be present in some patients. The rate of growth differs by the histopathological subtypes. It is sometimes difficult to make a clear distinction between lymphomas and non-neoplastic thyroid diseases by diagnostic imaging. A precise histopathological study following biopsy or resection is necessary for a definite diagnosis. The management strategies for thyroid lymphoma are similar to those for tumors with other extranodal origins.

4.2 Pathology

Most of the primary thyroid lymphomas are of B-cell origin and the most common subtypes are an aggressive "diffuse large B-cell lymphoma" (DLBCL) and an indolent "extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue" (MALT lymphoma) [1–3]. Transformation from MALT lymphoma to DLBCL may sometimes occur partially or totally. Other subtypes such as follicular, T-cell, or Hodgkin's lymphomas are rarely reported.

Treatment strategies differ by the subtypes. Characteristic features of the morphology, immunophenotype, cytogenetic abnormalities, and oncogenes are useful for performing a definite diagnosis. In some cases, we have to consider the possibility of partial transformation from MALT to DLBCL. If heterogeneous findings are shown by CT, MRI, or FDG-PET/CT, multiple biopsies including the most suspicious site are often recommended.

Distinctions between indolent lymphomas and non-neoplastic thyroid lesions such as chronic thyroiditis by ultrasound-guided fine needle biopsy specimens are sometimes controversial, and surgical open biopsy is required in some cases. MALT lymphomas are often suggested to be derived from chronic inflammatory diseases, and mixed features of indolent lymphoma and inflammation are often shown by microscopic examination.

4.3 Lymphoma Subtype for Radiation Therapy

Localized aggressive lymphomas such as stage I/II DLBCL are usually treated with immune/chemotherapy (R-CHOP) with or without radiation therapy. Localized indolent lymphomas such as stage I/II MALT or follicular lymphomas are usually treated with radiation therapy alone following biopsy.

4.4 Pretreatment Evaluation and Staging

CT, MRI, and FDG-PET/CT are used for staging. Ultrasound, bone marrow biopsy, and other systemic examinations are also performed. The Ann Arbor stage classification is most commonly used. Additionally, thyroid function tests should be done before and after treatment. Base-line imaging before any treatment should be considered for defining the clinical target volume (CTV) of radiation therapy planning.

4.5 Prognostic Factors

The histopathological subtype, stage, age, and treatment (radiation or surgery) have been suggested to be important prognostic factors [1–4]. The International Prognostic Index may be applicable for aggressive lymphomas. The histopathological subtype is one of the significant factors and patients with different subtypes often show a clear survival difference. Longer survival is expected in patients with MALT than those with DLBCL.

4.6 Treatment Strategy

4.6.1 DLBCL

DLBCLs are treated with immune/chemotherapy (R-CHOP) as the primary therapy regardless of the stage. Localized aggressive lymphomas such as stage I or II DLBCL are usually treated with immune/chemotherapy (R-CHOP) with or without radiation therapy. Relatively high doses of 30–40 Gy in 1.8- to 2-Gy fractions and involved site radiation therapy (ISRT) including the whole thyroid gland and suspected extrathyroidal extensions are recommended for localized aggressive lymphomas as consolidation following combined immune/chemotherapy (R-CHOP). After a complete response, a dose of 30 Gy of ISRT has been suggested to be sufficient. More than 40 Gy may be beneficial for chemoresistant or gross residual tumors after immune/chemotherapy. Advanced diseases are usually treated with immune/chemotherapy alone, but radiation therapy is sometimes effective for palliation.

4.6.2 MALT

Localized indolent lymphomas such as MALT and follicular lymphomas are usually treated with radiation therapy alone following biopsy. A dose of 24–30 Gy in 1.5- to 2-Gy fractions and ISRT including the whole thyroid gland and suspected extrathyroidal extensions are recommended for indolent lymphomas. Other treatment modalities are performed in some cases. Surgery with or

without radiation therapy, immunotherapy, or immune/chemotherapy with or without radiation therapy, and watchful waiting may become candidates. Radiation therapy alone is sometimes beneficial for patients with advanced stage III or IV diseases as well as those with localized I or II. Doses of 20 Gy or lower are effective for palliation and even 4 Gy in two fractions is often good for symptom control.

More disease-specific approaches using large cohorts are required to confirm the treatment strategies because the number of patients is limited compared with those with lymphomas at the other sites.

4.7 Radiation Therapy

4.7.1 Planning CT

The radiation therapy planning CT should be performed involving the whole neck including the entire thyroid gland and any suspicious lesions.

4.7.2 Gross Tumor Volume (GTV)

The GTV is the thyroid tumor and involved lymph nodes detected by CT, MRI, FDG-PET, etc.

4.7.3 Clinical Target Volume (CTV) and Planning Target Volume (PTV)

The CTV includes the GTV, whole thyroid gland, involved lymph nodes, and any suspicious lesions. The PTV could be contoured with at least a 1-cm margin from the CTV (Fig. 4.1). Baseline imaging before surgical resection or immune/chemotherapy should be considered for defining CTV. ISRT including the whole thyroid gland and GTV before the initiation of any treatment are recommended [5].

4.7.4 Dose

Relatively high doses of 30–40 Gy in 1.8- to 2-Gy fractions are recommended for localized aggressive lymphomas as consolidation following combined immune/chemotherapy. After a complete response, 30 Gy is often used. More than 40 Gy may be beneficial for chemoresistant or gross residual tumors.

Doses of 24–30 Gy in 1.5- to 2-Gy fractions are recommended for localized indolent lymphomas as primary therapy. Doses of 20 Gy or lower are effective for patients with advanced stages as palliation, and even 4 Gy in two fractions is often good for symptom control.

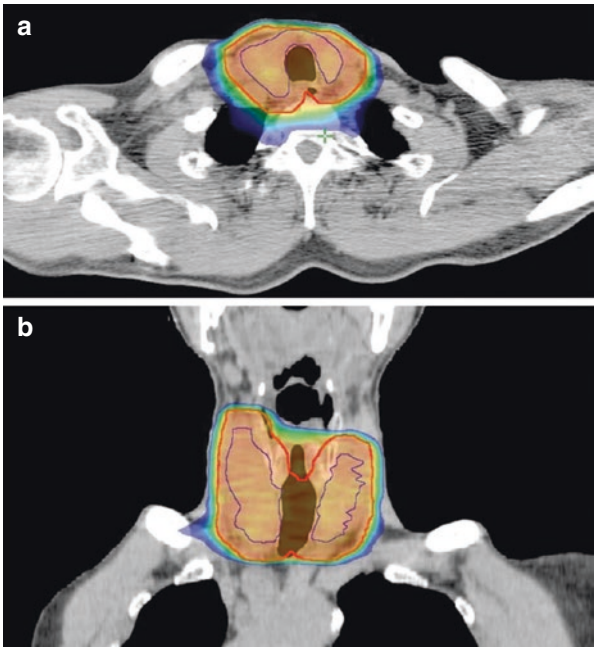

Fig. 4.1 Radiation treatment planning for extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) of the thyroid. Dose distributions of (**a**) axial and (**b**) coronal planes

4.7.5 Radiation Therapy Techniques

Three-dimensional conformal radiation therapy (3D-CRT) or intensity-modulated radiation therapy (IMRT) provides a better dose distribution and leads to the application of a lower dose to surrounding organs at risk such as the esophagus and spinal cord than 2-D planning.

4.8 Outcomes

The 5-year overall survival and cause-specific survival rates for stage I/II DLBCL and MALT lymphoma patients were reported to be 60–90% and 80–100%, respectively. The outcomes are similar to those with tumors of other extranodal origins.

4.9 Toxicity

Common acute toxicity or adverse events after radiation therapy are esophagitis scored as Grade 1 or 2 and dermatitis Grade 1. Hypothyroidism is often observed following radiation therapy as a late toxicity or adverse event, especially in patients with chronic thyroiditis.

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Pyothorax-Associated Lymphoma

5

Jun Itami

Abstract

Pyothorax-associated lymphoma (PAL) is a diffuse large B-cell lymphoma (DLBCL) originated from tuberculous pyothorax. PAL is latently infected by EB virus with a type III expression of EB virus-related proteins on the tumor cells. Artificial pneumothorax, which was performed in Japan often to manage pulmonary tuberculosis, seems to be etiologically related to PAL. PAL occurs 30–40 years after the artificial pneumothorax. Therefore, mean age of the patients is very high around 70 years. PAL tends to invade locally and some reach to a quite large size ≥10 cm. More than half of PAL are classified into stage I and II at the presentation. Therefore, an aggressive surgery of pleuropneumonectomy was reported to result in an excellent local control in some series, although number of the patients suited to the surgery is very limited because of the poor performance status seen in about half of the patients with PAL. Efficacy of CHOP or CHOP-like chemotherapy is variably reported. Radiation therapy is effective in controlling the local disease and long-term survival was obtained in some patients. Radiation therapy can be applied as a primary therapy to stage I and II as well as a salvage therapy after chemotherapy. ^{18}F-Fluorodeoxyglucose positron emission tomography is very helpful in delineating gross tumor volume (GTV). Clinical target volume (CTV) is defined by a concentric expansion of 3 cm from GTV. It remains unclear whether the pyothorax cavity should be included as CTV. Because of a large size of the tumor, more than 50 Gy seems to be necessary in some patients with PAL. Prognosis of PAL is poor with 5-year survival of 20–30%.

Keywords

Tuberculous pyothorax • EB virus • Diffuse large B-cell lymphoma • Radiation therapy

J. Itami
Department of Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan
e-mail: jitami@ncc.go.jp

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Non-Hodgkin's lymphoma (NHL) develops sometimes in the sites of chronic inflammation, such as in thyroid gland with Hashimoto's disease, parotid gland with Sjogren's disease, and stomach with atrophic gastritis caused by *Helicobacter pylori*. NHL occurring in the tuberculous pyothorax (pyothorax-associated lymphoma, PAL) also belongs to NHL developing in the chronic inflammation [1, 2] and has been reported mainly from Japan, although there are rare reports of PAL from other Asian [3] as well as Western countries [4]. Similar NHL arises in the patients with chronic osteomyelitis, metallic stent, and chronic skin ulcer [1]. PAL posed special problems to the oncologists because of the high age and poor performance status of the patients.

5.1 Etiology and Pathology

PAL was first described by Iuchi et al. from Japan in 1987 and reported to have pathological and immunohistochemical features of a diffuse large B-cell lymphoma (DLBCL) [5]. PAL develops from a margin of the pyothorax cavity [6], almost 40 years after artificial pneumothorax. In Japan, the artificial pneumothorax was performed very often to manage pulmonary and pleural tuberculosis in 1930–1950s and the resulting pleural space caused by the pneumothorax was secondarily infected most often by non-tuberculous agents resulting with a pyothorax cavity formation. The incidence of PAL is reported to be 2.2% in the patients with a tuberculous pyothorax [5], while it was not observed in the patients without a pyothorax. The artificial pneumothorax is considered to be a risk factor of PAL [7], although nation-wide survey in 2007 revealed that 20% of PAL develop without the history of artificial pneumothorax [8]. The precise mechanism of the causal relationships of PAL and the artificial pneumothorax remains to be studied. PAL occurs from the pleura at the periphery of pyothorax cavity and invades adjacent structures. Pathological diagnosis is mostly established through percutaneous biopsy of the tumor. Presence of extensive necrotic foci, which is not common in nodal DLBCL, necessitates often repeated biopsies to establish diagnosis. Some cases were diagnosed even by autopsy. Some patients with a tumor in a difficult site for the percutaneous biopsy could be diagnosed by cytological as well as immunological analyses of effusion in the pyothorax cavity, although it does not seem probable that all patients with PAL can be diagnosed with the procedure. Most of the PALs are classified into DLBCL with B-cell markers such as CD20, CD79a, and PAX5. Cases with aberrant T-cell marker expression were also reported. Immunoblastic and plasmoblastic feature can be seen in some cases [8, 9]. It remains unknown whether these different marker expressions have a clinical significance. Most of PALs are latently infected by EB virus [10, 11]. The latent infection can be diagnosed easily by an immunohistochemical method demonstrating EB virus-related proteins as well as by in situ hybridization of EB virus-encoded small RNA (EBER) [8]. Tumor cells are positive for EB virus nuclear

Table 5.1 Antigen expression profiles of latent infections of EB virus in various EB virus-related tumors

Latency	Gene products			Disease
	EBER	EBNA	LMP	
I	EBER	EBNA-1		Burkitt's lymphoma, gastric cancer
II	EBER	EBNA-1	LMP-1, LMP-2A, LMP-2B	Nasopharyngeal cancer, classic Hodgkin lymphoma
III	EBER	EBNA-1, EBNA-2, EBNA-3A, EBNA-3B, EBNA-3C	LMP-1, LMP-2A, LMP-2B	Lymphoproliferative disease in immunodeficiency, PAL, EBV+ DLBCL of elderly

DLBCL diffuse large B-cell lymphoma, *EBER* EB virus-encoded small RNA, *EBNA* EB virus nuclear antigen, *LMP* latent membranous antigen, *PAL* pyothorax-associated lymphoma

antigens (EBNAs)-1 and -2, EBERs, and latent membranous protein (LMP)-1. This type of antigen expression is classified as type III latent infection of EBV and seen also in lymphoproliferative disorders occurring in the immunocompromised patients (Table 5.1). Although the patients with PAL are immune competent and the expressed EB virus-related antigens of tumor cells are very immunogenic, PAL is tolerant to the immune surveillance, mechanism of which remains to be studied. Locally confined barrier to the immune surveillance around the pyothorax cavity can be plausible, which also explains that the PAL remains mostly locally limited at the presentation because the growth outside of the barrier would be difficult for the tumor cells. The differentiation of PAL from EB virus-related lymphoma of elderly, which is also DLBCL, is possible clinically only by the presence of a pyothorax cavity in PAL.

5.2 Clinical Presentation and Radiological Features

PAL mostly occurs 20–40 years after the artificial pneumothorax. Therefore, median age of the patients with PAL is quite high around 70 years [8, 9]. There is overwhelming male predominance of 17:1, which is much higher than the male predominance seen in the tuberculous pyothorax. Accordingly, an etiological influence of sex hormone is suggested. At the presentation, PAL is locally confined with 70% of the patients having stage I or II disease. PAL occurs from the pleura at the margin of pyothorax cavity and invades adjacent structures such as ribs, muscles, subcutaneous tissue, skin, diaphragm, vertebrae, and liver (Fig. 5.1). Tumor size often reaches more than 10 cm. Stage III–IV disease is less common, but at the time of relapse, extranodal involvements to the central nervous system and bone marrow are not rare. Local pain, tumor of the thorax surface, hemoptysis, cough, and fever are most common presenting symptoms of PAL. Almost half

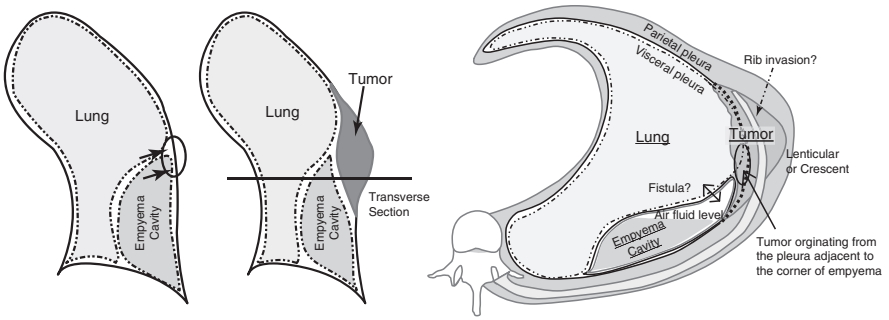

Fig. 5.1 PAL arises from a margin of the pyothorax cavity and invades adjacent structures. Reproduced from Fig. 6 in "Pyothorax-associated lymphoma: image findings" by Ueda T, et al. [6]

of the patients have poor performance status of ≥2 according to ECOG criteria, mainly because of the long-standing presence of the chronic inflammatory pyothorax and the related pulmonary dysfunctions [8, 9]. More than half of the patients with PAL are of high-intermediate or high risks according to the international prognostic index (IPI) [8]. Serum examinations of the patients with PAL show often elevated LDH, which reflects large tumor volume, and increased serum IgG antibody titer against viral capsid antigen (VCA) of EBV showing the presence of old EB virus infection.

