

X. When should radiotherapy be used in lymphoma?

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introduction

The dramatic effect of ionizing radiation on Hodgkin lymphoma (HL) tumours was reported as early as 1901, only a short time after Roentgen's discovery of 'X-rays'. Subsequently it became clear that lymphomas are typically radiosensitive tumours that die readily after radiation therapy (radiotherapy; RT) from a process that was initially called 'interphase death' that we now know as apoptosis. RT produces very high local complete response rates for all lymphoma subtypes and given this high clinical efficacy, it is not surprising that RT has played an important part in the curative treatment of a broad range of lymphomas over the past half century. Over the past decade, however, enthusiasm for using RT as part of combined-modality treatment has waned and many haemato-oncologists now view RT as outdated, unnecessary and simply replaceable with additional cycles of systemic therapy, using immunochemotherapy or other agents. This change in attitude towards RT appears unrelated to efficacy as illustrated in HL, where most experienced oncologists regard RT as the most active 'drug'. It is perhaps instead related to understandable concerns about late side-effects that have emerged in long-term survivors from the outdated RT techniques and doses used in the past. This brief review will highlight areas of current controversy and where RT should be considered in improving outcome for patients with lymphomas.

what is the role for RT as part of combined-modality treatment in aggressive lymphoma?

In the last century, involved-field radiotherapy (IFRT) established a role as part of combined-modality with abbreviated courses of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) treatment in early-stage diffuse large B cell lymphoma (DLBCL). IFRT was also commonly used as consolidation therapy for patients with advanced-stage bulky disease, such as mediastinal large cell lymphoma. The short-course chemotherapy followed by RT approach for early-stage disease was based on the results of the benchmark, randomized trial published in 1998 by the Southwest Oncology Group (SWOG) that demonstrated that three cycles of CHOP plus IFRT was a safer and significantly more effective treatment than eight cycles of CHOP alone [1]. The SWOG study demonstrated that substituting RT with

five cycles of CHOP (eight in total) resulted in inferior disease control and lower overall survival (OS) and was clearly more cardiotoxic and myelotoxic. The issue of acute infectious complications and later cardiac toxicity with more doxorubicin-based regimens remains even more relevant today, as increasing numbers of older people are presenting with DLBCL. The enthusiasm for short-course CHOP chemotherapy followed by IFRT, however, interestingly decreased following an update at American Society of Hematology 2001 (remains unpublished), which demonstrated that the progression-free survival (PFS) and OS curves of the two groups began to overlap at 7 years and at 9 years after treatment, respectively. This was secondary to the excess number of late lymphoma relapses in the group that received three cycles of CHOP plus IFRT. However, the benefit of IFRT appeared ongoing, given that the irradiated, originally involved sites remained fully controlled and further analysis of the three cycles of CHOP plus IFRT arm using a stage-modified International prognostic Index (IPI) (scoring stage II as an adverse factor) suggested that higher stage-modified IPI patients on this arm could potentially benefit from adding one or more courses of CHOP.

The role of consolidative IFRT versus more chemotherapy in the modern era of rituximab plus CHOP (R-CHOP) chemotherapy in the treatment of DLBCL remains controversial. Around the world treatment guidelines vary but many like the US National Comprehensive Cancer Network (NCCN) are permissive and recommend three cycles of R-CHOP followed by IFRT for early-stage, non-bulky disease, but also allow the administration of six to eight cycles of R-CHOP with or without IFRT [2]. The latter is also the NCCN recommendation for bulky disease. The reality is that many haemato-oncologists simply extend the chemotherapy course and omit RT. A recently published retrospective study from the MD Anderson Cancer Center (MDACC) has provided new data to reinvigorate the debate regarding the importance of RT in the modern era, with significant improvements in OS and PFS among patients who received consolidation RT after R-CHOP chemotherapy for DLBCL in patients with stage I and II disease [3]. The 5-year OS and PFS for stage I and II disease treated with R-CHOP and consolidative RT were 92% and 82%, respectively; whereas without RT, OS and PFS were 73% ($P = 0.0007$) and 68% ($P = 0.0003$), respectively. Interestingly improvements in PFS and OS were also seen for the minority of patients with stage III and IV disease receiving RT. The data appear robust for early-stage disease where there is no apparent selection

bias in favour of RT patients. Notably, in the MDACC study, none of the patients experienced treatment failure in the RT field. In contrast in the two Groupe d'Etudes des Lymphomes d'Adulte (GELA) studies, frequently quoted as reasons not to give IFRT, relapses occurred in irradiated sites alone at rates of 23% and 21% (LNH 93-1 and 93-4, respectively) [4, 5]. The lack of IFRT contribution in these GELA studies and the inferior results compared with other studies, raise the question of whether delays, quality and failure to receive IFRT affected the results. Randomized studies in early-stage or advanced-stage DLBCL using R-CHOP, the IPI and 18-FDG PET imaging examining the potential advantages of modern, better targeted, safer, and lower-dosage, consolidative RT have not been forthcoming and are notable for their absence.

