Role of radiation therapy in localised non-Hodgkin's lymphomas

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Introduction

The majority of patients with non-Hodgkin's lymphoma (NHL) present with advanced stage disease. However, localised disease is not uncommon. The clinical evaluation of the International Lymphoma Study Group Classification Project showed that more than 30% of all NHL present with localised disease (Ann Arbor stages I and II) [1]. Of 1403 cases collected from nine institutions worldwide, 33% of patients with follicular lymphomas and 51% of patients with diffuse large B-cell lymphomas presented with stage I–II disease [1]. In marginal zone lymphomas of extranodal type (MALT), stages I and II accounted for 66% of new cases. In other disease entities, such as mantle cell lymphoma (19%) or peripheral T-cell lymphoma (18%), stage I–II disease was less common, while in primary mediastinal lymphoma two thirds, (66%) of patients presented with disease limited to the chest. Radiation therapy is an extremely effective local treatment for lymphoma. However, as a local therapy, it has no curative potential in the presence of systemic disease. Its ability to cure is contingent upon the accurate identification of localised disease. Nonetheless, its ability to provide local control remains a powerful weapon in the management of all lymphomas. Local control with low to moderate doses of radiation (30–45 Gy) is achieved in 70–95% of patients [2]. Modern chemotherapy is an extremely effective treatment for lymphoma, but its curative potential falls short of 100% in diffuse large B-cell lymphoma, and there is no evidence for cure in follicular and other indolent lymphomas. Prior to the 1970s, radiation therapy was a standard form of management of lymphoma. The trials conducted in the 1970s and the1980s studied the role of chemotherapy in the management of localised lymphoma, and those conducted in the 1990s questioned the role of radiation therapy in diffuse large lymphomas treated with chemotherapy. Regrettably, the prospective trials performed to date do not solve the question of the optimal use of these two main treatment modalities. While it is accepted that doxorubicin-based chemotherapy cures a proportion of patients with diffuse large-cell lymphoma, the contribution of radiation therapy to the cure is hotly debated. The situation is different for follicular lymphomas. Today there is no firm evidence that chemotherapy cures follicular or MALT lymphomas. To re-examine the role of radiation therapy in localised disease, we will consider the management of localised follicular lymphoma as a paradigm for indolent lymphomas and the management of localised diffuse large-cell lymphoma as a paradigm for aggressive lymphomas. In addition, we will review the role of radiotherapy in the management of extranodal marginal zone lymphomas and several specific disease entities among primary extranodal lymphomas (see Table 1 for the principles of management of NHL).

Radiation therapy for NHL: technical aspects

The principles of RT are to deliver an adequate radiation dose to the target volume that includes the full extent of gross disease with an appropriate margin. The proper design of RT plans requires attention to all the information obtained from staging investigations, the awareness of normal anatomy, and the familiarity with common routes of lymphatic spread as well as the appreciation of the radiation tolerance of normal organs and tissues. The correct application of the dose and fractionation schedule should ensure local control with acceptable acute toxicity, and minimal late complications. The technique should guarantee reproducibility of treatment on a daily basis. Current RT techniques infer the use of custom designed fields that conform to an individual patient's anatomy and tumour location. The common terms used to describe the extent of RT are involved field, extended field and total lymphoid irradiation. Involved field RT is most commonly used in localised

Table 1
Principles of the management of non-Hodgkin's lymphomas

Basis for therapeutic decisions
– histological type
– stage
– site of presentation
Therapeutic recommendations
Indolent lymphomas (follicular lymphoma, MALT lymphoma)
– Stage I and II
Recommended treatment
– radiation therapy
– Stage III and IV
Recommended:
– observation
– non-doxorubicin-based chemotherapy
Aggressive large-cell lymphomas
– Stage I and II
Recommended:
– doxorubicin-based chemotherapy ± rituximab followed by involved field RT
– Stage III and IV
Recommended:
– doxorubicin-based chemotherapy ± rituximab
– adjuvant, or prophylactic RT in selected presentations
– CNS prophylaxis in selected presentations

MALT, marginal zone lymphomas of extranodal type; CNS, central nervous system; RT, radiotherapy.

