Curr. Treat. Options in Oncol. (2016) 17: 4
DOI 10.1007/s11864-015-0377-x

Lymphoma (JW Sweetenham, Section Editor)

Does Radiation Have a Role in Advanced Stage Hodgkin's or Non-Hodgkin Lymphoma?

Lena Specht, MD, PhD

Address
Department of Oncology, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100, Copenhagen, Denmark
Email: lena.specht@regionh.dk
[2]Department of Hematology, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100, Copenhagen, Denmark

Published online: 7 January 2016

This article is part of the Topical Collection on *Lymphoma*

Keywords Lymphoma · Hodgkin lymphoma · Non-Hodgkin lymphoma · Advanced stage · Radiation therapy · Involved site radiotherapy · Combined modality therapy

Opinion statement

Radiation therapy (RT) is one of the most effective agents available in the treatment of lymphomas. However, it is a local treatment, and today, with systemic treatments assuming a primary role for induction of response, RT is primarily used for consolidation. For advanced stage lymphomas, the indications for the use of RT have been questioned and debated, and proper randomized evidence is sparse. RT has significant long-term side effects, and the very extended RT fields of the past yielded unacceptable toxicity in many patients. Modern advanced imaging and conformal RT techniques now enable treatment of larger and anatomically more challenging target volumes with much less radiation to normal tissues and consequently much lower risks of long-term complications. The modern concept of involved site radiation therapy (ISRT) has now been accepted as standard in lymphomas. In advanced Hodgkin lymphoma (HL), RT to residual disease and/or initial bulk benefits some patients, depending on the chemotherapy regimen used. The more intensive the chemotherapy regimen, the fewer patients benefit from RT. In advanced aggressive non-Hodgkin lymphoma (NHL), most of the evidence comes from the most common type, the diffuse large B cell lymphoma (DLBCL). In patients treated with modern immunochemotherapy, RT to initial bulky disease or extralymphatic involvement is beneficial. For both HL and aggressive NHL, RT to residual masses after systemic treatment is of benefit. The role of PET in the evaluation and indication for RT to residual masses has not been tested in randomized trials. In advanced indolent NHL, very low dose RT offers excellent palliation with very few side effects. Modern RT in advanced lymphomas warrants further evaluation in randomized trials.

Introduction

Lymphomas are highly radiosensitive, and radiation therapy (RT) was the first curative treatment modality in these diseases. However, RT is a local treatment, and curative treatment with this modality alone is only possible if all lymphoma tissue can be included in the volume which is irradiated to the prescribed dose. Hence, only patients with early stage disease, with very few exceptions, could be treated with curative intent with radiation as single modality. Chemotherapy was first introduced as an adjuvant to the standard RT, but with the introduction in the 1980s of more effective anthracycline-containing regimens, the sequence of combined modality in Hodgkin lymphoma (HL) and aggressive non-Hodgkin lymphoma changed, with chemotherapy assuming a primary role for induction of response and with RT used for consolidation [1–3]. Today, RT is used as the primary treatment in early stage nodular lymphocyte predominant (LP) Hodgkin lymphoma (HL) and indolent non-Hodgkin lymphomas (NHL), and as part of combined modality treatment in early stage classical HL and aggressive NHL.

For patients with advanced lymphoma, the indications for the use of RT are less obvious and the evidence may be less robust. Hence, there has been significant variation in the use of RT in different lymphoma types and between treating physicians.

In the past, the use of RT in advanced lymphomas was limited by the toxicity of RT, which is a serious concern if large volumes of normal tissues are treated [4–23]. However, modern imaging and highly conformal RT techniques now enable treatment of larger and anatomically more challenging target volumes with much less radiation to normal tissues [24–28]; see Fig. 1. Moreover, radiation doses have been reduced based on large randomized trials [29••, 30, 31, 32••]. The International Lymphoma Radiation Oncology Group has recently published guidelines for modern RT of lymphomas, defining the concept of involved site radiation therapy (ISRT), and describing in detail the ISRT concept in different clinical situations [33••, 34••, 35••]. The ISRT concept has been accepted as the standard for modern radiation therapy for lymphomas by most centers and collaborative groups, including the National Comprehensive Cancer Network (NCCN) [36]. Hence, the time is ripe for revisiting the role of RT in advanced lymphoma.