To delineate and stage PAL, contrast-enhanced CT and MRI are useful. They are also helpful in guiding biopsy by showing necrotic areas, thereby biopsy avoiding the necrosis is possible. Important differential diagnosis is a tuberculous exacerbation where the same symptoms with PAL such as local pain, tumor formation, hemoptysis, and fever are seen. In the tuberculous lesions, tumor is occasionally formed outwardly from the center of a pyothorax cavity. In contrast, PAL tends to grow outwardly from the periphery of a pyothorax cavity (Fig. 5.1).

Positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (FDG) is helpful to localize local invasion of PAL [12] and is also required to stage PAL according to Lugano classification [13]. FDG-PET provides also very important information of target volume delineation at radiation therapy [14].

5.3 Management of PAL

Paucity of PAL hinders establishment of the standard management. In considering the therapeutic strategy of PAL, it is a significant problem that about half of the patients present with a poor performance status of ≥2 by ECOG criteria, which was reflected in that more than 10% of the patients could not tolerate any therapeutic interventions and underwent best supportive care only [8, 9]. Similar to other DLBCLs, stage I and II patients with PAL are treated by CHOP

(cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP-like chemotherapy followed by consolidating radiation therapy. Number of the chemotherapy cycles is dependent upon the tumor size and stage. Patients in more advanced stages are treated by more than six cycles of CHOP or CHOP-like chemotherapy with or without radiation therapy to the bulky lesions. There is only a case report of rituximab containing chemotherapy in PAL with an excellent response [15]. High incidence of a locally confined PAL even with a large tumor suggests that PAL remains locally for a long time. Therefore, very aggressive pleuropneumonectomy has been reported with an excellent 5-year survival of 85.7% [16]. However, intensive chemotherapy and aggressive pleuropneumonectomy are not indicated in many patients with PAL. Additionally, some authors emphasize only a transient response of PAL against chemotherapy [17]. Radiation therapy alone is indicated in such patients as a definitive treatment as well as a salvage therapy after chemotherapy [17]. Aruga et al. treated patients with stage I and II PAL with radiation therapy alone and a long-term local control was obtained [17].

5.4 Radiation Therapy

Radiation therapy plays a very significant role in the management of PAL, because more than half of the patients presents with locally confined disease and many patients cannot tolerate aggressive operation as well as intensive chemotherapy.

It remains unknown whether the whole pyothorax cavity neighboring PAL should be included as a clinical target volume (CTV). Aruga et al. demonstrated that inclusion of pyothorax cavity did not influence the local control of PAL [17]. In their series, one patient, in which the large pyothorax cavity was included in the CTV, succumbed to fatal pneumonitis. For delineation of gross tumor volume (GTV) and CTV, FDG PET/CT will be very useful and the pyothorax cavity not demonstrating FDG uptakes might be excluded from CTV [12, 14] (Fig. 5.2). Similar to the involved site radiation therapy [18], GTV equals to the tumor volume with FDG uptakes and CTV is defined by an expansion of GTV with margins of 3 cm. For a setup of planning target volume (PTV), respiratory movement and setup errors must be taken into account. Concentric margins of as large as 1.5 cm would be adequate in most patients considering reduced respiratory movement by the pleural adhesion.

There is no established standard of an applied radiation dose to PAL. Aruga et al. recommend 50 Gy in a conventional fractionation to PAL because DLBCL requires a higher dose than follicular lymphoma and the tumor size is often larger than 10 cm [18]. There are no reports of intensity modulated radiation therapy (IMRT) in the treatment of PAL. IMRT has a shortcoming of exposing a large volume of normal structures to a low dose radiation (radiation bath). Pulmonary function in the patients with PAL is frequently deteriorated by old tuberculous infection and it remains unclear whether this injured lung can tolerate a low dose radiation exposure by IMRT (Fig. 5.3).

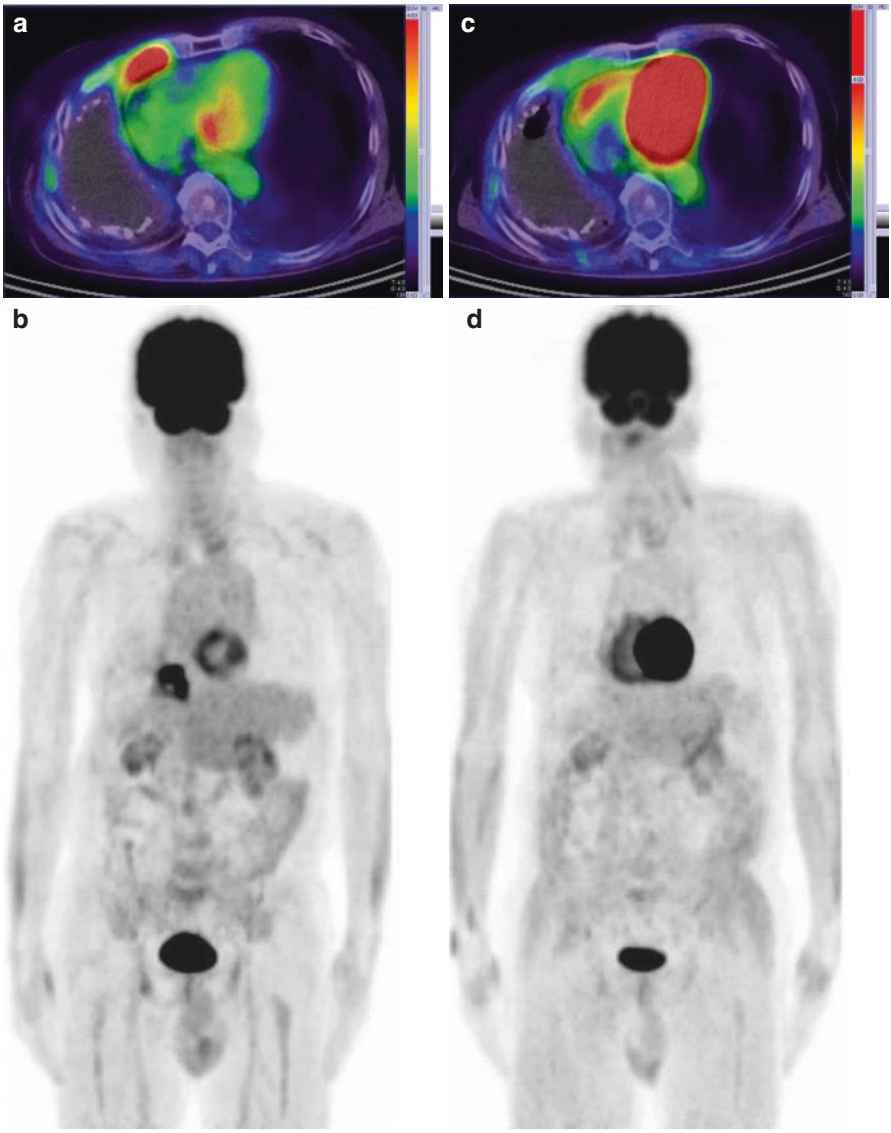

Fig. 5.2 FDG PET/CT images of an 80-year-old male patient with stage I PAL treated by radiation therapy not including pyothorax cavity. The patients lived without relapse more than 5 years after the radiation therapy. (**a**) Axial image before radiation therapy. PAL lies in the right anterior chest wall neighboring a pyothorax cavity in the right thorax. (**b**) Maximal intensity projection (MIP) frontal image before radiation therapy. (**c**) Axial image after radiation therapy. An uptake was no more seen in the right anterior chest wall. (**d**) MIP anterior image after radiation therapy

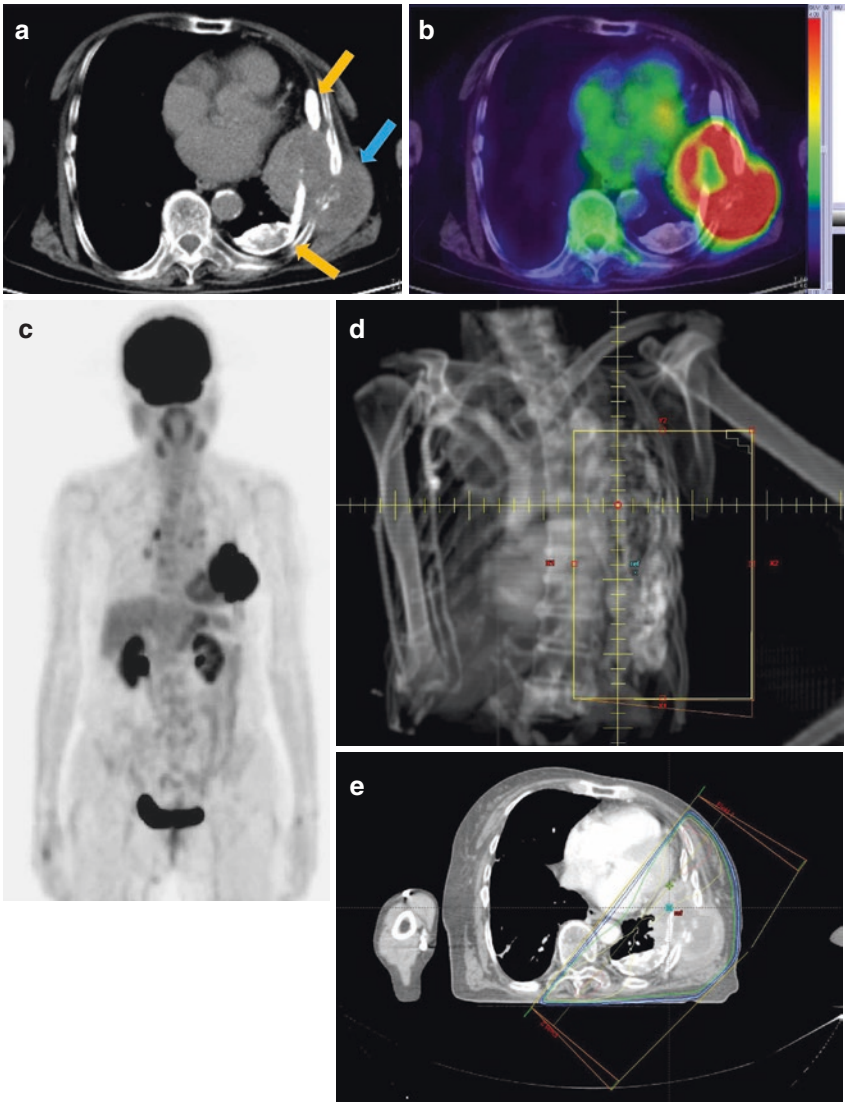

Fig. 5.3 Eighty-seven-year-old female with stage I PAL treated only by radiation therapy including pyothorax cavity. The patient lived without relapse 5 years after the radiation therapy. (**a**) Axial CT image of PAL (*blue arrow*) neighboring pyothorax cavities with calcification (*yellow arrows*) before radiation therapy. PAL destructed ribs and invaded to the subcutaneous fat. (**b**) Axial FDG PET/CT image before radiation therapy. Marked FDG uptake was seen in PAL. (**c**) MIP frontal image of FDG PET/CT before radiation therapy. (**d**) Digitally reconstructed radiography (DRR) of the initial radiation portal including pyothorax cavities. (**e**) Medial margins of the fields were aligned to reduce dose to the heart. In these fields, 40 Gy in 20 fractions were applied. (**f**) DRR of the coned-down fields after 40 Gy. (**g**) The heart was mainly spared with the coned-down fields and an anterior part of the pyothorax cavity was not irradiated. With these fields 16 Gy in 8 fractions were applied. (**h**) Axial CT image after radiation therapy. PAL regressed almost completely. (**i**) FDG PET/CT after radiation therapy did not reveal increased uptakes in PAL. (**j**) MIP frontal image of FDG PET/CT after radiation therapy

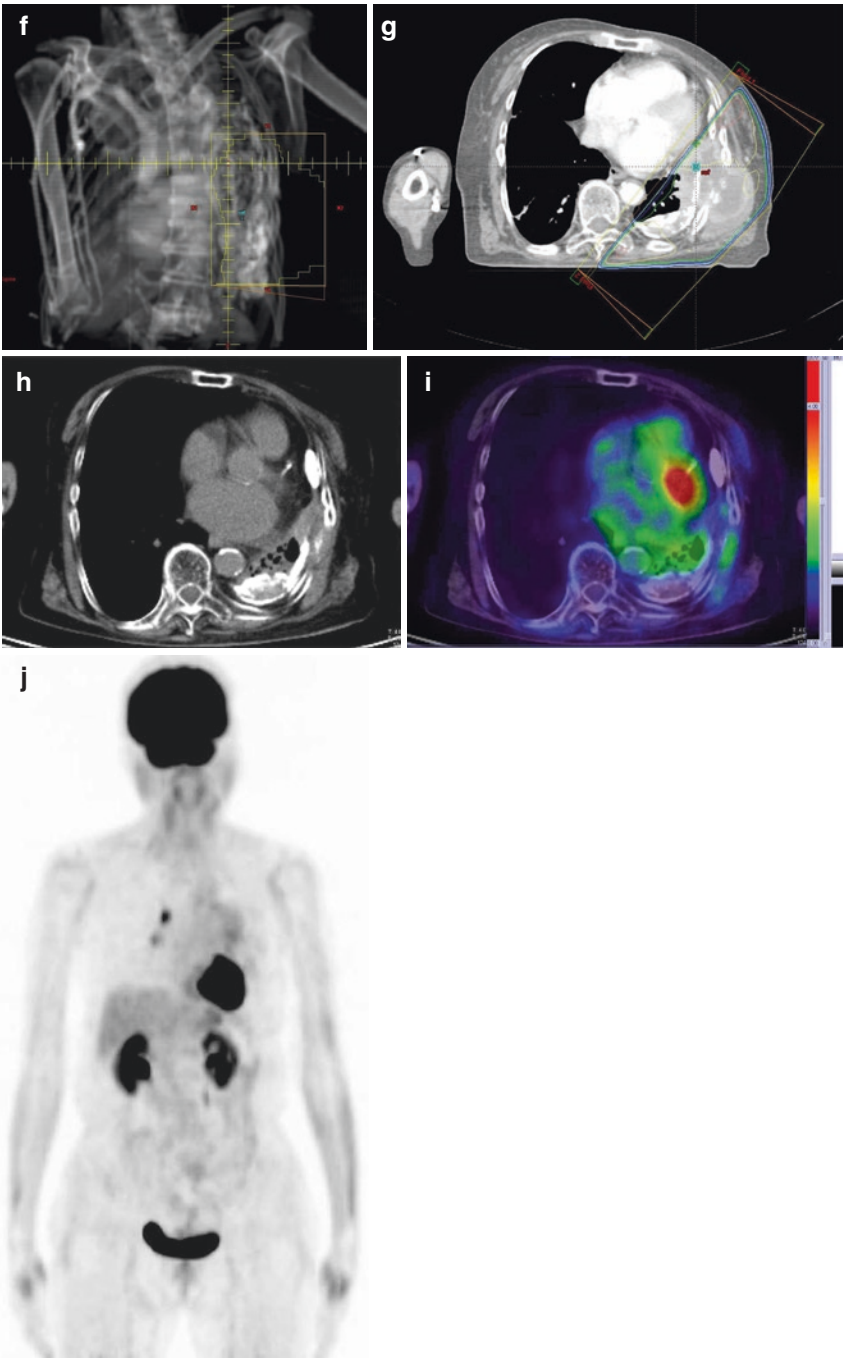

Fig. 5.3 (continued)

5.5 Prognosis

Prognosis of PAL is generally poor with 5-year survival of 20–30%. Most significant prognostic factor is performance status [8, 9, 19], followed by stage. Five-year survival was 47% and 35% in the patients in stage I and II, respectively, while more advanced stage showed only 15% 5-year survival.