lymphomas and implies treatment to the nodal region or extranodal site and, if involved, its immediate lymph node drainage area. A treatment plan including RT to the adjacent, second echelon lymph nodes would be considered "extended field RT". However, the use of these terms varies considerably. A survey of practice among the experts, performed by Tsang et al., demonstrated a considerable variation in the definition of radiation treatment fields and dose for identical clinical scenarios [3]. In the past decade, with the use of computerized tomography (CT) simulation and the introduction of conformal radiotherapy techniques, the volumes of tissues irradiated have been reduced to minimise treatment toxicity. Careful prospective monitoring is needed to ascertain that local control is maintained with these new planning techniques. The dose of RT required to achieve local control varies depending upon the histological type of lymphoma and tumour bulk. In follicular lymphomas and in combined modality therapy, excellent local control has been documented with RT doses of 30–35 Gy delivered in 1.75–3 Gy fractions [4,5]. All available information about RT dose is from retrospective reviews or phase II trials. There is insufficient information to assess the impact of doses lower than 35 Gy on local control in an unselected cohort of patients with follicular lymphomas. There is suggestion that a dose of 30 Gy is sufficient to control MALT lymphoma. However, occasional local failures have been reported [6]. Higher RT dose is required to secure local control in diffuse large-cell lymphoma. However, currently almost all patients with diffuse large B-cell lymphoma receive combined modality therapy. The usual RT dose of 30–35 Gy appears to be sufficient for patients who achieve complete response to chemotherapy [2,5]. The information about the RT dose required to control residual disease following CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy is sparse. There is a suggestion that a higher dose is required [7]. However, even RT doses in excess of 40 Gy may be insufficient and local failures have been observed in patients who do not respond, or develop local recurrence following chemotherapy.

Stage I and II follicular lymphoma

Stage I and II follicular lymphoma patients treated with RT alone have excellent survival and long-term local disease control [4]. The overall survival rates at 5 years range from 80% to 100%. RT doses of 30 to 35 Gy delivered in 15 to 20 fractions over 2 to 4 weeks result in local control in more than 95% of patients. There is no clear evidence that extended-field RT is beneficial. Reports of treatment of stage I and II follicular lymphoma demonstrate 10- to 15-year relapse-free rates of approximately 50% and cause-specific survivals rates of 70–75%. The long-term results of involved field RT in 285 patients treated at the Princess Margaret Hospital (PMH) between 1967 and 1986 showed overall survival rates at 10, 15 and 20 years of 65%, 57% and 44%, cause-specific survivals of 77%, 71% and 61% and failure-free rates of 52%, 47% and 47%, respectively. A plateau in relapse rates can be seen after 10 years, but due to prolonged survival after failure, a plateau in cause-specific survival is not expected. The 30 year results of involved field RT in stage I and II follicular lymphoma at PMH show a 30% relapse-free rate negating the impression that all patients with follicular lymphoma should be considered to have generalised disease [4]. However, long-term monitoring is recommended since patients may develop late relapse.

Several phase II trials have suggested an improved relapse-free survival, but no overall survival benefit for patients with stage I and II disease treated with chemotherapy and radiation [8]. The usefulness of combined modality therapy in follicular lymphomas is being tested in a prospective randomised trial conducted by Trans Tasman Radiation Oncology Group

in Australia (*www.newcastle.edu.au/centre/trog/Trials/9903.htm*).

Role of radiation therapy in marginal zone lymphoma

Over 65% of patients with MALT lymphomas present with stage I or II disease [1]. The most common presenting sites are stomach, orbit, skin, thyroid and salivary glands [6]. In addition, less commonly, MALT lymphomas presenting in breast, lung, urinary bladder, meninges, uterine cervix, duodenum, liver, prostate and kidney have also been reported. MALT lymphomas are very sensitive to treatment with radiation therapy. MALT lymphomas also respond to chemotherapy, but to date, there is no evidence that chemotherapy has curative potential in this disease. Involved field radiation therapy is very effective in the management of localised MALT lymphomas. Recent studies report 95–100% local control rates with RT doses of 25–35 Gy. There is paucity of reports with long-term outcomes, but at least 30% of patients develop distant recurrence, with a tendency for relapse in other extranodal sites, either mucosal or non-mucosal. The risk of relapse is lowest in gastric and thyroid lymphomas [6]. The management of gastric MALT lymphomas and orbital lymphomas is of most interest to radiation oncologists because of the special care needed to protect normal tissues.

Radiation therapy in specific MALT presentations

Gastric

The observation of complete regression of primary low grade B-cell gastric MALT lymphoma following treatment with antibiotics has shown that the eradication of *Helicobacter pylori* may be sufficient therapy for most patients with *Helicobacter pylori*-dependent MALT lymphoma of the stomach. The expected rates of eradication of *Helicobacter* are over 90%. Although eradication of *Helicobacter* is seen shortly after the completion of drug therapy, the regression of lymphoma may take several months, and a delay of up to 18 months to histological complete response has been documented. In a prospective series, Yahalom and colleagues [9] from Memorial Hospital achieved a 100% complete response rate in 17 patients with gastric MALT lymphoma treated to the median dose of 30 Gy (range 28.5–43.5 Gy). Only a few failures were observed. Tsang and colleagues [6] reported a local control rate of 100% in 9 patients treated with RT alone, with a median follow-up of 4 years. Radiation therapy for gastric lymphoma is challenging because of the variability in size and location of the stomach and proximity of the kidneys and liver. The aim is to deliver 30 Gy in 20 fractions. To minimise the tumour target volume, stomach distension should be avoided and the patient is best treated in a fasting state in the morning [10]. Given the limited radiation tolerance of the kidneys (20–22 Gy), the aim is to avoid irradiating the kidneys, and this is best achieved with conformal radiotherapy using a 3D planning process using CT simulation.