RT in indolent lymphomas

The extreme radiosensitivity of indolent lymphomas was reported in the early years of RT use. The efficacy of low-dose total body irradiation (1.5–2 Gy) with fractions of 0.1–0.25 Gy two to five times weekly in advanced-stage disease resulted in 70%–90% response rates and a 15%–25% 10-year relapse-free survival rate. IFRT may provide curative treatment for localized disease, albeit systemic relapses still occur >20 years after RT ([6] and refs therein). The conventional dose of curative RT used in the early studies was considerably larger at 30–40 Gy. However, a British randomized study demonstrated equivalence of 24 Gy with 40 Gy. More recently, low-dose RT (LDRT) with doses as low as 4 Gy delivered in 2 × 2-Gy fractions within 3 days has proved to be effective in selected patients with chemoresistant, indolent, non-HL with a 55% complete response rate in irradiated sites, with a median duration of 15–42 months [6]. Currently a randomized study of 24 Gy in 12 fractions versus 4 Gy in 2 fractions forms the basis of the UK NCRI FORT study. Localized LDRT appears to induce apoptosis and this follicular lymphoma cell death may then elicit a host immune response mediated by macrophages and dendritic cells [7]. This exquisite radiation-induced apoptosis and subsequent immune response may underlie the durability of responses seen with both LDRT and radioimmunotherapy (RIT). IFRT remains the treatment of choice for localized stage IA and selective stage IIA patients and delivers long-term disease-free survival and potential cure for some patients ([6] and refs therein).

RT in the treatment of extranodal lymphomas

Primary extranodal lymphomas have either no or only 'minor' nodal involvement along with a clinically 'dominant' extranodal component. Treatment strategies are dependent on the extent and/or location of the disease and the histological type, as well as other patient-related factors. In general, for stage I and II disease with low tumour burden, local RT is a relevant option both for cure and long-term local control. Recent studies have shown that site-tailored treatment strategies in testis and brain lymphoma may result in a significant outcome improvement. For primary testicular

DLBCL, RT to the contralateral testis and scrotal sac remains an important part of 'local control'.

The optimum management of patients with primary central nervous system lymphoma (PCNSL) remains to be established. Although high-dose methotrexate-based chemotherapy is largely accepted as an essential component of initial treatment, the relevance and optimum timing of whole brain RT (WBRT) remains a matter of debate. WBRT may be complicated by the development of chronic, late-delayed neurotoxicity and for this reason has been increasingly omitted as part of the first treatment of PCNSL. However, neurotoxicity risks are lower in young (<60 years) patients, deferring WBRT may not be necessary and may compromise disease control with higher rates of relapse. Deferring WBRT in chemosensitive patients seems to compromise PFS but not OS. Adopting this strategy of delaying WBRT reduces but does not eliminate RT as salvage WBRT is frequently required. As the objective of treatment in this population is cure, withholding WBRT may not be the best strategy and requires further investigation [9]. Combined chemotherapy and WBRT regimens are now being explored that use lower total doses of radiation and altered fractionation schedules with the aim of maintaining high rates of tumour control while minimizing neurotoxicity. The future direction is in developing pretreatment multifactor prognostic indices that may allow the selection of treatment regimens that strike an appropriate balance of risk and benefit for the individual PCNSL patient [10].

Lymphomas of the ocular adnexa are a heterogeneous group of malignancies with the most common subtype accounting for up to 80% of cases of primary ocular adnexal lymphoma, being marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) type. Radiotherapy plays an invaluable part of local control either as a single modality in low-grade lymphoma, with excellent long-term local control with doses between 20 and 30 Gy or as part of combined therapy with chemotherapy [11]. For gastrointestinal lymphoma the most frequently involved site is the stomach (60%–75% of cases), followed by the small bowel, ileum, cecum, colon and rectum. The most common histological subtypes are extranodal marginal zone B-cell lymphoma of the MALT type and DLBCL. The role of RT is most well established in early-stage gastric lymphoma. The primary treatment of limited gastric MALT lymphoma consists of *Helicobacter pylori* eradication; however, in cases of insufficient response to *H. pylori* eradication or in case *H. pylori* is absent, irradiation of the stomach and perigastric lymph nodes to a dose of 30–40 Gy in 15–20 fractions is indicated, with excellent long-term control. In patients with gastric DLBCL conservative treatment with anthracycline-based chemotherapy alone or in combination with IFRT is the preferred approach [12].