5.6 Future Perspective

Because of a decreasing incidence of the pulmonary tuberculosis and non-performance of the artificial pneumothorax in the management of tuberculous lung lesions, the incidence of PAL will surely decrease in Japan and other countries. However, PAL must be always considered as one of the differential diagnoses in the tumors growing in relation to a pyothorax. Additionally, the incidence of DLBCLs associated with chronic inflammation other than PAL remains apparently unchanged. The pathophysiological research of PAL will cast light onto the ontogeny of DLBCL associated with chronic inflammation. In such extranodal lymphomas, tumors are often confined to the primary site for a long time and radiation therapy might have a potential to control the local disease as well as to cure the disease.

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Stomach

6

Koichi Isobe

Abstract

The gastric lymphomas include several histological subtypes of lymphoma, including diffuse large B-cell lymphoma (DLBCL), marginal zone B-cell lymphoma of mucosa associated lymphoid tissue (MALT lymphoma), follicular lymphoma, mantle cell lymphoma, adult T-cell lymphoma/leukemia, and so on. Of these, DLBCL and MALT lymphoma account for approximately 90% of gastric lymphomas. For localized DLBCL, the 30 Gy of conventionally fractionated radiation therapy (RT) following the short course of anthracycline-based chemotherapy combined with rituximab, such as R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) is a treatment of choice. On the contrary, the antibiotics for *Helicobacter pylori* (*H. pylori*) are first line treatment for *H. pylori*-positive MALT lymphoma. The *H. pylori*-negative cases and those who fail *H. pylori* eradication therapy are candidates for RT. Irrespective of histological subtypes, clinical target volume is defined as whole gastric wall. During simulation and delivery of RT, the management of inter- and intrafractional gastric motion is indispensable for gastric lymphomas. RT with doses up to 30 Gy could produce excellent local control and long-term outcomes without significant late effects in MALT lymphoma.

Keywords

Gastric lymphoma • Interfractional motion • Intrafractional motion • Radiation therapy

K. Isobe
Department of Radiology, Toho University Sakura Medical Center,
564-1, Shimoshizu, Sakura, Japan
e-mail: isobeko@med.toho-u.ac.jp

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6.1 Introduction

The gastrointestinal (GI) tract is the most common site of involvement of extranodal lymphomas, which account for 30–40% of this type of lymphomas [1–5]. In Japan, as well as in Western countries, the stomach is the most common location of GI tract lymphomas [5]. On the other hand, small intestine lymphomas are more common in the Middle East, which indicates that there is some geographical difference in its proportions [1]. The incidence of GI tract lymphomas has increased over the past decades in Japan [5]. However, it is unclear that this may be due to true increase of the disease or to improved diagnostic tools.

It is well known that *Helicobacter pylori* (*H. pylori*) infection is the major risk factor for gastric marginal zone B-cell lymphoma of mucosa associated lymphoid tissue (MALT lymphoma), and celiac disease for enteropathy type T-cell lymphoma. However, other risk factors developing GI tract lymphoma are still undefined. The leading histological subtype of gastric lymphomas is diffuse large B-cell lymphoma, not otherwise specified (DLBCL), and MALT lymphoma follows [5–7]. These two histological subtypes account for approximately 90% of gastric lymphomas, and this chapter will focus on these lymphomas.

The median age of the gastric DLBCL is approximately 60 years with abdominal pain as most common presenting symptom. Some patients complain of nausea, vomiting, and melena. The endoscopic patterns are ulcerative or elevated, which are similar to the findings of advanced gastric adenocarcinoma. The etiology of gastric DLBCL remains unknown; however, *H. pylori* infection is present in 35% of cases and the administration of *H. pylori* eradication therapy could obtain durable complete remission in some cases [8]. The gastric MALT lymphoma occurs over a wide range of age, with a mean of approximately 60 years. The clinical presentation is poorly specific, symptoms including dyspepsia, epigastralgia, and appetite loss. Some patients are diagnosed incidentally without any clinical symptoms at health screening by endoscopic examination. Although the endoscopic findings may appear as a clear malignant lesion, it is frequently characterized simply by multiple erosions and/or ulcers, small submucosal nodules, thickening of gastric folds, which generally suggested benign conditions. The gastric MALT lymphoma is strongly associated with *H. pylori* infection. It has been demonstrated that *H. pylori*-related chronic gastritis is the main preceding condition of gastric MALT lymphoma. However, the fact that high prevalence of *H. pylori* infection in general population with low incidence of gastric lymphoma indicates that some particular factors are indispensable for lymphoma development [9].

6.2 Pathology

Irrespective of the site of involvement of lymphoma, the accurate pathological diagnosis and the staging are indispensable for appropriate management of this disease. Therefore, the diagnosis should be confirmed by an experienced hematopathologist in accordance with the current World Health Organization (WHO) classification

system [10]. The various histological subtypes of NHL (non-Hodgkin's lymphoma) could occur in the stomach. The DLBCL is the most common subtype, which consists of nearly 50% of gastric lymphomas. The MALT lymphoma follows, and account for approximately 40% of them. The other B-cell lymphomas, such as mantle cell lymphoma, follicular lymphoma, and several types of T- or natural killer (NK) cell lymphomas, would also occur with low incidence. It should be assessed whether there is active *H. pylori* infection on histochemical examination. In addition to histopathological evaluations, fluorescence in situ hybridization (FISH) studies for detection of *t*(11;18) (q21;q21) may be useful for identifying patients who are less likely to respond to *H. pylori* eradication therapy [11, 12].

6.3 Pretreatment Evaluation and Staging [13–16]

Most patients with gastric lymphoma present with some symptoms, which are generally related to the local lesion such as dyspepsia, abdominal pain, nausea and vomiting, anorexia, and bleeding. Some patients are diagnosed incidentally without any clinical symptoms at health screening by endoscopy. After the diagnosis of lymphoma is confirmed, the patients should receive comprehensive history including age; sex; absence or presence of B symptoms (fevers to more than 38.3°, drenching night sweats, or unexplained body weight loss more than 10% of body mass over 6 months); performance status; and history of their disease. Physical examination includes measurement of accessible peripheral lymph nodes and the size of the spleen and liver in centimeters below their respective costal margins in the midclavicular line. An ear, nose, and throat examination is also recommended for gastric lymphomas to exclude concomitant involvement of MALT lymphoma in the head and neck regions. Laboratory tests include complete blood counts with chemistry including lactate dehydrogenase (LDH), soluble interleukin 2 receptor (sIL-2R), β2-microglobulin, human immunodeficiency virus, hepatitis C virus and hepatitis B virus serology. If the presence of active *H. pylori* infection is not demonstrated by histopathological examination, it must be evaluated by serology, urea breath test, and/or stool antigen test. A bone marrow aspirate and/or biopsy is recommended [11]. The positron emission tomography (PET)–computed tomography (CT) using fluorodeoxyglucose (FDG) as a tracer has become standard for staging and response assessment of FDG avid lymphomas. In gastric lymphomas, although DLBCL is well recognized as FDG avid lymphoma, the efficacy of FDG PET-CT for MALT lymphoma is still controversial. Thus, a contrast-enhanced CT scan of the neck, chest, abdomen, and pelvis is preferable for staging in some histological subtypes. In addition to these imaging studies, endoscopy for upper and lower GI tract are essential to evaluate the extent of disease and to obtain biopsy specimen for histopathological evaluations. The endoscopic ultrasound (EUS) has gained a great role to assess both the depth of gastric wall invasion and the regional node involvement [17]. Furthermore, the recent technical advances enable us to detect more detailed gastric pits destruction, pit size irregularity by magnifying endoscopy [18].

The most appropriate staging system for GI tract lymphomas is controversial. The Lugano staging system has been widely accepted in the past two decades [19], but, more modern system, Paris staging system, has been proposed by EGILS (European Gastro-Intestinal Lymphoma Study Group, Table 6.1) [20]. This system has been constructed by the combination of TNM system and the classical Ann

Table 6.1 Paris staging system for primary gastrointestinal lymphomas[a,b] (from [20] with permission)

TX	Lymphoma extent not specified
TO	No evidence of lymphoma
T1	Lymphoma confined to the mucosa/submucosa
T1m	Lymphoma confined to mucosa
T1sm	Lymphoma confined to submucosa
T2	Lymphoma infiltrates muscularis propria or subserosa
T3	Lymphoma penetrates serosa (visceral peritoneum) without invasion of adjacent structures
T4	Lymphoma invades adjacent structures or organs
NX	Involvement of lymph nodes not assessed
NO	No evidence of lymph node involvement
N1[c]	Involvement of regional lymph nodes
N2	Involvement of intra-abdominal lymph nodes beyond the regional area
N3	Spread to extra-abdominal lymph nodes
MX	Dissemination of lymphoma not assessed
MO	No evidence of extranodal dissemination
M1	Non-continuous involvement of separate site in gastrointestinal tract (e.g., stomach and rectum)
M2	Non-continuous involvement of other tissues (e.g., peritoneum, pleura) or organs (e.g., tonsils, parotid gland, ocular adnexa, lung, liver, spleen, kidney, breast)
BX	Involvement of bone marrow not assessed
B0	No evidence of bone marrow involvement
B1	Lymphomatous infiltration of bone marrow
TNM	Clinical staging: status of tumor, node, metastasis, bone marrow
pTNMB	Histopathological staging: status of tumor, node, metastasis, bone marrow
pN	The histological examination will ordinarily include six or more lymph nodes

[a]Valid for lymphomas originating from the gastroesophageal junction to the anus (as defined by identical histomorphological structure)

[b]In case of more than one visible lesion synchronously originating in the gastrointestinal tract, give the characteristics of the more advanced lesion

[c]Anatomical designation of lymph nodes as "regional" according to site: (a) stomach: perigastric nodes and those located along the ramifications of the coeliac artery (that is, left gastric artery, common hepatic artery, splenic artery) in accordance with compartments I and II of the Japanese Research Society for Gastric Cancer (1995); (b) duodenum: pancreaticoduodenal, pyloric, hepatic, and superior mesenteric nodes; (c) jejunum/ileum: mesenteric nodes and, for the terminal ileum only, the ileocolic as well as the posterior caecal nodes; (d) colorectum: pericolic and perirectal nodes and those located along the ileocolic, right, middle, and left colic, inferior mesenteric, superior rectal, and internal iliac arteries

Arbor staging system with adaptation of Musshoff [21], which describes more accurately the depth of gastric wall invasion as assessed by EUS. This parameter might predict response to *H. pylori* eradication therapy in gastric MALT lymphoma [22].

6.4 Prognostic Factors

Several prognostic scoring systems have been proposed for each histological subtype respectively, such as follicular lymphoma international prognostic index (FLIPI), international prognostic index (IPI) for aggressive lymphoma [23, 24]. The IPI consisting of five prognostic factors with age, stage, serum LHD, performance status, and number of extranodal sites would be applicable for gastric DLBCL. However, prognostic scoring model or system has yet to be established for gastric MALT lymphoma.

6.5 Treatment Strategy

6.5.1 Gastric DLBCL

The advanced or disseminated DLBCL is treated with 6–8 cycles of anthracycline-based chemotherapy combined with rituximab, such as R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone). For localized disease, approximately two decades has passed since surgery employing partial or total gastrectomy had been the mainstay of treatment with curative intent [25, 26]. A Danish Lymphoma Study Group reported that gastric lymphoma patients who received radiation therapy (RT) as part of their treatment experienced less recurrence [27]. Other group reported that surgery followed by 3–4 courses of chemotherapy achieved comparable outcome to that of chemotherapy alone [28]. However, several investigators have reported that chemotherapy plus RT produced similar outcome to those who received surgery followed by chemotherapy, and then, surgery would be preserved only for patients with perforation or uncontrollable active bleeding [7, 29, 30]. Furthermore, a multicenter randomized trial from the IELSG (International Extranodal Lymphoma Study Group) formally evaluated the role of RT in patients with gastric DLBCL [31]. Although this study closed prematurely due to poor accrual, it demonstrated that involved field RT to patients achieving CR after CHOP-like chemotherapy is able to prevent local relapse. Thus, stomach-preserving therapy consisting of brief chemotherapy with R-CHOP followed by RT would be a treatment of choice for gastric DLBCL.

6.5.2 Gastric MALT Lymphoma

Since the identification of the fact that gastric MALT lymphoma is closely associated with chronic *H. pylori* infection, it is generally accepted that eradication of *H. pylori* with proton pump inhibitor (PPI), amoxicillin, and clarithromycin for 7 days should

be an initial treatment for gastric wall confined MALT lymphoma. This regimen achieved complete response rate of approximately 75%. If the patients do not show response to first line eradication therapy, they should receive a combination of PPI, amoxicillin, and metronidazole for 7 days as a second line treatment. The successful *H. pylori* eradication would be accomplished in approximately 90% of patients by the antibiotic therapy. It is controversial whether *H. pylori* eradication therapy is appropriate for *H. pylori*-negative cases [32]. Some investigators reported that several factors have been associated with resistant to antibiotic therapy, including deep gastric wall invasion and chromosomal translocation such as t(11; 18) [11, 12, 22]. The length to obtain a remission can vary from a few months to more than a year following antibiotic therapy. Therefore, it is reasonable to wait for at least 12 months before initiating salvage treatment in patients who have clinical and endoscopic improvement, albeit having persistent lymphoma on histopathological examination [14].

In patients who do not achieve regression of their lymphoma following antibiotic therapies or is negative for *H. pylori* infection, conventional oncological modalities would be considered. Although there are no published randomized trials with regard to optimal intervention for this condition, RT has been the preferred choice of treatment. Several groups have reported that RT could achieve excellent disease control for gastric MALT lymphoma [33–35].

6.6 Radiation Therapy

6.6.1 Indication

RT is used as adjuvant treatment for patients with localized DLBCL after brief course of R-CHOP chemotherapy. For MALT lymphoma, RT is a treatment of choice when *H. pylori* is absent or when lymphoma does not regress following appropriate antibiotic therapy, or recur after *H. pylori* eradication treatment. For patients who have persistent lymphoma following *H. pylori* eradication therapy, but do not develop any symptoms, surveillance would be one of the treatment options. Some patients would receive RT in palliative setting.

6.6.2 Preplanning Preparations

The management of inter- and intrafractional gastric motions are indispensable for RT to the patients with gastric lymphoma [36–38]. The examples of inter- and intrafractional gastric motions are shown in Figs. 6.1, 6.2, 6.3, and 6.4. To reduce interfractional gastric deformation, the physicians should give instructions for their patients to avoid a heavy meal at supper, and overnight fast to minimize gastric volume. The patients are also educated to avoid deep breathing during simulation and each treatment sessions to reduce intrafractional gastric motion. Furthermore, radionuclide scintigraphy is useful to estimate each renal function separately before determining RT plan.