Orbital lymphomas

Much of the experience with RT for orbital MALT lymphomas are inferred from reports of patients treated for "low grade" orbital lymphoma and "pseudolymphoma", with many of these cases now being recognised as MALT lymphoma [11,12]. Conjunctiva is most commonly involved, with characteristic salmon-pink infiltration. Other frequent sites of presentation include a mass in the lacrimal gland, periorbital soft tissues and in the retro-orbital tissues. Occasionally, multiple lesions are found within the orbit. The bilateral involvement, either at diagnosis or later, has been observed, particularly in conjunctival presentations. Patients are generally symptomatic with irritation, pain, and epiphora even with small tumour bulk, resulting in significant morbidity particularly if retro-orbital infiltration was present which may cause proptosis and diplopia. For the majority of patients with stage IE disease (localised to one or both orbits), treatment is directed at cure, preservation of vision and the integrity of the orbit. Therefore, extensive surgery should be avoided. Radiation therapy is the standard treatment and achieves local control in over 95% of cases [12,13]. Detailed ophthalmological assessment prior to radiation therapy to document the vision and the presence of any ophthalmological co-morbidity is recommended. The radiation target volume includes the whole orbit, without coverage of the regional lymph nodes or the contralateral orbit. RT restricted to the gross tumour infiltration without covering the whole orbit is not recommended because the whole conjunctival surface is at risk. For patients with conjunctival involvement and no retro-orbital extension, a single direct anterior field with either high energy electrons or photon energies ranging from cobalt-60 to 6 MV from a linear accelerator is sufficient. This technique is simple, reproducible and it also allows the opportunity to provide shielding to the lens, anterior chamber, and the macula by suspending a 1-cm-diameter cylindrical eye bar directly over the cornea ("pencil" eye shield). For electron beams, a similar eye shield of lesser thickness (1–1.5 cm, lead) can be used [12]. The prescribed dose of 25

Gy in 10–15 fractions will result in a dose of 20–24 Gy to most of the retro-orbital tissues. For patients with retro-orbital mass, two wedged fields (anterior, and anterior oblique directions) will achieve a homogeneous dose distribution, and lens shielding is omitted to avoid shielding the retro-orbital disease. For patients requiring bilateral orbital radiation, either lateral opposed fields are used, or a 3-field technique with the addition of an anterior field with shielding of the midline structures between the orbits. A moderate dose of radiation of 25–30 Gy will result in mild acute side effects of skin erythema, epilation of eye lashes, conjunctival irritation, and epiphora lasting a few weeks. In the longer term, the RT dose of 30–35 Gy without lens shielding will result in cataract formation in over 90% of patients. If the lens was shielded, cataract formation occurs in less than 10% of cases [12]. Apart from the cataract risk, the RT described herein is within the tolerance of the eye and deterioration of vision due to RT is rarely observed. The higher risks reported in the literature have been due to higher doses of 35–40 Gy [13], which are unnecessary for MALT lymphoma. A mild degree of permanent dryness of the eye may be observed if the lacrimal gland was treated with the full dose. Therefore, ophthalmological follow-up is important.

Stage I and II diffuse large-cell lymphoma

Prior to the late 1970s, most patients with stage I and II diffuse large-cell lymphoma were treated primarily with RT alone. Overall, radiation alone was curative in 40–50% of all patients. A small group of patients, comprising those with asymptomatic stage I and II localised disease, < 60 years, and small bulk disease (< 2.5 cm) achieved 70–80% relapse-free rates following treatment with involved field RT alone [2]. The use of pathological staging helped to select a group suitable for RT alone, but with the success of CT+RT, this approach is no longer appropriate. However, it is important to remember that treatment with RT alone provides long-term event-free survival in 30–50% of patients. Since recurrences are predominantly distant, combined modality was introduced to improve the event-free and overall survival. In the setting of combined modality therapy, excellent local control has been obtained with doses of 30 to 35 Gy delivered in 1.75 to 3 Gy fractions over 3 to 4 weeks. The use of various combined modality regimens has resulted in an improved relapse-free probability and overall survival. Currently, patients with stage I and II DLC lymphoma who complete prescribed therapy achieve 75–80% progression-free rate and 80–90% survival rate at 5 years. Unfortunately, longer follow-up shows a considerable late-relapse rate. This has been shown especially in patients managed with short courses of chemotherapy. Recent data [14] suggest that late recurrences in diffuse large-cell lymphoma have the same clonal abnormalities as the primary disease, suggesting failure of chemotherapy to eradicate occult disseminated disease.