RT plays a critical role in the management of localized (IE and IIE) extranodal NK/T-cell lymphoma, nasal type (NKTCL) for long-term local control. In one study of 105 patients, 83 stage IE and 22 stage IIE, RT as primary therapy resulted in good outcome in early-stage disease, and the addition of chemotherapy to RT was not accompanied by an improvement in survival [13]. More recent prospective

studies (JCOG0211) using concurrent chemoradiotherapy have, however, reported improved therapeutic outcomes [14] with patients receiving RT/DeVIC chemotherapy having excellent survival and a high locoregional control rate of 96%. This type of lymphoma is relatively radioresistant and the angioinvasive histopathological characteristics of NKTCL are suggested to lead to hypoxia, and doses of ≥ 50 Gy are recommended.

is there a role for RT in the modern management of HL?

The use of RT in HL has been transformed from a single modality used in a radical, extensive, high-dose therapy that cured the majority of patients, into an important component of a combined-modality programme with chemotherapy. The aim of any such programme is to cure more patients with as few late side-effects as possible. The concerns that led to long-term toxicity were associated with radical RT, given to volumes of normal tissues and at higher doses that are no longer used. Modern RT uses lower radiation doses following chemotherapy to encompass only the clinically involved sites. This change has considerably reduced the long-term complications that were associated with the now-outdated radical RT approach. The use of RT also allows a shorter and safer course of chemotherapy. The combination of reduced chemotherapy followed by mini-RT has produced disease control and even overall results that are significantly superior to those achieved with chemotherapy alone.

In order to overcome the shortfall in statistical power of small studies, the Cochrane Haematological Malignancies Group recently performed a meta-analysis of all published prospective randomized trials comparing combined-modality therapy with chemotherapy alone in early-stage HL. The analysis included five randomized controlled trials involving 1245 patients. Although the complete remission rate was similar in the two groups, both tumour control and OS were significantly better in patients receiving combined-modality therapy. The authors' conclusions were that adding RT to chemotherapy improves tumour control and OS in patients with early-stage HL [15]. The European HL study groups recently introduced an additional reduction in the size of the involved radiation field. The field is tailored to the involved lymph-node areas, not the whole region where they reside (as in IFRT) and is thus termed involved node RT (INRT) [16]. Most importantly, for RT involving the mediastinum or the abdomen, INRT is designed according to the post-chemotherapy volume, which is often markedly less than the initial volume. There has been no prospective randomized comparison of INRT with IFRT, although a recent well-controlled retrospective comparison of sequential HL patients treated with only two cycles of ABVD followed by either extended-field RT, IFRT or markedly reduced IFRT similar to INRT showed similarly excellent disease control and OS in all RT groups without any difference in in-field or marginal relapse. There are currently intense efforts to determine whether functional imaging using 18-FDG PET may allow the identification of patients with CR in whom treatment may be further reduced and this forms the basis of

a number of important clinical trials in early- and advanced-stage disease. At this present time this PET-directed approach to omit RT remains experimental and cannot be recommended outside of a clinical trial.

Lymphocyte-predominant HL (LPHL) is known to have a different biology and >75% of patients with LPHL present at an early stage with the disease commonly limited to one peripheral site (neck, axilla or groin), and involvement of the mediastinum is extremely rare. The treatment recommendations for LPHL differ markedly from those for classic HL, and IFRT alone is recommended as the treatment of choice for early-stage LPHL. It should be emphasized that even if regional radiation fields are selected, the uninvolved mediastinum should not be irradiated, thus avoiding the site most prone to short-term and long-term RT-related adverse effects.

concluding remarks

RT remains an important component of curative treatment for many types of lymphoma. For many common lymphomas the omission of RT is likely to lead to deterioration in outcome for some patients. The use of smaller and better-defined radiation volumes allows the use of more conformal RT, based on better imaging; computerized planning programs lead to improved therapeutic ratio and decreased late effects. Although it will take many more years of careful follow-up of patients in randomized studies to display the full magnitude of risk tapering by reductions of radiation field and dose, recent data suggest that reduced risk of late effects is likely. The use of risk-adjusted therapies utilizing functional imaging with 18-FDG PET to determine who requires RT remains the subject of intense investigation in HL and other types of lymphoma, but to date remains unproved, and prospective randomized trials are ongoing. Until such time as we have these data and are able to accurately predict which patients can be safely treated without RT without compromising outcome, the current evidence supports RT being an important component in combined-modality treatment for common lymphomas such as HL, DLBCL and many extranodal lymphomas

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