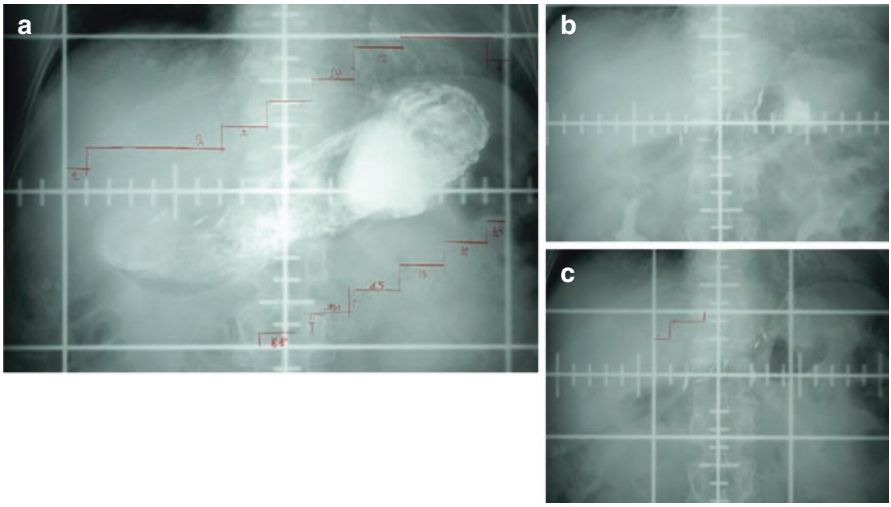

Fig. 6.1 Interfractional gastric motion on fluoroscopic examination with oral contrast media. Three films (**a**–**c**) were taken on different days. Note difference in the shape of stomach and the location of clips placed around GTV

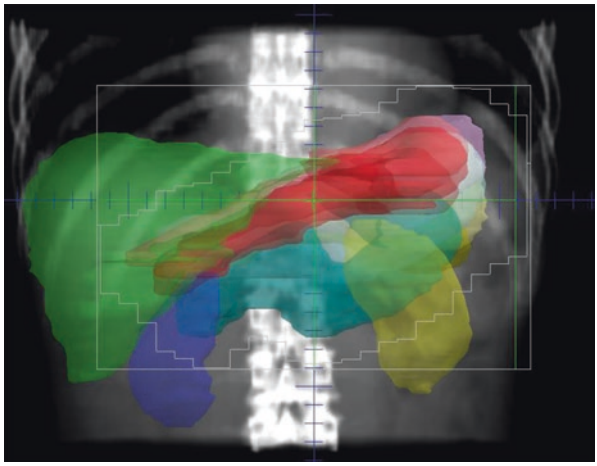

Fig. 6.2 Interfractional gastric motion on DRR (Digitally Reconstructed Radiograph). Note difference of the gastric shape (*red* vs. *cyan*)

6.6.3 Simulation

Patients are always simulated and treated with an empty stomach before having breakfast. Patients should be in supine position with their arms up using customized immobilization device. The planning CT should be obtained at three phases with free shallow breathing, mild inhale, and exhale to evaluate intrafractional gastric motion. The four-dimensional (4D) CT system is more useful, because it is able to provide information with regard to the respiratory movement of stomach under normal free breathing (Fig. 6.4). The fluoroscopic examination with oral contrast media

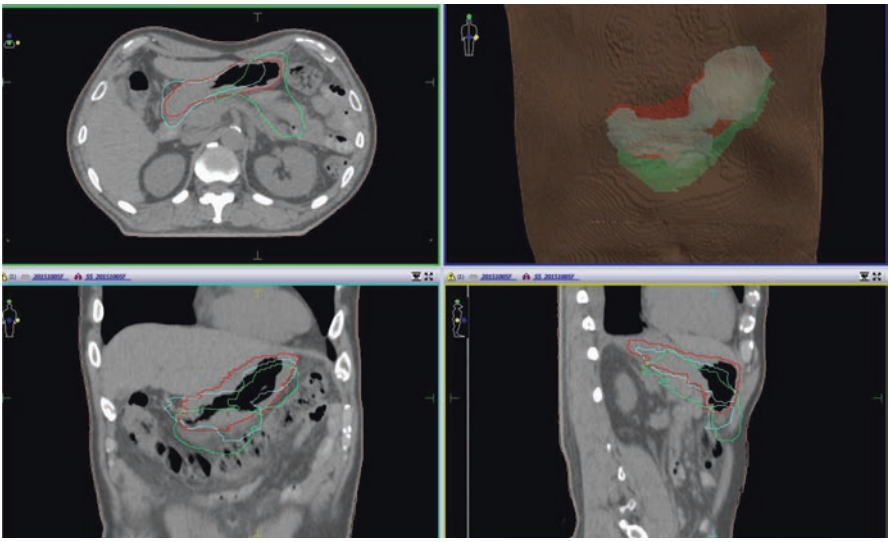

Fig. 6.3 Intrafractional gastric motion. CTV in different breathing phases (mild exhale, *cyan*; mild inhale, *light green*; free breathing, *red*)

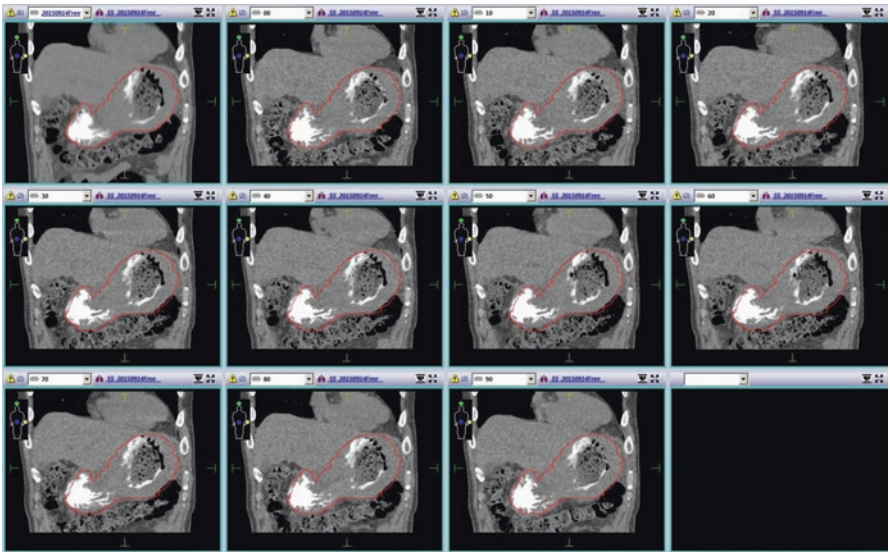

Fig. 6.4 Intrafractional gastric motion on 4D CT images. Note that CTV on free breathing (*red* contouring) fail to include oral contrast media in some breathing phases

is also beneficial to estimate intrafractional gastric movement. The repeated courses of planning CT are desirable before treatment volume has been confirmed in the light of interfractional gastric deformity.

6.6.4 Delineation

The gross tumor volume (GTV) is a gross disease and pathologically enlarged nodes. However, in many cases with MALT lymphoma, the GTV cannot be exactly defined because of its poor visibility on planning CT. The clinical target volume (CTV) is defined as GTV plus entire gastric wall from gastroesophageal junction to duodenal bulb. The internal target volume (ITV) is determined by 4D CT or by fluoroscopic examination to encompass intrafractional gastric motion during respiration. The planning target volume (PTV) is influenced by setup variation in each institutions, and it is recommended to add an additional 1–2 cm margin to ITV. These target volumes are delineated on each CT study set, and all of them are transferred to the index planning CT to determine final irradiated volume. The organs at risk to be contoured are liver, kidneys, spinal cord, heart, lungs, and bowel.

6.6.5 Dose

RT is delivered to doses up to 30 Gy for both MALT lymphoma and DLBCL with a fraction size of 1.5–1.8 Gy. In the palliative settings, lower dose regimen would successfully relief local symptoms of patients.

6.6.6 Technique

Nowadays, the two-dimensional technique has already been obsolete for gastric lymphoma. The three-dimensional conformal RT technique (Fig. 6.5) or intensity modulated radiation therapy (IMRT) (Fig. 6.6) is recommended not only to achieve adequate target coverage but also to reduce doses to surrounding organs at risk such as liver and kidneys as low as reasonably achievable. The most simple beam orientation is 4-field technique consisting of anteroposterior (AP), posteroanterior (PA), and two lateral fields. On the other hand, Princess Margaret Hospital used conformal 5-field technique [39]. Recently, International Lymphoma Radiation Oncology Group (ILROG) published guidelines with regard to RT for extranodal lymphomas including gastric lymphoma [40]. Furthermore, it is desirable to verify that gastric motion and deformation are adequately included in the irradiated volume by cone beam CT and/or on-board kilo-voltage imaging device in each treatment sessions.

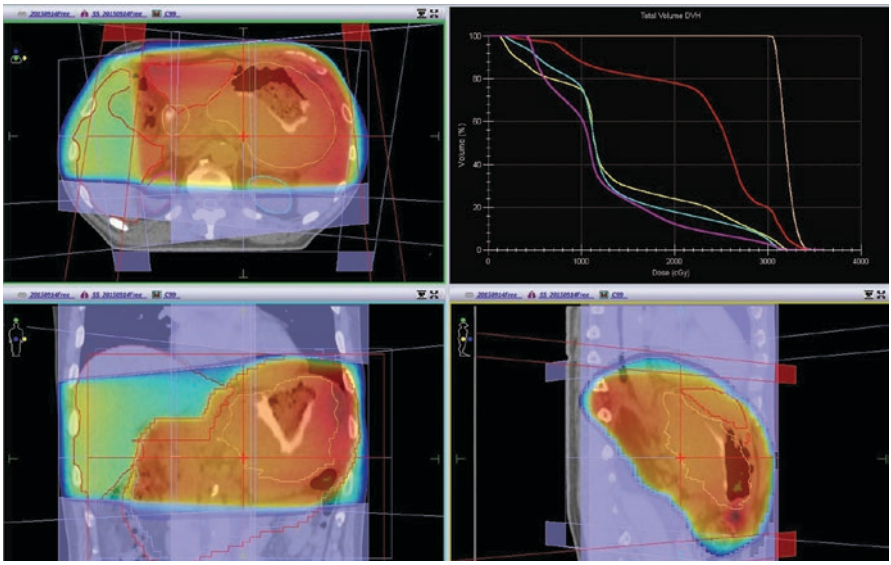

Fig. 6.5 Dose distribution and DVH (dose volume histogram) of 3D conformal RT. In the DVH column, spinal cord, *yellow*; liver, *red*; left kidney, *cyan*; right kidney, *pink*; CTV, *orange*

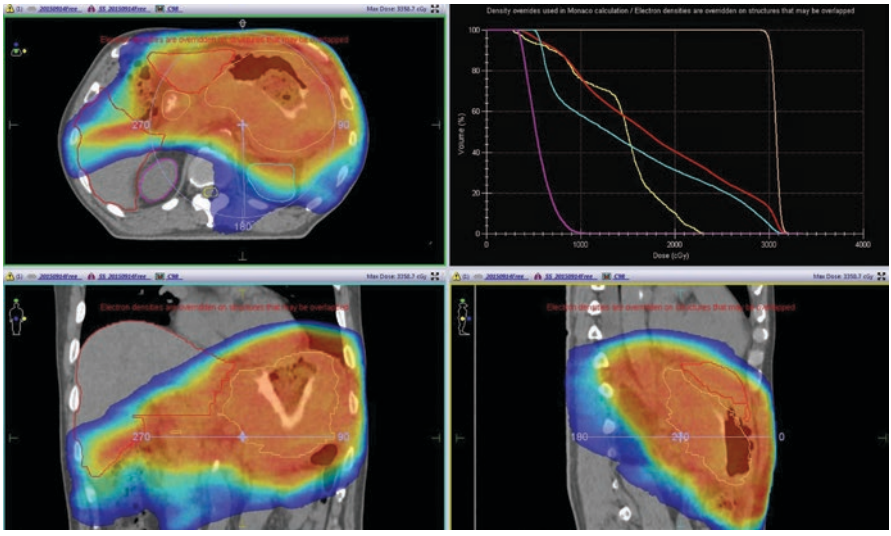

Fig. 6.6 Dose distribution and DVH of VMAT (*lines* in DVH are identical to Fig 6.5)

6.7 Outcomes

Gastric DLBCL patients achieved high local control rate, in the range of 90%. Overall survival (OS) and event-free survival (EFS) for patients with localized disease have also ranged from 70% to 80% [1, 41, 42]. It has been reported that the local control rate, OS, EFS for patients with MALT lymphoma exceed 90% [1, 15, 35, 41–43]. Although the outcome of MALT lymphoma is excellent, long-term follow-up is advisable, because some patients might experience late relapse.

6.8 Toxicity

Appetite loss, nausea, vomiting, fatigue, and abdominal pain are common acute toxicities from RT. Some patients, especially those who receive VMAT (volumetric modulated arc therapy), experience liver dysfunction or bone marrow suppression by blood exam. Although the late toxicities have been rarely reported so far [34, 35], it should be remembered that several researchers investigating the long-term effect of childhood cancer survivors demonstrated delayed renal dysfunction at relatively low doses of RT from TBI (total body irradiation) [44, 45]. Some cases with large intrafractional gastric motion might develop radiation pneumonitis as late adverse event.

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Intestinal Lymphomas

7

Alisa Harada and Masahiko Oguchi

Abstract

The intestinal follicular lymphoma is recognized as a variant of low grade follicular lymphoma in the 2008 edition of WHO classification. The standard treatment has not been established yet for early stage intestinal lymphomas. Among the treatment strategy including observation, pharmaceutical treatment, and radiation therapy, the 24 Gy of involved site radiation therapy is recommended for localized low grade intestinal follicular lymphoma.

Keywords

Intestinal lymphoma • Duodenal lymphoma • Follicular lymphoma • Involved site radiation therapy

7.1 Introduction

The incidence of malignant lymphomas arising in intestinal tracts is very rare, information on the clinical features and prognosis are limited. B-cell lymphomas such as follicular lymphoma (FL), diffuse large B-cell lymphoma and marginal zone B-cell lymphoma MALT type have higher incidence than that of T-cell lymphomas in Japan [1]. While T-cell lymphomas, such as enteropathy-associated T-cell lymphoma, has higher incidence in the Western society than Asian [2].

The intestinal follicular lymphoma is recognized as a variant of FL in the 2008 edition of WHO classification [3]. Yamamoto et al. have reported in extensive

A. Harada, M.D. • M. Oguchi, M.D., Ph.D. (✉)
Radiation Oncology Department, The Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-8-31, Ariake, Kouto-ku, Tokyo 135-8550, Japan
e-mail: oguchi@jfcr.or.jp

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literature review of 249 patients that gastrointestinal FL share a common feature of localized disease distribution, low histological grade, and early staging [4–6].

7.2 Pathology

Intestinal FL share common pathological characteristics with nodal FL, such as CD10+ and BCL2+. However, GI-FL, especially duodenal FL, has unique pathological characteristics, such as villous colonization, expression of mucosal homing receptor α4β7, VH gene deviation, and disrupted follicular dendritic cell networks [7–13]. The follicular dendritic cell network plays important role on development of follicle and germinal center formation. The lack of follicular dendritic cell networks might be related to the low proliferation of intestinal FL.

7.3 Pretreatment Evaluation and Prognostic Factors

The standard staging procedure including bone marrow biopsy and FDG-PET/CT for indolent lymphoma is recommended [14, 15]. Staging should be diagnosed according to the Lugano staging classification for primary gastrointestinal tract lymphoma (Table 7.1). The FDG-PET/CT has limited role on staging because of low accumulation rate of FDG to the primary site.

The primary follicular lymphoma of the intestinal tract may involve any site, although the duodenum is most frequent [7, 16–18]. In a retrospective study of 125 patients, Takata et al. reported that the most common involved site was duodenal second portion (81%) followed by the jejunum (40%), with either single or multiple lesions involved [6]. Screening modality such as wireless capsule endoscopy (WCE) or double-balloon endoscopy (DBE) may be efficient to examine the

Table 7.1 Lugano staging system of primary gastrointestinal lymphoma

Stage	Extent of lymphoma
I	Confined to GI tract (single primary, or multiple noncontiguous lesions)
I 1	Confined to mucosa
I 2	Infiltrating the gastric wall up to the serosa
II	Extending into abdomen from primary GI site
II 1	Local nodal involvement
II 2	Distant nodal involvement
II E	Penetration of serosa to involve adjacent organ or tissues Specify site of involvement, e.g., IIE (pancreas)
	If both nodal involvement and involvement of adjacent organs, denote stage using both a subscript (1 or 2) and E, e.g., II1E (pancreas)
IV	Disseminated extra-nodal involvement or concomitant supra-diaphragmatic nodal involvement

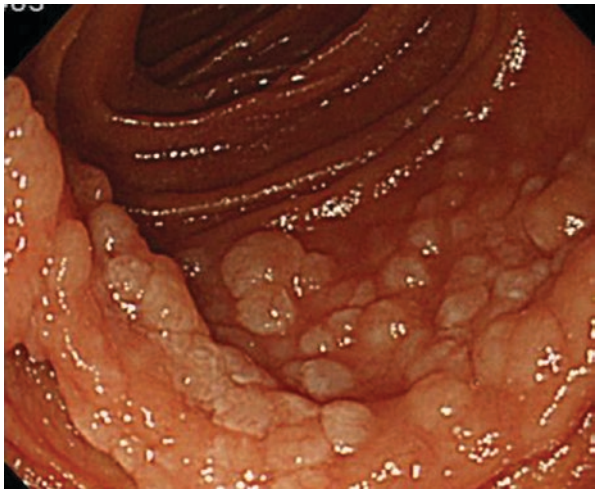

Fig 7.1 Endoscopic finding of follicular lymphoma duodenal type. The example of endoscopic finding of duodenal follicular lymphoma

whole gastrointestinal tract, although it is difficult to perform those procedure for all of our patients because of limited resources. Endoscopic finding of intestinal follicular lymphomas are multiple nodules type with white granular surface.