Although several trials have documented improved disease-free and overall survival with combined modality therapy, the evidence for benefit of combined chemotherapy and radiation over chemotherapy alone was absent until recently (Table 2). In 1995, Glick and associates reported the results of a phase III ECOG trial of CHOP alone versus CHOP plus radiation therapy for intermediate-grade stage I

Table 2
Stage I and II aggressive lymphoma – trials of CMT vs. CT

Author [Ref.]	Institution	No. pts.	Treatment	5 yr PFS	5 yr Survival
Miller et al., 1998 [17]	SWOG	200	CHOP × 3 + RT (40–55 Gy)	77%	82%
	8736**	201	CHOP × 8	64%	72%
				$P = 0.02$	$P = 0.02$
Horning et al., 2001 [15]	ECOG	352	CHOP × 8 + RT (30–40 Gy)	57% (10 yr)*	64% (10 yr)
	E1484^		CHOP × 8	46% (10 yr)*	60% (10 yr)
				$P = 0.04$	$P = 0.23$
Fillet et al., 2002 [19]	GELA, Europe	455	CHOP × 4 + RT (40 Gy)	64%	70%
	LNH 93-4	Age > 60	CHOP × 4	69%	78%
	Interim results	IPI 0		$P = 0.4$	$P = 0.2$
Reyes, 2002 [20]	GELA, Europe	631	CHOP × 3 + RT (30–40 Gy)	74±5%	80±5%
	LNH 93-1	Age ≤ 60	ACVBP × 3 + CT consolidation	83±5%	89±4%
	Interim analysis	IPI 0		$P = 0.004$	$P = 0.02$

* Disease-free survival rate, ^Excluded stage I non-bulky patients, ** Excluded stage II with tumour bulk ≥10 cm.

and II lymphoma. These results were recently updated by Horning [15,16]. Three hundred and fifty two previously untreated patients with bulky or extranodal stage I and II disease were treated with CHOP for eight cycles. Patients achieving complete response with CHOP were randomised to consolidation radiation therapy (30 Gy) or observation. The 10-year disease-free survival was 46% in the CHOP arm and 57% in the CHOP and radiation therapy arm ($P = 0.04$). The time to progression was 63% for chemotherapy alone and 73% for CHOP plus RT ($P = 0.07$). The overall survival was 60% for CHOP alone and 64% for CHOP and RT ($P = 0.23$). All patients achieving a partial response to CHOP received RT to 40 Gy and 28% converted to CR after RT. While there is no evidence for improved overall survival, the improved disease-free and time to progression suggest benefit for radiation therapy. The results are available in abstract only and future publication of the full results of this study should shed additional light on the pattern of failure.

The Southwest Oncology Group (SWOG) has reported the results of a phase III trial comparing 3 cycles of CHOP plus involved field RT versus 8 cycles of CHOP without RT for patients with stage I and II disease [17]. Extranodal lymphomas were included and accounted for 37% of the cases while stage II patients with bulky disease (tumour mass $\geq$ 10 cm) were excluded. The RT dose was 40 Gy with a boost to 50 Gy for partial responders. The 5-year projected progression-free survival rates were 77% for CHOP–RT versus 64% for CHOP alone ($P = 0.03$), and 82% and 72% respectively for overall survival ($P = 0.02$). With a longer follow-up the survival advantage is no longer seen because of late distant failures in the brief chemotherapy arm [18]. The risk factors predicting for a poor outcome included stage II disease, age > 60 years, increased LDH and ECOG performance status of > 1. This raises a concern that patients who have adverse prognostic factors had inadequate chemotherapy in the brief chemotherapy and RT arm. A longer course of chemotherapy followed by radiation therapy may be optimal in patients presenting with poor risk features, and rare or unfavourable extranodal sites (bone, extradural, testes, etc.). The publication of the updated results is awaited.

The Groupe d'Etude des Lymphomes de l'Adulte (GELA) LNH 93-4 study of 455 patients with aggressive lymphoma found no survival advantage for involved field radiotherapy (40 Gy) following four courses of CHOP in patients $\geq$60 years of age with stage I–II good prognosis aggressive NHL (5 yr OS – CHOP 78%; CHOP+RT 70%). A subgroup analysis showed that in patients over the age of 69 years the overall survival was better in the chemotherapy-alone arm [19]. The study report is available in abstract form only. The LNH 93-1 trial of 631 patients less than 60 years of age showed that an intensive chemotherapy regimen (ACVBP followed by sequential consolidation treatments) had more favourable results compared to CHOP×3 followed by RT. The 5-year survival and event-free survival was 89% and 83% for chemotherapy and 80% and 74% for CHOP×3 plus RT [19]. The GELA and the SWOG trials suggest that more aggressive chemotherapy may produce an improved overall survival in patients with stage I and II aggressive lymphoma. It has to be determined whether adjuvant RT is required in patients who achieve CR to these aggressive regimens. The GELA LNH 93-1 trial questions the routine use of RT in diffuse large-cell lymphoma treated with an intensive chemotherapy regimen.