Any prognostic model has not been reported to be applicable to predict survival of intestinal FL such as International Prognostic Index or Follicular Lymphoma International Prognostic Index [19, 20] (Fig. 7.1).

7.4 Treatment Strategy

The standard treatment has not been established yet for early stage intestinal lymphomas. The therapeutic options such as surgery, chemotherapy, radiation therapy (RT) or either combination and watchful waiting (observation) has been performed as initial therapy for early stage intestinal FL. In the largest case report of 63 patients with early stage intestinal FL, four main treatment strategies of watch and wait, RT, rituximab monotherapy, and various chemotherapy were applied [21]. Among them, 19 patients underwent radiation therapy and have achieved 100% complete remission. Although complete remission was also achieved in the remaining therapies, RT was superior in local control. For asymptomatic patient with stage I FL, observation is acceptable because of low incidence of later intervention.

7.5 Chemotherapy and or Immunotherapy

The role of rituximab monotherapy and various regimens of chemotherapy are limited.

7.6 Radiation Therapy (Indications)

The definitive local RT, namely involved site RT (ISRT), is recommended for patients with symptomatic stage I [22–24]. The palliative treatment is applicable for patients with symptomatic stage II, because of the lower progression-free survival rate than stage I group.

7.7 Radiation Therapy (Treatment Procedures: Involved Site Radiation Therapy)

7.7.1 RT Planning

The RT planning CT should be obtained with oral and intravenous contrast media. The 4-dimensional CT is recommended, if possible, that provide the information of respiratory movement of intestinal tracts [23, 24].

7.7.2 Target Volumes

7.7.2.1 Gross Tumor Volume (GTV)

The GTV is interposed on RT planning CT with endoscopic findings.

7.7.2.2 Clinical Target Volume (CTV)

The CTV include entire duodenum wall and suspicious volumes.

The internal target volume (ITV) and planning target volume (PTV) could be contoured with at least 1 cm margin from CTV (Figs. 7.2, 7.3, and 7.4).

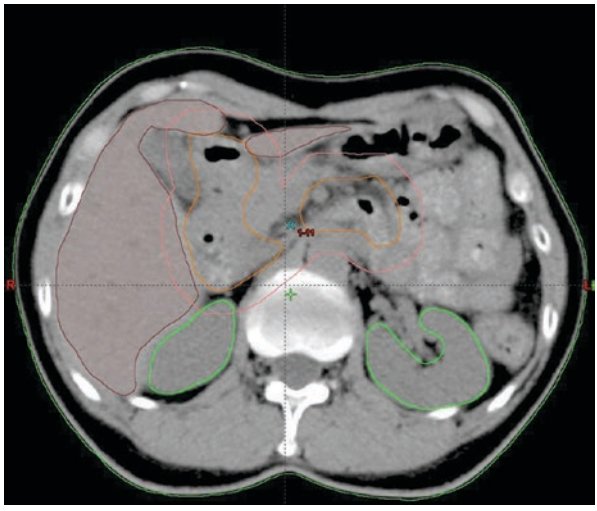

Fig 7.2 CTV (*orange line*), and PTV (*pink line*). The example of delineation of clinical/planning target volumes for stage I follicular lymphoma duodenal type

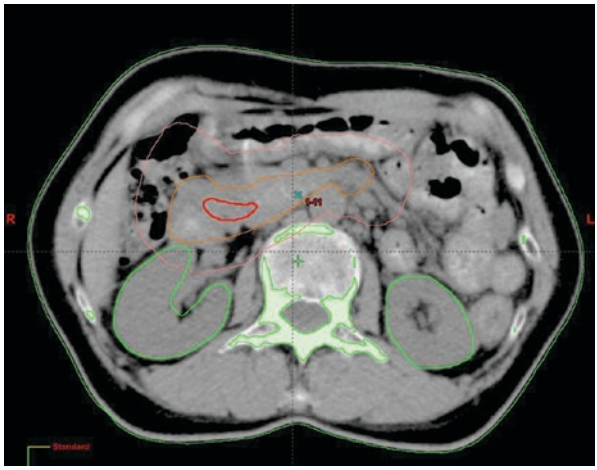

Fig 7.3 GTV (*red line*), CTV (*orange line*), and PTV (*pink line*). The example of delineation of gross tumor volume and clinical/planning target volumes for stage I follicular lymphoma duodenal type

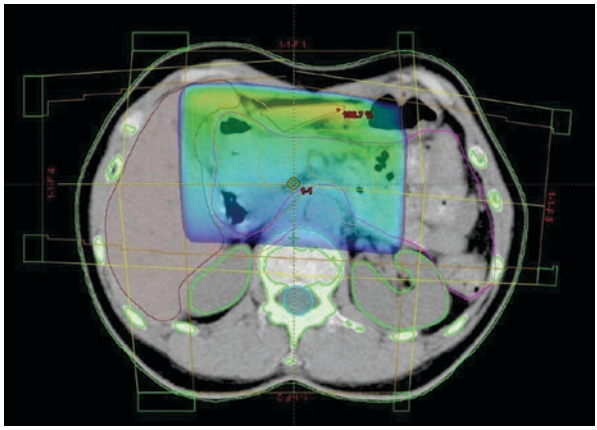

Fig 7.4 The dosimetry of 3-dimentional conformal radiation therapy for follicular lymphoma duodenal type

7.7.2.3 Radiation Delivery

The three-dimensional conformal radiation therapy or intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT) provides better dose distribution and lower dose to surrounding organs at risk such as kidneys, liver, stomach, and small bowel than 2-D planning.

7.7.2.4 Dose and Fractionation

The high local control rate of intestinal follicular lymphoma is obtained with medium dose from 20 to 36 Gy that is lower than tolerable dose of intestinal tracts. The dose of 24 Gy for intestinal FL is recommended based on the UK randomized trial for nodal FL [24].

Table 7.2 Survival data (stage I)

		n	5-year PFS(%)	Relapse free	Ref.
Austria and Germany	Watch and wait	24		22/24	[21]
	Rituximab alone	5		5/5	
	Chemotherapy	8		5/8	
	Radiation alone	19		19/19	
USA	Watch and wait	11		9/11	[22, 23]
	Surgery alone	3		6/6	
	Chemotherapy	5		4/5	
	Radiation alone	6		6/6	
	Combined	3		3/3	
Japan	Watch and wait	33	86		[7]
	Rituximab alone	29	92		
	R-CHOP like	42	97		
Japan	Radiation alone	21	76		[24]

7.8 Outcomes

7.8.1 Survival

The 5 year OS rates were reported 90% or higher with the DFS 80% and LRFS rates were 100% with local RT, respectively [7, 21, 23, 24] (Table 7.2).

7.8.2 Failure Pattern

The relapses after RT occurred in homing sites: intestine and mesenteric node. Duodenal FL express mucosal homing receptor named α4β7 that affects the relapsed site. Intestine and mesenteric lymph nodes, where the ligand named MadCAM-1 is expressed, have possibility to be relapse sites [7, 21, 23, 24].

Some cases of histological transformation were reported that indicate initial therapeutic intervention, such as ISRT [25–28].

7.9 Toxicity

The acute RT toxicities including anorexia are minor and the any late toxicities are scored as Grade 0 or limited to Grade 1 [7, 21, 23, 24].

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Primary Testicular Lymphoma

8

Keisuke Sasai

Abstract

Primary testicular lymphoma (PTL) usually occurs as a diffuse large B-cell lymphoma in elderly males. The first diagnostic and therapeutic procedure in a patient with PTL is inguinal orchiectomy. The guidelines of the International Lymphoma Radiation Oncology Group recommend rituximab combined with CHOP or more aggressive regimens as the first-line systemic treatment, with prophylactic intrathecal or intravenous methotrexate to avoid disease relapse in the CNS, the most common site of tumor recurrence. Because the testis is a sanctuary, the tumor in this organ is not responsive to systemic chemotherapy. The contralateral testis should be irradiated to prevent recurrence.

Keywords

Blood–testicular barrier • Prophylaxis of CNS relapse • R-CHOP • Radiation therapy of the contralateral testis

8.1 Introduction

Primary testicular lymphoma (PTL) is a rare disorder with several unusual characteristics. Like the central nervous system (CNS) and intraorbital area, the testis is an immunoprivileged site and is therefore not immune protected. Moreover, analogous

K. Sasai
Department of Radiation Oncology, Juntendo University, Graduate School of Medicine,
2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan
e-mail: ksasai@juntendo.ac.jp

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to the blood–brain barrier, the blood–testicular barrier diminishes the potency of chemotherapeutic agents [1]. These common features account for the similarities between lymphomas arising in the CNS and testis.

PTL accounts for 1–9% of all testicular tumors and 1% of all non-Hodgkin's lymphomas [2]. It usually manifests as a diffuse large B-cell lymphoma (DLBCL). In a survey of the Surveillance, Epidemiology, and End Results (SEER)–Medicare database in the USA, Olszewskia found that PTL accounted for 1.9% of all DLBCLs and 5.9% of extranodal DLBCLs [3]. The frequency of PTL increases with age, such that it is the most frequent testicular tumor in men over the age of 50 years [1].

A unilateral painless testicular mass is the only apparent symptom of early-stage PTL, but there may be contiguous spread to the rete testis, epididymis, spermatic cord, and, rarely, the tunica albuginea. On clinical examination of a unilateral parenchymal mass, ultrasound additionally reveals a hydrocele in 43% of patients [2, 4]. Synchronous bilateral involvement occurs in 6–10% of PTL patients [5, 6], but in 8–50%, the contralateral testis will eventually be involved during the course of the disease [1, 7, 8]. The prognosis of patients with isolated bilateral testicular involvement is similar to that of patients with stage I/II disease, such that these cases are considered to be stage I [6]. About 90% of patients with PTL are within stage I/II disease, 50–60% of them are in stage I and 20–30% in stage II [8]. The tumor usually remains confined to the scrotum, but sometimes spreads to the retroperitoneal lymph nodes.

Tumor relapse is most frequently in the CNS. Riemens et al. evaluated nine patients who had a combination of testicular and vitreo-retinal DLBCL. Seven of the patients also had concurrent CNS involvement [9]. Contralateral recurrence is frequently observed in patients without prophylactic irradiation to the initially uninvolved testis.

Given the absence of reliable randomized clinical trials, current guidelines for the treatment of PTL are based on the results of retrospective studies, phase 2 trials, and expert consensus [7, 10].

8.2 Pathology and Anatomy

8.2.1 Pathology

As a DLBCL, 80–90% of PTLs have an activated B-cell phenotype [8, 11]. In contrast to nodal and extranodal lymphomas at other sites, loss of HLA class I and II occurs very frequently in PTL [12]. In fact, Magnoli et al. suggested that DLBCLs in testis are biologically and clinically distinct entities from those in other organs [13].

The follicular lymphomas arise in the testicular regions of young adults and children [13]. They differ from adult nodal follicular lymphomas but are very similar to pediatric extranodal follicular lymphomas. Their morphology is frequently grade 3,

but the outcome of patients with these tumors is often more favorable than of those with the usual follicular lymphomas [14]. Other types of lymphomas include Burkitt lymphomas and T-cell lymphomas [15].

8.2.2 Anatomy of the Testis and Scrotum [16]

The testes are located in the scrotum and are the primary male reproductive organ. The epididymis lies along the lateral part of the posterior border of the testis. The efferent duct is the continuation of the epididymal duct and runs with the vessels and nerves through the inguinal canal to the deep inguinal ring.

The testicular capsule enclosing the testis is composed of the tunica vaginalis (visceral layer), the tunica albuginea, and the vessel-containing tunica vasculosa. The tunica albuginea is a dense membrane of white fibrous tissue. The scrotum is a cutaneous and fibromuscular sac containing the testes and the lower portions of the spermatic cords. It consists of the skin and the dartos muscle, together with the external spermatic, cremasteric, and internal spermatic fasciae. The scrotal septum is composed of all layers of the scrotal wall, except the skin.

The left and right testicular arteries arise from the anterior aspect of the aorta, slightly below the renal arteries. Each passes as part of the spermatic cord through the inguinal canal to enter the scrotum. The testicular veins enter the abdomen through the deep inguinal ring. On the right, the vein drains into the inferior vena cava, just below the level of the renal veins; on the left side, it flows into the left renal vein. Lymph vessels from the testis also run in the spermatic cord, ending in the lateral aortic and pre-aortic lymph nodes. Therefore, in testicular cancer, the regional lymph nodes are those in the vicinity of the abdominal aorta and inferior vena cava [17].

8.2.3 Blood–Testicular Barrier [18]

The blood–testicular barrier hinders the delivery of chemotherapeutic agents to the testis. It consists of the mechanical tight junctions of cells, active efflux pumps, and elements of the immune system. The barrier shares many properties with the blood–brain barrier but also differs from it. Thus, in the testis, three different cell layers comprise the physicochemical barrier, of which the Sertoli-cell layer is the most important. The barrier's efflux pumps are located in different cell types: the luminal aspect of endothelial cells expresses P-glycoprotein and the basal aspects of Sertoli and Leydig cells MRP1. In the brain, however, the physicochemical barrier is constituted mainly of endothelial cells, which also express efflux pumps on their surfaces.

As an immune-privileged site, the physicochemical barrier of the testis also blocks antibodies. The existence of the Fas-Fas ligand system is unique in the testis.

8.3 Treatment

8.3.1 Staging

The first diagnostic and therapeutic procedure in a patient with PTL is inguinal orchiectomy. Besides the standard workup for lymphomas at other sites or involving other organs, staging procedures should include routine CNS imaging, cerebrospinal fluid cytology, and flow cytometry [15]. ^{18}F-Fluoro-deoxyglucose (FDG)-PET/CT has greater sensitivity than that of conventional staging using CT alone, but it is difficult to distinguish FDG uptake in the malignant tumor from the normal physiologic activity of the testis [19].

8.3.2 Chemotherapy

The guidelines of the International Lymphoma Radiation Oncology Group (ILROG) [10] recommend rituximab combined with CHOP (R-CHOP) or more aggressive regimens and intrathecal (IT) or intravenous methotrexate (MTX) to prevent disease relapse in the CNS. Radiation therapy (RT) should be administered to the involved testis (if not resected) and to the remaining testis and scrotum because of the high risk of relapse in the contralateral testis. Patients with stage IIE disease should undergo RT of the involved abdominopelvic nodes.

In the study of Mazloom et al., patients with testicular DLBCL treated with R-CHOP, scrotal RT, and IT chemotherapy had a higher 5-year overall survival (OS) than that of those who were not treated with this regimen [20]. Over the past five decades, the OS of patients with PTL has improved gradually due to (1) the use of doxorubicin-based chemotherapy, specifically CHOP and later R-CHOP, and (2) the combined modality approach, in which prophylactic IT chemotherapy is added to scrotal RT [20].

A low CNS relapse rate among patients treated with R-CHOP without IT prophylaxis has been reported [21]. Although R-CHOP was shown to reduce the incidence of relapse of DLBCL in the CNS [5], prophylaxis using IT MTX and/or systemic high-dose MTX (HDMTX) is mandatory [22, 23]. CNS relapse, mostly parenchymal, occurs in 10–25% of patients with IT treatment alone, rendering it insufficient as a sole CNS-directed modality [15]. The systemic administration of high doses of CNS-bioavailable agents such as MTX or cytarabine may be effective in reducing the incidence of this dismal complication [2]. The British

Committee for Standards in Haematology recommended systemic HDMTX, at a dose of 3–5 g/m^2, together with folinic acid rescue, as an additional CNS-directed therapy in high-risk patients [24]. However, there is as yet no evidence to support the routine use of HDMTX.

8.4 Radiation Therapy

Although RT is frequently omitted in modern treatment strategies for DLBCL occurring at sites other than the testis, irradiation of the non-resected contralateral testis after a complete response to the combined chemotherapy of R-CHOP is mandatory.

8.4.1 Target Volume

The clinical target volume for stage I disease is the contralateral testis. Irradiation of the skin of the scrotum is unnecessary if it is not involved [1]. In stage II disease, it should also include the involved intrapelvic, paraaortic, and paracaval lymph nodes.