Management of primary extranodal lymphoma

Primary extranodal lymphomas present frequently as localised disease and are therefore especially important to radiation oncologists. They account for approximately 37–45% of all lymphomas. Gastric lymphoma is a very common presentation followed by primary Waldeyer's ring lymphomas (tonsil is the most common site). The other commonly encountered primary extranodal lymphomas include those presenting in bone, extradural locations, skin, brain and many other less common sites. Some of these presentations are discussed below.

Diffuse large B-cell lymphoma of the stomach

The modern approach to the management of diffuse large B-cell lymphoma of the stomach follows the principles for treatment of nodal lymphoma. Patients are staged clinically with a CT abdomen, gastroscopy and endoscopic ultrasound. The combined modality approach with CHOP chemotherapy followed by involved field radiation therapy is the standard management for stage I and II disease. Toxicity of radiation therapy can be reduced using 3D conformal techniques and minimising the radiation therapy dose to the kidneys and the liver [10]. Studies of the reproducibility of 3D gastric radiation therapy are currently ongoing. In cases where tumour regression is observed following CHOP chemotherapy, excellent permanent local control and survival are observed. The approach to treatment of gastric lymphoma has radically changed in the past decade. With conserva-

tive approaches having proven successful, the need for routine gastrectomy has been eliminated. However, the approach to this disease is not consistent. Gastric lymphoma is at the crossroads of the expertise of gastroenterologists, oncologists, and haematologists. The gastroenterologists are more likely to use endoscopic ultrasound to stage these patients and are far more inclined to recommend surgery, while haematologists and oncologists are more likely to stage the patients with the emphasis on systemic disease, and use chemotherapy with or without radiation therapy.

Testicular lymphoma

Malignant lymphoma of the testis is a rare disease. Lymphoma, however, is still the most common testicular tumour in men older than 60 years of age. Bilateral testicular tumours may be found at diagnosis or contralateral involvement may develop years later and has been observed in up to 35% of cases. The demonstration of monoclonality in metachronous contralateral testis lymphoma suggests that bilateral involvement is a manifestation of the same disease. Most testicular lymphomas are diffuse large B-cell lymphomas. Isolated cases of NK/T-cell lymphomas, nasal type, T-cell lymphomas and follicular lymphomas have been reported. Orchiectomy is both diagnostic and therapeutic, providing local tumour control. Primary testicular lymphoma has been recognised as a highly lethal disease, with overall 5-year survival rates ranging from 16% to 50% with a median survival of 12 to 24 months. The introduction of adjuvant chemotherapy resulted in an improved relapse-free rate and survival [21]. Connors et al. [21] treated patients with either a 6-week course of MACOP-B or 3 cycles of CHOP and observed survival of 93% with a median follow-up of 44 months. Unfortunately, the other authors did not observe these excellent survival results, although chemotherapy appears to have improved the short-term survival [22]. The pattern of failure in the CNS has led to a recommendation for routine CNS prophylaxis with, at least, intrathecal chemotherapy [22,23]. Its value, however, is controversial because CNS failures have been observed in patients who received intrathecal chemotherapy. Many CNS failures occur in brain parenchyma rather than meninges and some also occur several years after the initial presentation. Failure in the contralateral testis is well documented and occurs in 5% to 35% of patients. Low dose radiation therapy (25–30 Gy in 10–15 daily fractions) to the contralateral testis eliminates the risk of failure at this site and is recommended for all patients with primary testicular lymphoma. The International Extranodal Lymphoma Study Group (IELSG) conducted a retrospective study of 373 patients with a diagnosis of primary testicular diffuse large-cell lymphoma [24]. The 5-year survival was 48% and the 10-year survival was 27%. The outcome of patients who received anthracycline-based chemotherapy was better than those who did not receive it. The actuarial 5- and 10-year risk of CNS relapse were of 20% and 35%. Prophylactic intrathecal chemotherapy was associated with an improved progression-free survival. A continuous risk of recurrence in the contralateral testis (15% at 3 years, 40% at 15 years) was observed in patients who had not received prophylactic scrotal radiation therapy. The IELSG data suggest that the use of chemotherapy, prophylactic intrathecal chemotherapy and prophylactic scrotal radiation therapy is associated with an improved outcome. Furthermore, the recent report of improved response to treatment and improved survival in elderly patients with the addition of rituximab to CHOP chemotherapy is promising. The IELSG data suggest that intrathecal chemotherapy may indeed control microscopic meningeal disease. Intrathecal chemotherapy may decrease the risk of meningeal failure but is unlikely to affect the risk of failure in brain parenchyma. Prevention of parenchymal brain relapse can be addressed with the use of methotrexate chemotherapy or prophylactic cranial radiation therapy. In small-cell lung cancer, prophylactic cranial radiation therapy is used in patients with limited disease who achieve complete remission. It has been shown to reduce the rate of CNS metastasis and improve the progression-free and overall survival. Noting the frequency of CNS relapse in testicular lymphoma, control of occult CNS disease may well increase the overall survival in these patients. There are little published data regarding the benefit of prophylactic cranial radiation therapy in testis lymphoma.