8.4.2 Dose

The ILROG recommends a total dose of 25–30 Gy in 1.5- to 2-Gy fractions [10]. For patients with stage II lesions, total doses of 30–36 Gy in 15–18 fractions administered to the involved site, may be necessary.

8.4.3 Radiation Therapy Techniques

Irradiation of the contralateral testis usually consists of an anterior field with an electron beam of 9–12 MeV or a photon beam of 4–6 MV with appropriate bolus [10]. Two oblique photon beams with wedges can provide good dose coverage. For patients receiving photon irradiation with oblique beams, position verification should be performed at each treatment session [1]. Figure 8.1 shows two of our representative irradiation techniques using an anterior electron beam and two oblique fields of 4-MV X-rays.

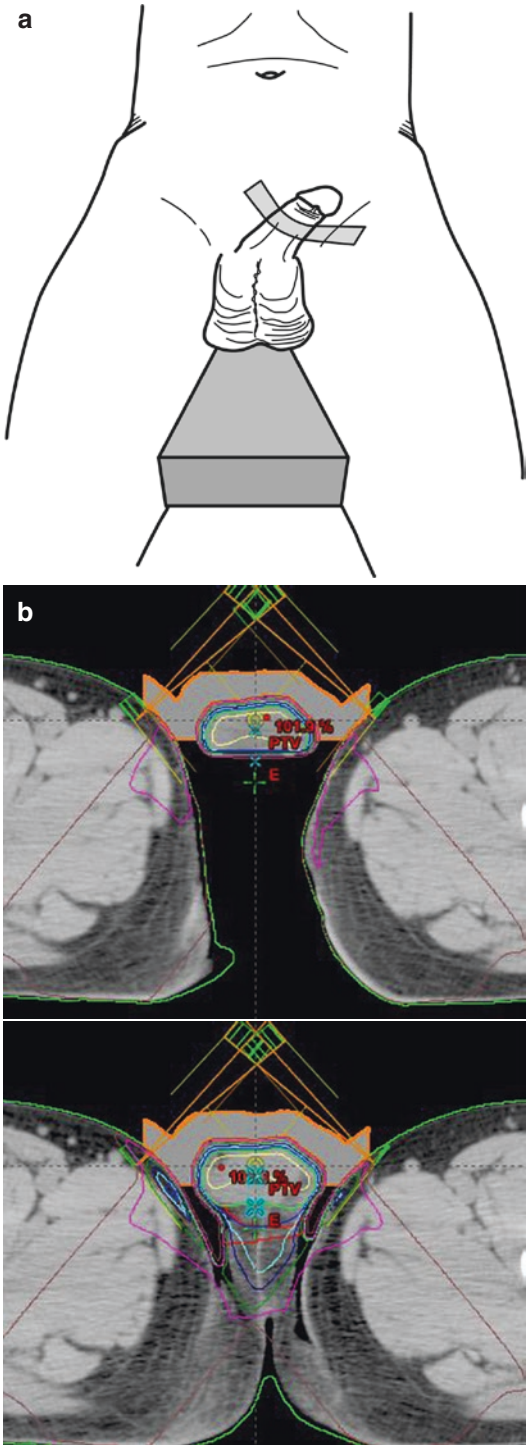

Fig. 8.1 (**a**) Patient positioning for contralateral testicular irradiation using an anterior electron beam. The penis is lifted and taped to the abdominal wall. The scrotum is fixed by placing a styrene foam block underneath it. (**b**) An example of dose distribution using two oblique photon beams with wedges

8.5 Treatment Outcome

8.5.1 Survival

The treatment results reported by the various studies are shown in Table 8.1 [7, 21, 22, 25–29]. Although 5-year OS is higher in patients with PTL than in those with nodal DLBCL, the disease often recurs long after treatment [8].

Prognostic factors include those of the International Prognostic Index, B symptoms, disease stage, anthracycline-containing combined chemotherapy, chemotherapy combined with rituximab, irradiation of the contralateral testis, age, elevated serum lactate dehydrogenase, resection of the involved testis, poor Eastern Cooperative Oncology Group (ECOG) performance status (≥2), infiltration of adjacent tissues (spermatic cord, epididymis, or scrotum), and bulky disease (tumor mass >9 cm) [8, 20, 25, 26].

Table 8.1 Reported treatment results for patients with primary testicular lymphomas

Author/year	Number of patients	Chemotherapy	Radiation	5-year OS (%)
Sasai K 1997 [29]	8 Stage IE-IV	DOX including (7 pts)	Paraaorta	45
Zucca E 2003 [25]	373	CHOP like (255 pts) IT Chemo (68 pts)	Contralateral (133 pts)	48 58 (stage I) 46 (stage II) 22 (stage III-IV)
Gundrum JD 2009 [7]	769			2.4[a] '86–'90 (76 pts) 5.0[a] '91–'95 (130 pts) 5.0[a] '96–'00 (83 pts) 5.0[a] Stage I-II (538 pts) 1.9[a] Stage III-IV (179 pts) 1.8[a] Stage unknown (52 pts)
Mazloom A 2010 [20]	75 Stage IE (34) Stage IIE (13)	DOX including (37 pts) R-CHOP (22 pts) IT-Cx (32 pts)	Scrotum (27 pts) Scrotum + others (18 pts) 30.6 Gy (24.0–56.0 Gy)	53 15.4 (15 pts treated in –'77) 56.3 (40 pts treated '77–'99) 86.6 (20 pts treated after '00)

(continued)

Table 8.1 (continued)

Author/year	Number of patients	Chemotherapy	Radiation	5-year OS (%)
Vitolo U 2011 [22]	53 stage IE (40 pts) stage IIE (13 pts)	R-CHOP (6–8 cycles) IT-Cx (50 pts)	Contralateral 24–40 Gy (47 pts) IFRT for stage II 23–45 Gy (9 pts)	85
Wang Y 2013 [26]	39	Anthracycline + (32 pts) Anthracycline − (2 pts) CNS prophylaxis (21 pts)	contralateral (1 pt) IFRT (4 pts)	47.3 (whole group) 5.3[a] Stage I-II (24 pts)
Kim J 2014 [21]	14 Stage IE (9 pts) Stage IIE (1 pt) Stage IV (4 pts)	R-CHOP (12 pts) CHOP (2 pts) No pt received IT Cx	Contralateral (12 pts) Median 32 Gy (24–36 Gy)	89 (3-year OS)
Mihaljevic B 2014 [28]	10 Stage IE (5 pts) Stage IIE (4 pts) Stage IV (1 pt)	R-CHOP	Contralateral (7 pts)	4.0[a]
Ichikawa K 2015 [27]	12 stage IE (11 pts) stage IIE (1 pt)	R-CHOP[b] (9 pts) IT-Cx (9 pts)	Contralateral (10 pts)	73 (4 years whole group) 86 (4 years CX + IT + Rx 7 pts) 50 (4 years others 5 pts)
Deng L 2015 [5]	280	CHOP[b] (223 pts) Rituximab (161 pts) IT-Cx (83 pts)	Contralateral (96 pts)	58 (whole group) 63 (stage IE-IIE) 42 (stage IIIE-IV) 68 (with Rituximab) 48 (without Rituximab) 82 (Cx + IT + RT) 52 (Cx)

pts patients, *R-CHOP* CHOP with Rituximab, *OS* overall survival rate, contralateral:contralateral testis, *IFRT* involved field radiation therapy, *RT* radiation therapy, *IT* intrathecal, *Cx* chemotherapy, *DOX* doxorubicin

[a]Median survival time (year)

[b]CHOP or CHOP like

8.5.2 Failure Patterns

Deng et al. reported that PTL has a continuous risk of relapse, with the CNS (6–16%) and contralateral testis as the most commonly involved sites [5]. Other extranodal and nodal sites of relapse have also been reported, including Waldeyer's ring (4–6%), the skin (0–36%), and the lungs, pleura, soft tissue, bone, bone marrow, and kidney [2, 20, 29]. Patient who suffer disease relapse have a very poor prognosis, as recurrence of these tumors is rarely curable [15].

Leptomeningeal and parenchymal relapses in the CNS occur in equal proportions in 20–35% of patients not treated by effective prophylaxis [15]. Based on a large study, Zucca et al. estimated that the 5- and 10-year risks of CNS relapse were 19% (95% CI, 14–25%) and 34% (95% CI, 25–46%), respectively. Only 20% of the patients with relapse in the CNS had received IT prophylaxis as part of their frontline therapy [25].

Contralateral testicular recurrence is also frequent in patients who are not treated with irradiation. A continuous risk of recurrence (15% at 3 years, 42% at 15 years) was determined in patients who did not receive RT to the contralateral testis [25]. Prophylactic RT to the contralateral testis was also associated with a better survival rate.

8.6 Toxicity

Because of the low total radiation doses typically administered for the treatment of PTL, no major sequelae, other than those caused by systemic chemotherapy, are usually observed. Testicular irradiation may cause acute dermatitis [6]. The major long-term toxicities are infertility and hypogonadism.

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Cutaneous Lymphomas

9

Naoto Shikama and Kazunari Miyazawa

Abstract

Primary cutaneous lymphoma (PCL) is the second most common type of extranodal lymphoma. PCL has different clinical behavior and prognosis than those of extranodal lymphomas arising from other sites, and requires a different pretreatment evaluation system and treatment strategy. All patients with PCL should be reviewed by a multidisciplinary team to decide an appropriate treatment strategy. PCL has three major disease entities including T-cell and natural-killer (NK)-cell lymphoma, B-cell lymphoma, and precursor hematological neoplasm. Mycosis fungoides is the most common type of cutaneous T-cell lymphoma, and its clinical behavior is indolent with slow progression. The treatment strategies of mycosis fungoides are based on a "Stage-based" approach, and "Expectant policy" is a reasonable treatment option for early stage disease. Total skin electron beam therapy (TSEBT) and adjuvant therapy may be applied for the patients with stage IB-IIB. The European Organization for Research and Treatment of Cancer proposed the technical guidelines of TSEBT. The standards of care for PCLs, other than mycosis fungoides and Sézary syndrome, have not been established because of their infrequency. The treatment strategies for each PCL subtype should be decided according to disease subtype, stage, clinical features, and patient's condition.

Keywords

Primary cutaneous lymphoma • Mycosis fungoides • Sézary syndrome • Total skin electron beam therapy • Radiotherapy

N. Shikama, M.D., Ph.D. (✉) • K. Miyazawa, M.D.
Department of Radiation Oncology, Juntendo University,
2-1-1 Hongo, Bunkyo, Tokyo 112-0012, Japan
e-mail: nshikama0525@gmail.com

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9.1 Introduction

Primary cutaneous lymphoma is the second most common type of extranodal lymphoma, with an estimated annual incidence of one per million [1–5]. The term "primary cutaneous lymphoma" refers to hematological neoplasms which are present in the skin with no evidence of extracutaneous disease at the time of diagnosis [4]. Primary cutaneous lymphoma has a significantly different clinical behavior and prognosis from those of other extranodal lymphomas arising from other sites, and requires a different treatment strategy. Primary cutaneous lymphoma includes heterogeneous disease entities, and requires each optimal treatment strategy. There were formerly some differences between the European Organization for Research and Treatment of Cancer (EORTC) classification systems for primary cutaneous lymphomas and the World Health Organization (WHO) classification, and various debate and confusion on terminology and disease entities had existed [6, 7]. These differences were resolved by representatives of both classification systems in the consensus meetings, and WHO-EORTC classification for cutaneous lymphomas has been established (Table 9.1) [4]. In the last decade, the international consensus of staging classification for cutaneous lymphoma, clinical endpoints and response criteria, and technical guidelines of total skin electron beam therapy (TSEBT) have been reported [4, 8–15]. And local therapies including topical therapy and phototherapy and novel systemic therapies including immuno-chemotherapy have been investigated [9, 10, 12, 16, 17]. In this chapter, the current standards of care and adequate radiotherapy techniques for primary cutaneous lymphomas are mainly described.

Table 9.1 WHO-EORTC* classification of cutaneous lymphomas with primary cutaneous manifestations [4]

Cutaneous T-cell and natural-killer (NK)-cell lymphomas
Mycosis fungoides
Mycosis fungoides variants and subtypes
Folliculotropic mycosis fungoides
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome
Adult T-cell leukemia/lymphoma
Primary cutaneous CD30+ lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Primary cutaneous peripheral T-cell lymphoma, unspecified
Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)
Cutaneous gamma/delta T-cell lymphoma (provisional)

Table 9.1 (continued)

Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional)
Cutaneous B-cell lymphomas
Primary cutaneous marginal zone B-cell lymphoma
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
Primary cutaneous diffuse large B-cell lymphoma, other
Intravascular large B-cell lymphoma
Precursor hematologic neoplasm
CD4+/CD56+ hematodermic neoplasm (blastic NK-cell lymphoma)

**WHO* World Health Organization, *EORTC* European Organization for Research and Treatment of Cancer

9.2 Pathology

The diagnosis and classification of primary cutaneous lymphomas should always be based on a combination of clinical features, histological findings, and immunephenotypical data [8, 16, 18]. Repeated skin biopsies are often required to achieve a confidential diagnosis [15]. It is always best to biopsy the most indurated area of skin. There are three main disease entities of primary cutaneous lymphomas including cutaneous T-cell and natural-killer (NK)-cell lymphoma, B-cell lymphoma, and precursor hematological neoplasm according to WHO-EORTC classification [4].

9.2.1 Mycosis Fungoides and Sézary Syndrome

The atypical cells are small- to medium-sized and mostly confined to the epidermis. They characteristically colonize the basal layer of the epidermis. They express CD3, CD4, CD45RO, CD8, and memory T-cell phenotype, but frequently lose the expression of CD8 and other pan T-cell antigens [4, 19]. The International Society for Cutaneous Lymphomas (ISCL) recommended the criteria for diagnosis of Sézary syndrome including the following factors: erythroderma defined as erythema covering at least 80% skin surface area, demonstration of a T-cell clone in the peripheral blood by molecular or cytogenetic methods, an absolute Sézary cell count of at least 1000 cells/mm^3, a CD4/CD8 ratio more than 10 (due to the clonal expansion of CD4+ T-cells), and loss of any or all of the T-cell antigens [4, 19, 20].

9.2.2 CD30-Positive Lymphoproliferative Disorders

Primary cutaneous anaplastic large-cell lymphoma shows dense nodular dermal infiltration of large pleomorphic, anaplastic, or immunoblastic cells. Immunephenotypically, CD30, CD4, and CD8 are expressed in most patients with various loss of pan T-cell

antigens [9, 21]. The pathological features of lymphomatoid papulosis are various and four pathological subtypes are delineated [9]. Immunephenotypically, CD30-positive tumor cells express CD4 in most patients, and CD8 and CD56 are expressed in some patients.

9.2.3 Extranodal NK/T-Cell Lymphoma, Nasal Type

Extranodal NK/T-cell lymphoma, nasal type is nearly always associated with Epstein–Barr virus, and it has small-, medium-, or large-cells with NK/T-cell, or more rarely a cytotoxic T-cell phenotype. The neoplastic cells express CD2, CD56, cytoplasmic CD3Ɛ, and cytotoxic proteins, but lose the expression of CD3 [4].

9.2.4 Primary Cutaneous B-Cell Lymphoma

Primary cutaneous marginal zone B-cell lymphoma becomes nodular to diffuse infiltrates while sparing the epidermis. The infiltrates are composed of small lymphocytes, marginal zone B-cells, lymphoplasmacytoid cells, and plasma cells admixed with small numbers of centroblast-like cells or immunoblast-like cells, and many reactive T-cells [4]. The marginal zone B-cells express CD20, CD79a, and bcl-2, but lose the expression of CD5, CD10, and bcl-6. Primary cutaneous follicle center lymphoma consists of centrocytes, relatively few centroblasts, and many reactive T-cells [4]. CD20, CD79a, and bcl-6 are expressed, and staining for CD5 and CD43 is negative.