Nasal NK/T-cell lymphoma

Sinonasal lymphomas are relatively rare in the Western world, but in Asian countries they are the second most frequent lymphoma after lymphomas of the gastrointestinal tract. Two main types of lymphoma are found in the sinonasal area: diffuse large B-cell lymphoma and extranodal NK/T-cell lymphoma. In the Western world most series show a low incidence of sinonasal lymphoma. The Kiel registry of 33,402 cases showed only 0.14% of lymphomas occurred in the nasal cavity. When locally advanced, these tumours invade the adjacent nasopharynx, paranasal sinuses, oropharynx, and palate. NK/T-cell lymphomas are more commonly associ-

ated with angioinvasion, necrosis and bone erosion. Because of these destructive features, sinonasal lymphomas were often included with the descriptive yet non-specific name of lethal midline granuloma. However, the extranodal NK/T-cell lymphoma of nasal type is now recognised as a distinct clinicopathologic entity. These tumours are $CD3^+$, $CD56^+$ with T-cell receptor genes in a germline configuration, consistent with NK (natural killer) cell lymphoma. Occasionally, tumour cells express surface CD3 and show clonal rearrangement of the T-cell receptor genes. In virtually all cases Epstein–Barr virus can be detected in neoplastic cells. Stage IE lesions were most common with over half being limited to the nasal cavity and with others demonstrating extension beyond the nasal cavity. At 5 years the overall survival for limited IE lesions was 90% and 57% for extensive IE lesions. The addition of chemotherapy to radiation appears to be of no benefit, although local failure with radiation therapy was substantial [25]. A recent report of 79 cases of early stage NK/T-cell nasal lymphoma treated with curative intent (combined modality therapy or radical RT) in Hong Kong showed a 5-year survival of only 37.9% [26]. The CR rate was 68.4%, but almost half of those relapsed. The factors associated with improved outcome included stage I disease, and younger age. Both local and distant failures were observed. The use of anthracycline-based chemotherapy did not appear to improve the overall survival. The use of CT/MR for radiotherapy planning and the use of >50 Gy RT dose were associated with improved local control. The optimisation of radiation therapy planning and dose-fractionation schedules are important in stage I disease. In addition, in NK/T-cell lymphoma of nasal type, early treatment intensification with high dose chemotherapy and stem cell support is being tested in clinical trials.

Primary central nervous system lymphoma (PCNSL)

Non-Hodgkin's lymphomas arising in and limited to the central nervous system are called primary CNS lymphomas. The most common site of PCNSL is the brain. Primary leptomeningeal lymphoma, without parenchymal brain disease accounts for only 7% of PCNSL. Primary spinal cord lymphoma is even less common. The eye, a direct extension of the CNS, is another site of PCNSL. These anatomical areas are all well known sanctuary sites to most systemically delivered treatments.

Lymphoma of the brain

Traditionally, treatment for primary brain lymphoma was with corticosteroids and whole brain irradiation. The disease is extremely sensitive to treatment with a rapid symptomatic response. The recommended RT dose is 40–50 Gy to the whole brain in 1.8–2 Gy fractions, followed by a 10–15 Gy boost to the tumour. Local recurrence frequently occurs within the first two years following RT. Median survival has been reported to be 12–18 months with 2-year and 5-year survival rates of 28% and 3–4% respectively. The prognostic factors for survival include age < 60 years, Karnofsky score (KPS) ≥ 70, tumour limited to hemispheres, RT dose of 40–50 Gy. Given the localised presentation, and the use of high dose RT, the lack of local control in primary brain lymphoma remains unexplained. Nonetheless, the prospective trial, RTOG (Radiation Therapy Oncology Group) 8315, found that despite total doses of 60 Gy, the tumour recurred within the radiated volume in 83% of patients, in stark contrast to non-CNS nodal lymphomas [27]. No molecular differences between brain and nodal lymphomas of the same histology have so far been identified. Performance status, age, and solitary tumour constitute important prognostic factors in primary brain lymphoma. In the PMH experience, patients with KPS > 60 had 56% actuarial 5-year survival versus 10% for those with KPS < 60 [28]. Patients whose age was <60 years, had 42% survival versus 9% for those over the age of 60. For those with solitary lesions, a 30% 5-year survival rate was observed versus 15% for those with multiple lesions. Recent reports have suggested an improved median survival for patients receiving RT and chemotherapy. The French National Federation Against Cancer has approached PCNSL with methotrexate chemotherapy and reported 19% 5-year survival. The French experience and another trial reported by Reni have confirmed that methotrexate is the most active single agent in this tumour [29]. Combinations of high-dose methotrexate, vincristine, and procarbazine prior to radiotherapy have been used at Memorial Hospital [30]. An RTOG and SWOG trial showed an improved survival rate using combined modality therapy over radiotherapy alone with a median survival of 30 months [31]. Other blood–brain barrier penetrating chemotherapy (methotrexate and high dose cytosine arabinoside) followed by whole brain RT was used by DeAngelis in a cohort of 31 patients with a median survival of 42.5 months. These reports show that PCNSL is a chemosensitive disease when agents crossing the blood–brain barrier are used. The major problem is the significant neurotoxicity in patients treated with combined high dose methotrexate and RT, and high rates of local failure in those treated with chemotherapy alone. In a series from the Memorial Hospital, 11.5% of 1-year