9.3 Lymphoma Subtype for Radiation Therapy

9.3.1 Mycosis Fungoides and Variant Subtypes, and Sézary Syndrome

Mycosis fungoides is the most common type of cutaneous T-cell lymphomas and accounts for 50% of them [4]. The clinical behavior is indolent with slow progression [17]. The median time from symptoms' onset to diagnosis is approximately 4 years, but exceeds four decades in some patients [14, 19]. The median age at diagnosis is the mid-50s, and men are affected twice as often as women [17, 19]. Folliculotropic mycosis fungoides is a variant type characterized by the presence of folliculotropic infiltrates. Most patients show mucinous degeneration of the hair follicles, and secondary bacterial infections are frequently observed. Pagetoid reticulosis is a variant type characterized by the presence of localized patches or plaques with an intraepidermal proliferation of T-cell neoplasms [4]. Sézary syndrome is defined as a leukemic condition of cutaneous T-cell lymphoma associated with erythroderma, and accounts for 5% of cutaneous T-cell lymphoma [19, 22]. It has an aggressive clinical behavior, and the treatment goals are long-term disease control and prompt symptom relief.

9.3.2 Primary Cutaneous CD30-Positive Lymphoproliferative Disorders

Primary cutaneous CD30-positive lymphoproliferative disorders are the second most common conditions of cutaneous T-cell lymphomas, and include primary cutaneous anaplastic large-cell lymphoma and lymphomatoid papulosis [9]. They have an excellent prognosis, and half of them show spontaneous regression. The patients with lymphomatoid papulosis have a risk of second cutaneous or nodal lymphoid malignancies, including mycosis fungoides, cutaneous and nodal anaplastic large-cell lymphomas, and Hodgkin lymphoma [23].

9.3.3 Subcutaneous Panniculitis-Like T-Cell Lymphoma

Subcutaneous panniculitis-like T-cell lymphoma with alpha/beta T-cell phenotype and no evidence of hemophagocytic syndrome has an excellent prognosis [8]. A hemophagocytic syndrome is associated with extremely aggressive clinical behavior, and the patients with hemophagocytic syndrome should be treated with intensive treatment [8].

9.3.4 Extranodal NK/T-Cell Lymphoma, Nasal Type

Extranodal NK/T-cell lymphoma, nasal type has an aggressive clinical behavior and poor survival rate [8]. Although intensive multi-agent chemotherapy might be applied, it often indicates resistance to chemotherapy. High-dose radiotherapy to the primary site might be required for good tumor control.

9.3.5 Primary Cutaneous Peripheral T-Cell Lymphoma, Unspecified

Primary cutaneous peripheral T-cell lymphoma, unspecified has three provisional subtypes, and they have generally aggressive clinical behavior and poor survival rate [8]. Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma and cutaneous gamma/delta T-cell lymphoma are progressive diseases, and require intensive treatment [1]. On the other hand, primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma is an exception, and a solitary lesion has an excellent outcome after local radiotherapy or surgical excision [1].

9.3.6 Primary Cutaneous B-Cell Lymphoma

Primary cutaneous marginal zone B-cell lymphoma and primary cutaneous follicle center lymphoma have indolent behavior with an excellent treatment outcome [4]. Primary cutaneous diffuse large B-cell lymphoma, leg type has an unfavorable prognosis, and requires intensive treatment.

9.4 Pretreatment Evaluation and Staging

Staging procedures including complete physical examination, complete blood count, differential white blood cell count, serum biochemistry, and appropriate imaging techniques should be performed for all patients, and bone marrow aspiration and biopsy might be required for the selected patients with advanced disease [8, 10, 16]. Standardized photographs are recommended to document the appearance of skin lesions at the time of baseline and at the time of disease progression [10]. Imaging with computed tomography (CT) is routinely undertaken for patients with mycosis fungoides T3-4 disease to assess visceral and nodal involvement, but is less valuable for patients with T1-2 disease [15, 17]. Positron emission tomography (PET) can increase the sensitivity of detection of involved lymph nodes and is useful to evaluate treatment response in patients with advanced mycosis fungoides [17].

ISCL and EORTC revised the staging system and classification for mycosis fungoides and Sézary syndrome in 2007 [16]. The ISCL and EORTC staging system should be applied specifically to mycosis fungoides and Sézary syndrome (Table 9.2). T1 category for mycosis fungoides is defined as limited patches, papules, and/or plaques covering 10% or less skin surface area, T2 as patches, papules, and/or plaques covering 10% or more skin surface area, T3 as one or more tumors which are 1 cm diameter or larger, and T4 as condition of erythema covering 80% or more skin surface area [16]. N classification is diagnosed for abnormal peripheral lymph nodes, M classification for visceral involvement, and B rating for abnormal tumor cells in the peripheral blood. Total body skin scoring should be performed for evaluation of initial skin lesions and assessment of response [10]. The most widely used methods for skin scoring are the Severity Weighted Assessment Tool (SWAT) and modified-SWAT [22, 24]. ISCL and EORTC proposed a separate TNM classification for the primary cutaneous T-cell lymphomas other than mycosis fungoides and Sézary syndrome [11].

Table 9.2 The International Society for Cutaneous Lymphomas (ISCL) and EORTC revision to the staging of mycosis fungoides and Sézary syndrome [16]

Clinical stage	T	N	M	B
IA	1	0	0	0, 1
IB	2	0	0	0, 1
IIA	1, 2	1, 2	0	0, 1
IIB	3	0–2	0	0, 1
III	4	0–2	0	0, 1
IIIA	4	0–2	0	0
IIIB	4	0–2	0	1
IVA_1	1–4	0–2	0	2
IVA_2	1–4	3	0	0–2
IVB	1–4	0–3	1	0–2

9.5 Prognostic Factors

For patients with mycosis fungoides and Sézary syndrome, four risk factors, including stage IV, age over 60 years, large-cell transformation, and elevated serum lactate dehydrogenase level, are independent prognostic factors for poor survival [3, 13]. Combining these four factors in a prognostic index model can identify the three different risk groups, and the 5-year overall survival rates of the low-risk group (zero to one factor) is 68%, that of the intermediate-risk group (two factors) is 44%, and that of the high-risk group (three to four factors) is 28%. Other poor prognostic factors include folliculotropic type, elevated soluble interleukin-2 receptor level, and T-cell clonality in the skin and peripheral blood [22, 23, 25]. Advanced stage, elevated beta-2 microglobulin, and elevated lactate dehydrogenase level are associated with the risk of large-cell transformation [1, 22].

Poor prognostic factors of cutaneous B-cell lymphoma include unfavorable histology (diffuse large cell type or immunoblastic large cell type) and unfavorable skin sites (trunk, legs, disseminated) [26, 27]. Poor prognostic factors of indolent cutaneous B-cell lymphoma consist of elevated serum lactate dehydrogenase level, morphology of the lesion (non-nodular lesion), and multiple lesions (>1) [28].

9.6 Treatment Strategy

Reliable histological diagnosis and complete pretreatment staging evaluation are essential, and all patients should be reviewed by a multidisciplinary team to decide an appropriate treatment strategy [15].

9.6.1 Mycosis Fungoides

Most mycosis fungoides are low-grade malignancies with long survival time, but the patients with advanced diseases and aggressive variant subtypes show poor prognosis [3, 22]. The treatment strategies of mycosis fungoides are based on a “Stage-based” approach [3]. Patients with limited patches or plaques (stage IA; T1N0M0B0-1) have a normal life expectancy, and “Expectant policy” is a legitimate treatment option [1, 14, 15]. Over-aggressive therapy with multiagent chemotherapy and/or high-dose radiotherapy should be avoided [1]. For the patients with stage IA, skin-directed therapy including topical corticosteroids, topical chemotherapy, topical retinoid, phototherapy (psoralen-ultraviolet A light therapy [PUVA]), and local radiotherapy are recommended [1, 14, 15]. If a skin-directed therapy fails to obtain an adequate response, a rotation to other skin-directed therapies should be attempted before aggressive systemic therapies or TSEBT. The patients with stage IB (T2N0M0B0-1) and IIA

(T1-2N1-2M0B0-1), the folliculotropic variant, and large-cell transformation require more aggressive treatment, but skin-direct therapies including topical corticosteroids, topical chemotherapy, phototherapy, and local radiotherapy should be administrated rather than systemic therapies [1, 14, 15]. For patients with rapidly progressive generalized or thickened plaque lesions, TSEBT might be considered as the initial therapy rather than skin-directed therapy alone. TSEBT followed by adjuvant therapy including skin-directed therapy and extracorporeal photopheresis (ECP) produces a significant benefit of relapse-free survival, but not overall survival [1, 12, 18, 23]. For the patients with stage IIB (T3N0-2M0B0-1) and stage III (T4N0-2M0B0-1), PUVA plus alpha-interferon, TSEBT plus local radiotherapy, and retinoid plus alpha-interferon are recommended [1, 14].

Repeated TSEBT is an optional salvaged treatment for the selected patients with relapsed diseases after standard-dose TSEBT [29, 30]. The following eligibility criteria for second-course TSEBT are the initial response to TSEBT, a long disease-free interval from the initial therapy, exhaustion of other treatment approaches, and diffuse skin involvement [31].

9.6.2 Sézary Syndrome

Several retrospective studies reported that combination therapy with TSEBT and ECP and/or multi-agent chemotherapy produced favorable treatment outcomes [8, 17, 18]. European Society for Medical Oncology guidelines recommended ECP and/or other systemic approaches for Sézary syndrome [3, 8]. Many systemic therapeutic regimens, including cytotoxic drugs and novel molecular target therapies, have been investigated [3].

9.6.3 Cutaneous CD30-Positive Lymphoproliferative Disorders

EORTC, ISCL, and United States Cutaneous Lymphoma Consortium (USCLC) reported consensus statements for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders [9]. Surgical excision and radiotherapy are most common and best documented therapies for solitary or localized cutaneous anaplastic large-cell lymphoma [2, 9]. Spontaneous regression of cutaneous lesion has been observed in about 40% of patients with cutaneous anaplastic large-cell lymphoma, and patients should be informed that the outcome after spontaneous regression of initial relapse tumors is excellent [15]. Chemotherapy may be used in patients with multifocal lesions and relapsed diseases. Topical steroids, phototherapy, and low-dose methotrexate are most common treatments for lymphomatoid papulosis [8, 9, 15]. For large lymphomatoid papulosis lesion, which persists for months, surgical excision or local radiotherapy might be recommended as an alternative approach to a wait for spontaneous regression [21, 23].

9.6.4 Subcutaneous Panniculitis-Like T-Cell Lymphoma

A solitary lesion of subcutaneous panniculitis-like T-cell lymphoma with no evidence of hemophagocytic syndrome might be treated with local radiotherapy alone [8]. A lesion with hemophagocytic syndrome has an aggressive clinical behavior, and it should be treated with intensive multi-agent chemotherapy. High-risk patients with hemophagocytic syndrome have generally been treated with anthracycline-based chemotherapy and radiotherapy [4, 15].

9.6.5 Extranodal NK/T-Cell Lymphoma, Nasal Type

Extranodal NK/T-cell lymphoma, nasal type has a chemotherapy-resistant behavior, and high-dose local radiotherapy is the first choice for the localized lesion [8]. The patients with advanced disease might be treated with multi-agent chemotherapy including platinum-based regimens with or without local radiotherapy; however, the treatment outcome is disappointing [4, 15, 32].

9.6.6 Cutaneous B-Cell Lymphoma

The ISCL and EORTC reported the consensus statements for the management of the three subtypes of cutaneous B-cell lymphoma [8]. Primary cutaneous marginal zone B-cell lymphoma and primary cutaneous follicle center lymphoma are indolent types. Local radiotherapy or surgical excision might be chosen as the first-line therapy for the patients with localized and solitary lesion. Wait-and-see policy, local radiotherapy, rituximab, or single agent chemotherapy might be selected for the patients with multifocal lesions [4, 8, 33, 34]. Interferon alpha or anthracycline-based chemotherapy might be suggested as alternative therapies [4]. Primary cutaneous diffuse large B-cell lymphoma, leg type has an aggressive behavior, and multi-agent aggressive chemotherapy and/or local radiotherapy might be performed. Rituximab and/or local radiotherapy will be suggested as alternative therapies [8].

9.7 Radiation Therapy

9.7.1 Radiotherapy Techniques of Local Radiotherapy

9.7.1.1 Planning CT

Planning CT is essential to obtain an appropriate dose distribution. The radiopacity marker is useful to grasp the tumor extension in CT images.

9.7.1.2 Gross Tumor Volume (GTV)

GTV is defined as a visible and palpable lesion. For tumor lesions, evaluation using CT and/or magnetic resonance image (MRI) is required.

9.7.1.3 Clinical Target Volume (CTV), Planning Target Volume (PTV), and Radiation Field

CTV for patients with patch and/or plaque disease should cover the epidermis and dermis [12, 23]. The thickness of the epidermis and dermis varies from a minimum of approximately 2 mm at the trunk to a maximum of approximately 4.5 mm at the hands and soles of the feet. Local radiotherapy for cutaneous lymphoma is based on involved-site radiotherapy (ISRT) [35]. No prophylactic regional node irradiation is required for the majority of primary cutaneous lymphoma. PTV could be considered according to the fixation, reproducibility, and physiological motion. The lateral field margin of local radiotherapy of curative intent can be limited 2–3 cm beyond GTV [3, 23, 34]. For the palliative radiotherapy, the visible lesion with a margin of 1–2 cm of surrounding healthy-looking skin might be covered [34, 36].

9.7.2 Dose of Local Radiotherapy

Appropriate electron beam energy should be selected for the thickness of the patch and plaque lesions, and photon beams might be considered for tumor lesions. A 0.5–1 cm tissue equivalent plastic plate (bolus) is used daily to prescribe 80–90% iso-dose line to cover each lesion [3].

9.7.2.1 Mycosis Fungoides

Dose-response relationship has been obtained, and the optimal radiation dose of curative intent for mycosis fungoides is higher than 30 Gy in 1.2–2 Gy per fraction [1, 3, 37]. The standard-dose radiotherapy 31–36 Gy have a trend toward a higher overall response rate and longer event-free survival rates comparing with lower-dose regimens [1, 38]. And also radiotherapy is useful for palliative therapy. Although the clinical response after 4 Gy in two fractions is unacceptable and the remission time is very short for the symptomatic mycosis fungoides, symptom relief after 8 Gy in two fractions is favorable with a complete response rate over 90% [29, 34, 36]. A single fraction of 7–8 Gy produces excellent palliative effects with complete response rate of 94%, and the mean time for relapse is around 9 months [39].

9.7.2.2 Primary Cutaneous CD30-Positive Lymphoproliferative Disorders

EORTC, ISCL, and USCLC recommended that local radiotherapy of 40 Gy in 20 fractions was applied as first-line monotherapy for primary cutaneous anaplastic large cell lymphoma [9, 21]. On the other hand, the National Comprehensive Cancer Network (NCCN) recommended a total dose of 30–36 Gy for primary cutaneous anaplastic large cell lymphoma [35].

9.7.2.3 Subcutaneous Panniculitis-Like T-Cell Lymphoma

Although there is little information on the appropriate radiation dose for subcutaneous panniculitis-like T-cell lymphoma, the International Lymphoma Radiation Oncology Group (ILROG) recommended high-dose radiotherapy more than 40 Gy [34].

9.7.2.4 Extranodal NK/T-Cell Lymphoma, Nasal Type

The NCCN recommended a radiation dose of 45–60 Gy when combined therapy including chemotherapy and radiotherapy might be applied [35]. ILROG recommended that 50 Gy to the initial lesion followed by boost irradiation of 5–10 Gy to residual lesion might be applied [34].

9.7.2.5 Primary Cutaneous Peripheral T-Cell Lymphoma, Unspecified

The NCCN recommended that a radiation dose of 30–36 Gy might be used for consolidation radiotherapy, and 40–50 Gy might be used for the patients who do not achieve a complete response [35]. The ILROG recommended a radiation dose of 24–30 Gy for the primary cutaneous gamma/delta T-cell lymphoma [34].

9.7.2.6 Cutaneous B-Cell Lymphoma

A total dose of 24–30.6 Gy for cutaneous marginal zone B-cell lymphoma and primary cutaneous follicle center lymphoma has been recommended [33–35]. Symptomatic relief after a low-dose palliative radiotherapy of 4 Gy in two fractions is comfortable for the patients with these indolent lymphomas [34–36]. For the patients with primary cutaneous diffuse large B-cell lymphoma, leg type, total dose of 30–40 Gy is applied for consolidation after chemotherapy, and the patients with partial response after chemotherapy require 40–50 Gy [34, 35].

9.7.3 Radiotherapy Techniques of Total Skin Electron Beam Therapy (TSERT)

The EORTC proposed the technical consensus guidelines of TSEBT for mycosis fungoides [12]. And some other technical reports and review articles are available to optimize the clinical practice in each institute [3, 29, 40–43].

9.7.3.1 Target Volume of TSEBT

CTV for patients with patch and plaque lesions should include epidermis, adnexal structures, and the dermis [12, 23]. For the patients with tumor lesions with thickness of more than 5 mm and infiltrative lesions, CT and MRI are useful to evaluate the depth of lesions.

9.7.3.2 Treatment Schedule and Dose of TSEBT

EORTC recommended a total dose of 31–36 Gy prescribed to the skin surface to produce a dose of at least 26 Gy at a depth of 4 mm in trunk skin along the central axis [12]. Twenty percent iso-dose line should be within 20 mm from the skin surface to minimize dose to underlying structures. Two Gy will be given to the entire skin surface over the course of a 2-day treatment cycle [23]. This treatment cycle repeats for 4 days per week for a total of 8–9 weeks with a 1-week break, and a total dose of 32–36 Gy is given to the skin surface over 9–10 weeks. A small fraction size of less than 1.2 Gy per day does not compromise effectiveness, but a large fraction size more than 2 Gy leads to late adverse effects [12]. Total radiation dose less than

30 Gy have a trend to lower overall response rate and shorter event-free survival [38]. Although the short-course TSEBT of 30 Gy in 20 fractions over 5 weeks produces acceptable toxicities and reliable effects, the short-course regimen is under investigation [43]. Low-dose TSEBT regimens (e.g., 10 Gy in 1 Gy over 12 days) are well-tolerated and achieve short-term palliation [25, 38].

9.7.3.3 TSEBT Delivery Techniques

Three TSEBT delivery techniques, which include large electron field techniques, rotation techniques, and patient's shift during irradiation, correspond with the EORTC recommendations [3, 40]. The dual-large field electron beam techniques have been applied in many institutes, and the radial dose homogeneity can be obtained even in a medium sized radiotherapy room with a source-to-surface distance of approximately 4 m [3, 12, 23]. Dose inhomogeneity in the air at the source-to-surface distance should be less than 10% within vertical and lateral dimensions [12]. Short treatment distance may require the use of beam-scattering devices, but these devices increase photon contamination. The total dose to bone marrow from photon contamination should be less than 0.7 Gy [12]. The beam-scattering devices using lucite plate attenuate the electron energy from the nominal 6 MeV to approximately 4 MeV at the treatment source-to-surface distance [42]. The beam-scattering devices are placed as close as possible to the patient surface in order to degrade and further scatter the electrons [3]. Electron beam energy should be decided after the actual measurement using phantom and radiographic film [42]. A combination of low-energy electron beams and more penetrating high-energy beams will be required to achieve appropriate dose coverage [12]. The heterogeneity of the dose within the main target can be minimized by using supplemental regional patch irradiations to the low-dose areas to compensate. The dose rates range from 0.2 Gy per minute to 1 Gy per minute depending on the source-to-surface distance [40]. The treatment time affects an appropriate patient positioning during irradiation [40]. Support devices might be useful to keep the patient in the same position during irradiation.

Patients should be positioned to maximize unfolding of skin to improve dose homogeneity [12]. Keeping the correct orientation toward the beam, setting the joints in the limbs at appropriately large angles, and slightly bending the trunk and hips to expose folds in the lower trunk are essential. In total, there are six treatment positions, namely antero-posterior, right anterior oblique, left posterior oblique, postero-anterior, left anterior oblique, and right posterior oblique positions [12, 23, 34]. Each treatment position is treated with both upper and lower fields to improve dose homogeneity in the vertical dimension of dual-large field electron beams. Routine measurements of the heterogeneity of TSEBT are essential to monitor the low-dose and high-dose areas [12]. The soles of feet, vertex of head, perineum, trunk wrinkles, medial thighs, and infra-mammary regions are low-dose areas which require supplemental regional patch irradiation. Conversely, the hands, dorsal sites of the feet, and dorsal penis may be overdosed and require shielding to limit the dose to less than 36 Gy [23].

9.7.3.4 Supplemental Regional Patch Irradiation

The perineum, vertex of head, and the soles of the feet are low-dose areas, and supplemental regional patch irradiation is required. Other potentially low-dose areas or "Shadowed areas" include upper medial thighs, buttocks-thighs, inframammary folds, trunk wrinkles, and the flatter regions of the face and trunk [23, 34, 40]. Careful unfolding of skin with the use of tape, netting, bras, expanded polystyrene wedges, and extreme positioning can minimize patch irradiation for low-dose areas. The supplemental regional patch irradiation is transmitted through tissue equivalent bolus. At the Yale-New Haven Hospital, the supplemental regional patch irradiation to the perineum of 1 Gy per day is applied during the first 9 and last 9 treatment days, and that to the soles of feet of 1 Gy per day is applied during the first 7 and last 7 treatment days [23, 42].

9.7.3.5 Boost Irradiation for Tumor Lesions

Tumor lesions with a thickness of more than 5 mm require the supplemental boost irradiation to cover the target with an appropriate dose. Fields require a minimal margin, and higher-energy electron beams are used [23]. The supplemental dose should be less than 20 Gy, administered in 10–15 fractions. The early use of supplemental boost irradiation for tumor lesions will lead to appropriate dose distribution of TSEBT. For the patients with symptomatic lesions, boost irradiation before TSEBT might be useful for symptom relief, and a local radiation field of 4–6 Gy is given 1–2 weeks before the start of TSEBT [12].

9.7.3.6 Shielding

The high-dose area around the risk organs should be shielded to avoid severe adverse events. The eye globe should not receive more than 15% of the prescribed dose [12]. At the Yale-New Haven Hospital, the external eye shields are applied at the first 11 cycles, and the internal eye shields are applied at the last 7 cycles [23, 42]. The lip shield is applied at the first 1–4 cycles. The hand and fingernails shields are required to avoid the high-dose which leads to a decline in quality of life. The lead mitts for hands are used every other cycle (cycles 1, 3, 5, 7, and 9). The dorsal sites of the feet require shields during cycles 1–3, 5, 7, 9, 11, 13, 15, 17, and 18. The dorsal penis shields are used with perineum boost irradiation only. In some patients, ears and ankles are overdosed and require shielding [23].

9.8 Outcomes

9.8.1 Mycosis Fungoides and Sézary Syndrome

The 10-year overall survival rate of patients with limited plaque disease is 80%, that of patients with generalized plaques is 45%, and that of patients with tumor is 25% [1, 4, 17, 31]. After the local radiotherapy for the solitary lesion, the 10-year relapse-free rates are approximately 50–70% [23, 29, 44]. After TSEBT

for extensive patch and plaque lesions (stage IB; T2N0M0B0-1), the 10-year relapse-free survival rates are only 10–20% [23, 29]. The patients with visceral involvement have poor prognosis, and the median survival is less than 2 years [1]. Most patients with Sézary syndrome dies of opportunistic infections which are due to immunosuppression [4, 38].

In 2011, the consensus statement of response criteria in mycosis fungoides and Sézary syndrome was reported by ISCL, USCLC, and EORTC [10]. For the solitary lesion of mycosis fungoides, the mean overall duration of response to local radiotherapy of 30.6–36 Gy in 17–20 fractions ranges from 24 to 42 months [44]. The rates of in-field relapses range from 0 to 25%, and that of outside relapses of radiation field range from 0 to 33%. Complete response rates after TSEBT are approximately 90% for patients with patch and plaque lesions and approximately 70% for patients with erythroderma (T4N0-2M0B0-1, stage III) [14, 23]. However, more than half of them demonstrated skin relapse within one year after treatment [38].

Multiple-course TSEBT will be an optional treatment for selected patients [29, 31]. The salvage TSEBT of 23.5 Gy after the initial TSEBT produces complete response in 40% of patients and partial response in 60% of patients [31]. The patients with partial response develop the systemic disease, and the interval from the second course of TSEBT to death ranges from 2 to 66 months. Low-dose TSEBT of 12 Gy in 12 fractions over 3 weeks produces reliable and rapid reduction of disease burden, but the median duration of clinical benefits is 17 months [30]. For the symptomatic mycosis fungoides, the clinical response after palliative local radiotherapy of 4 Gy in two fractions is only 30%. The clinical response after 8 Gy in two fractions is more than 90% [36]. The size and thickness of the lesions don't affect the clinical response rates.

9.8.2 Primary Cutaneous CD30-Positive Lymphoproliferative Disorders

The 5- and 10-year overall survival rates of patients with primary cutaneous anaplastic large cell lymphoma are 83% and 78%, respectively [21]. After local radiotherapy for patients with solitary lesion of primary cutaneous anaplastic large cell lymphoma, the 5- and 10-year disease-specific survival rates are 95% and 90%, respectively [4, 23]. Although local radiotherapy or surgical excision is applied for localized lesion as first-line monotherapy, relapse after local therapy occurs in approximately 40% of patients [9]. Local relapses in the skin are not associated with worsened prognosis. On the other hand, spontaneous regression of tumor has been observed in about 40% of patients. Lymphomatoid papulosis has an excellent prognosis with a 5-year overall survival rate of 98–100% [4, 23]. Only 4% of patients with lymphomatoid papulosis develop a systemic disease, and only 2% of patients died of systemic disease with a median follow-up period of 6 years [4, 21].

9.8.3 Subcutaneous Panniculitis-Like T-Cell Lymphoma

The 5-year overall survival rate of subcutaneous panniculitis-like T-cell lymphoma may be more than 80% [4]. The 5-year overall survival rate of patients with and without hemophagocytic syndrome are 46% and 91%, respectively [8].

9.8.4 Extranodal NK/T-Cell Lymphoma, Nasal Type

The extranodal NK/T-cell lymphoma, nasal type has an aggressive behavior. A median survival of patients with cutaneous lesion alone is 27 months, and that of patients with cutaneous and extracutaneous lesions is only 5 months [4].

9.8.5 Primary Cutaneous Peripheral T-Cell Lymphoma, Unspecified

The prognosis of primary cutaneous peripheral T-cell lymphoma, unspecified is disappointing with 5-year overall survival rate of 16% [4]. A median survival time is 32 months in patients with primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma (provisional entity) [4]. It trends to disseminate to other visceral sites including lung, testis, and central nervous system. Most patients with cutaneous gamma/delta T-cell lymphoma (provisional entity) have aggressive disease resistance to multi-agent chemotherapy and radiotherapy, and the median survival time is only 15 months [4]. Patients with primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional entity) have a relatively favorable prognosis with 5-year overall survival rate of 75% [4].

9.8.6 Cutaneous B-Cell Lymphoma

Primary cutaneous marginal zone B-cell lymphoma has risk of relapse compared with gastric marginal zone B-cell lymphoma [33]. After local radiotherapy, half of the patients with cutaneous marginal zone B-cell lymphoma developed relapse in other skin sites, which are outside of the radiation field [33]. Although the 10-year progression-free survival rate is approximately 50%, the 5-year overall survival rate is almost 100% because of effective salvage therapy and indolent nature [4]. Cutaneous relapses after radiotherapy occur in 20% of patients with primary cutaneous follicle center lymphoma; however, the 5-year overall survival rate is more than 95% [4]. According to the prognostic index of indolent cutaneous B-cell lymphoma including elevated serum lactate dehydrogenase, morphology, and number of lesions, the low-risk group without risk factors has a 5-year progression-free survival rate of 91%, the intermediate-risk group with one risk factor has that of 64%, and the high-risk group with two or three risk factors has that of 48%,

respectively [27, 28]. Primary cutaneous diffuse large B-cell lymphoma, leg type has an unfavorable prognosis, and the 5-year overall survival rate after systemic chemotherapy and/or local radiotherapy is approximately 26–55% [4, 27, 45].

In case of palliative radiotherapy for indolent cutaneous B-cell lymphoma, the clinical response rate after the low-dose radiotherapy of 4 Gy in two fractions is more than 80% [35, 36]. The clinical response after radiotherapy is obtained within 1 month, and its duration is approximately 6 months. The size and thickness of the lesion don't affect the response rate. The low-dose radiotherapy of 4 Gy in two fractions can be repeated as needed.

9.9 Toxicity

9.9.1 Acute Toxicities

TSEBT is well tolerated in the majority of patients. Mild or moderate general fatigue is observed in 38–98% of patients, grade 1–2 skin reaction including pruritus, hyperpigmentation, edema, and erythema in 47–95%, alopecia in 66–95%, xerosis in 58%, nail loss in 13–16%, and problems with temperature regulation in 7% [3, 18, 23, 38, 43]. The most uncomfortable adverse effects during treatment are edema of the hands and feet in 26–50% of patients, and bullae in the feet are shown in 19% of patients (Fig. 9.1) [18, 23, 43]. Skin infection is shown in 31% of patients, and cutaneous abscess is rarely observed during treatment [43]. These symptoms

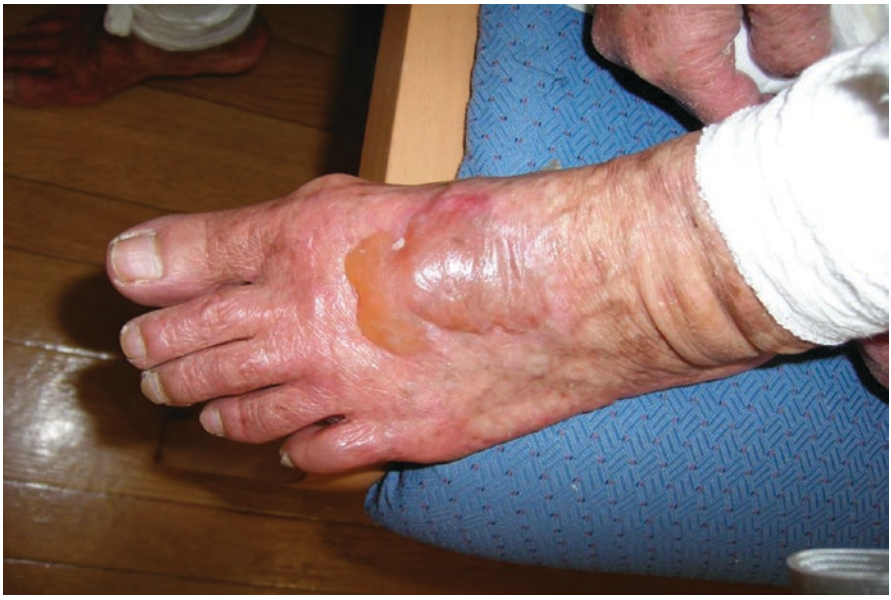

Fig. 9.1 Bullae in feet were observed during the total skin electron beam therapy

are nearly always temporary and mostly ameliorate after 2 or 3 weeks [29]. Rare acute adverse effects after TSEBT include nasal bleeding and parotiditis [23, 43].

9.9.2 Late Toxicities

Long-term adverse effects after TSEBT are typically mild, and may include permanent nail dystrophy, xerosis, telangiectasia, hyperpigmentation, hyperkeratosis, partial scalp alopecia, and fingertip dysesthesia [23, 29, 38]. Hair typically returns, but the color and texture of the hair may be different when it regrows [3, 29]. Nails might be brisk, and edema of hands and feet will be observed. Uncommon adverse effects include blisters on the fingers and feet, anhidrosis, skin infection, minor parotitis, gynecomastia, and corneal abrasion due to internal eye shield [3]. Young patients should be thoroughly counseled regarding risks of gonadal toxicity. The safety of multiple-course TSEBT has been reported. When an interval between two courses of TSEBT is sufficiently long, two courses TSEBT of total dose 56 Gy is feasible with mild toxicities including erythema, edema, alopecia, and dry skin [31]. Both local radiotherapy and TSEBT are associated with risk of development of squamous cell carcinoma, basal cell carcinoma, and malignant melanoma within the radiation field [18, 23, 44]. Benign secondary neoplasms including diffuse lipoma and eccrine poroma have been reported [29].

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