survivors developed dementia [31]. Clearly, the optimal approach to both controlling the tumour while minimising late neurological toxicity remains to be defined. In this rare disease, international cooperation is required to complete the necessary trial.

Summary

Radiation therapy plays an essential role in the management of localised NHL. Its application varies from monotherapy management of localised follicular and MALT lymphomas with intent to cure, to being an integral part of combined modality therapy for diffuse large-cell lymphoma. In addition, the role of radiation therapy in the management of specific extranodal lymphomas deserves special attention. Regrettably, the emphasis on drug therapy has overshadowed research efforts to optimise the application of radiation therapy in the management of lymphomas. Recent advances in conformal radiation therapy techniques need to be applied to the management of lymphomas to further improve RT toxicity, while offering the patients the benefits of permanent local disease control.

References

1 The non-Hodgkin's lymphoma classification project: a clinical evaluation of the International Lymphoma Study Group Classification of Non-Hodgkin's Lymphoma. Blood 1997, 89(11): 3309–3918.
2 Tsang RW, Gospodarowicz MK. Management of localized (stage I and II) clinically aggressive lymphomas. Ann Hematol 2001, 80(Suppl 3): B66–B72.
3 Tsang RW, Gospodarowicz MK, O'Sullivan B. Staging and management of localized non-Hodgkin's lymphomas: variations among experts in radiation oncology. Int J Radiat Oncol Biol Phys 2002, 52(3): 643–651.
4 Gospodarowicz M, Lippuner T, Pintillie M et al. Stage I and II follicular lymphoma: Long term outcome and pattern of failure following treatment with involved field radiation therapy alone. Int J Radiat Oncol Biol Phys 1999, 45: 217A.
5 Shenkier TN, Voss N, Fairey R, Gascoyne RD, Hoskins P, Klasa R, et al. Brief chemotherapy and involved-region irradiation for limited-stage diffuse large-cell lymphoma: an 18-year experience from the British Columbia Cancer Agency. J Clin Oncol 2002, 20(1): 197–204.
6 Tsang RW, Gospodarowicz MK, Pintilie M, Bezjak A, Wells W, Hodgson DC et al. Stage I and II MALT lymphoma: results of treatment with radiotherapy. Int J Radiat Oncol Biol Phys 2001, 50(5): 1258–1264.
7 Aref A, Narayan S, Tekyi-Mensah S, Varterasian M, Dan M, Eilender D et al. Value of radiation therapy in the management of chemoresistant intermediate grade non-Hodgkin's lymphoma. Radiat Oncol Investig 1999, (3): 186–191.
8 Seymour JF, McLaughlin P, Fuller LM, Hagemeister FB, Hess M, Swan F et al. High rate of prolonged remissions following combined modality therapy for patients with localized low-grade lymphoma. Ann Oncol 1996, 7(2): 157–163.
9 Schechter NR, Yahalom J. Low-grade MALT lymphoma of the stomach: a review of treatment options. Int J Radiat Oncol Biol Phys 2000, 46(5): 1093–1103.
10 Wirth A, Teo A, Wittwer H, MacManus M, Ryan G. Gastric irradiation for MALT lymphoma: reducing the target volume, fast! Australas Radiol 1999, 43(1): 87–90.
11 Cahill M, Barnes C, Moriarty P, Daly P, Kennedy S. Ocular adnexal lymphoma — comparison of MALT lymphoma with other histological types. Br J Ophthalmol 1999, 83(6): 742–747.
12 Le QT, Eulau SM, George TI, Hildebrand R, Warnke RA, Donaldson SS et al. Primary radiotherapy for localized orbital MALT lymphoma. Int J Radiat Oncol Biol Phys 2002, 52(3): 657–663.
13 Stafford SL, Kozelsky TF, Garrity JA, Kurtin PJ, Leavitt JA, Martenson JA et al. Orbital lymphoma: radiotherapy outcome and complications. Radiother Oncol 2001, 59(2): 139–144.
14 De Jong D, Glas AM, Boerrigter L, Hermus MC, Dalesio O, Willemse E et al. Very late relapse in diffuse large B-cell lymphoma represents clonally related disease and is marked by germinal center cell features. Blood 2003, 20: 20.
15 Horning SJ, Glick JH, Kim K, Earle JD, O'Connell MJ. Final Report of E1484: CHOP v CHOP + Radiotherapy (RT) for Limited Stage Diffuse Aggressive Lymphoma. In: American Society of Haematology; 2001: Blood; 2001. p. 724a.
16 Glick JH, Kim K, Earle JD, MJ OC. An ECOG Randomized Phase III Trial of CHOP vs. CHOP + Radiotherapy (XRT) for Intermediate Grade Early Stage Non-Hodgkin's Lymphoma (NHL). In: American Society of Clinical Oncology; 1995: J Clin Oncol 1995.
17 Miller TP, Dahlberg S, Cassady JR, Adelstein DJ, Spier CM, Grogan TM et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med 1998, 339(1): 21–26.
18 Miller TP, LeBlanc M, Spier C, Chase E, Fischer RI. CHOP alone compared to CHOP plus radiotherapy for early stage aggressive non-Hodgkins lymphomas: update of the Southwest Oncology Group (SWOG) randomized trial. In: Proc Am Soc Haematol 2001, Blood, 2001, 724a–725a.
19 Fillet G, Bonnet C, Mounier N, Thieblemont C, Ferme C, Quesnez B et al. Radiotherapy is unnecessary in elderly patients with localized aggressive non-Hodgkin's lymphoma: results of GELA LNH 93-4 study. Blood 2002, 110(11): abstr 337.
20 Reyes F, Lepage E, Munck JN, Morel P, Coiffier B, Lederlin P, Simon D, Bosly A, Fabiani B, Bordessoule D, Ganem G, Tilly H for the GELA. Superiority of chemotherapy alone with the ACVBP regimen over treatment with three cycles of CHOP plus radiotherapy in low risk localized aggressive lymphoma: the LNH93-1 GELA study. Blood, 100(11), 93a (abstr 343).
21 Connors JM, Klimo P, Voss N, Fairey RN, Jackson S. Testicular lymphoma: improved outcome with early brief chemotherapy. J Clin Oncol 1988, 6: 776–781.
22 Sasai K, Yamabe H, Tsutsui K, Dodo Y, Ishigaki T, Shibamoto Y et al. Primary testicular non-Hodgkin's lymphoma: a clinical study and review of the literature. [Review] [15 refs]. Am J Clin Oncol 1997, 20(1): 59–62.
23 Touroutoglou N, Dimopoulos MA, Younes A, Hess M, Pugh W, Cox J et al. Testicular lymphoma: late relapses and poor outcome despite doxorubicin-based therapy. J Clin Oncol 1995, 13(6): 1361–1367.

24 Zucca E, Conconi A, Mughal TI, Sarris AH, Seymour JF, Vitolo U et al. Patterns of outcome and prognostic factors in primary large-cell lymphoma of the testis in a survey by the International Extranodal Lymphoma Study Group. J Clin Oncol 2003, 21(1): 20–27.

25 Li S, Ross DT, Kadin ME, Brown PO, Wasik MA. Comparative genome-scale analysis of gene expression profiles in T cell lymphoma cells during malignant progression using a complementary DNA microarray. Am J Pathol 2001, 158(4): 1231–1237.

26 Cheung MM, Chan JK, Lau WH, Ngan RK, Foo WW. Early stage nasal NK/T-cell lymphoma: clinical outcome, prognostic factors, and the effect of treatment modality. Int J Radiat Oncol Biol Phys 2002, 54(1): 182–190.

27 Nelson DF, Martz KL, Bonner H, Nelson JS, Newall J, Kerman HD et al. Non-Hodgkin's lymphoma of the brain: can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315 [see comments]. Int J Radiat Oncol Biol Phys 1992, 23(1): 9–17.

28 Laperriere NJ, Cerezo L, Milosevic MF, Wong CS, Patterson B, Panzarella T. Primary lymphoma of brain: results of management of a modern cohort with radiation therapy. Radiother Oncol 1997, 3(3): 247–252.

29 Reni M, Ferreri AJ. Therapeutic management of primary CNS lymphoma in immunocompetent patients. Expert Rev Anticancer Ther 2001, 1(3): 382–394.

30 Abrey LE, Yahalom J, DeAngelis LM. Treatment for primary CNS lymphoma: the next step. J Clin Oncol 2000, 18(17): 3144–3150.

31 DeAngelis LM, Seiferheld W, Schold SC, Fisher B, Schultz CJ. Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93-10. J Clin Oncol 2002, 20(24): 4643–4648.