In principle, there are two different ways of using RT in advanced lymphoma:

1. RT may be used as an integral part of the planned treatment approach. In this situation, the timing, target volume, and dose of RT have been decided up front. This strategy should be based on knowledge of the pattern of relapse in patients treated with systemic treatment only, with RT administered to sites with a high risk of recurrence.
2. RT may be used in case of insufficient response to the systemic treatment, which is administered up front. In this situation, the indication for RT and, if indicated, the timing, target volume, and dose of RT will be decided at some point during or after systemic treatment according to criteria, which should ideally have been decided up front. Today, these criteria will very often rely on fluorodeoxyglucose (FDG)-PET scans performed either during or after treatment. However, most of the available evidence concerning RT in this scenario is from the pre-PET era, thus making extrapolation to present treatments difficult.

In the following, the available data will be reviewed for HL, aggressive NHL, and indolent NHL.

Advanced HL

Chemotherapy is always used, and the standard regimen is doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). Unfortunately, no randomized trial testing RT with this regimen in advanced disease has been carried out. The European Organization for Research and Treatment of Cancer (EORTC) performed a study in stage III–IV HL treated with mechloretamine, vincristine,

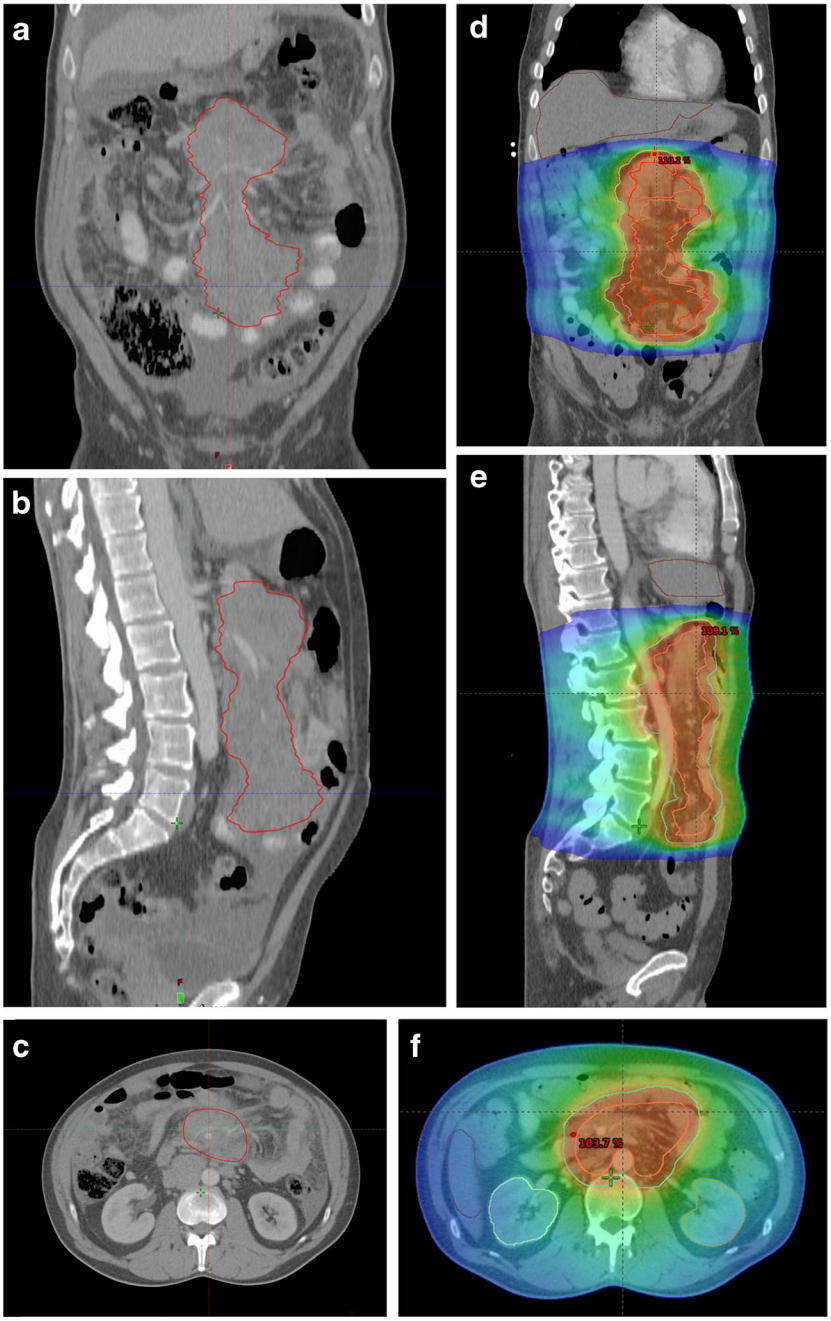

Fig. 1. Involved site radiation therapy (ISRT) to initially bulky disease. **a–c** Pre-chemotherapy CT scan (coronal, sagittal, and axial slices) from a 52-year-old man with double-hit DLBCL stage IVB with a large mass (contoured in *red*) in the mesentery. **d–f** Post-chemotherapy RT plan encompassing the tissue volume which contained bulky disease before chemotherapy, modified for anatomical changes during chemotherapy (coronal, sagittal, and axial slices). The patient was PET-negative after systemic therapy and was treated to a total dose of 30 Gy. Note that the prescribed dose (*red*) was delivered to a volume which conformed very precisely to the defined target, with only small doses (*blue*) to the surrounding normal structures. Apart from loose stools, the patient had few side effects during RT.

procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine (MOPP-ABV) where patients who achieved a complete remission (CR) were randomized to +/− RT, 24 Gy to all initially involved nodal areas and 16–24 Gy to all initially involved extranodal sites [37•]. No difference in outcome was found. Response was evaluated with CT, and only 57 % of patients achieved CR. Thirty-three percent of patients achieved a partial remission (PR), and these patients were all treated with RT, 30 Gy to all initially involved nodal areas, 18–24 Gy to all initially involved extranodal sites, boost up to 10 Gy was given if indicated [38•]. These patients had the same outcome as patients who achieved CR after chemotherapy, indirectly indicating that RT is of benefit in patients achieving only PR after chemotherapy.

The UK Lymphoma Group performed a randomized trial of ABVD versus two other multidrug regimens [39]. The study protocol specified that RT should be considered for original bulk disease and for residual masses (evaluated by CT), and a dose of 30 Gy was recommended. However, the use of RT was left to the discretion of the treating physician. RT was given to 43 % of patients, and these patients had more adverse characteristics than the patients who did not receive RT. Nevertheless, the patients receiving RT had significantly better progression-free survival (PFS) and overall survival (OS), suggesting a beneficial effect of RT. There was no suggestion of any difference in the effect between subgroups of patients.

The German Hodgkin Study Group (GHSG) has carried out large randomized studies in advanced HL using a more intensive chemotherapy regimen. In the HD12 trial [40], patients were randomized to either eight cycles of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) or four cycles of escalated followed by four cycles of baseline BEACOPP, and patients were also randomized to +/− consolidation RT (30 Gy) to initial bulk (>5 cm) or residual disease (≥1.5 cm) after chemotherapy. PET was not available at the time of the trial, and, unfortunately, over 20 % of patients randomized to no RT were irradiated. However, the analyses of the study showed significantly better freedom from treatment failure (FFTF) in patients with residual disease if they were irradiated, whereas there was no difference in patients with initial bulk if they were in complete remission (CR) after the chemotherapy.

These results were implemented in the HD15 trial, the next trial in advanced disease from the GHSG, where patients were randomized between three different variations of the BEACOPP regimen. RT (30 Gy) was given only to patients with a residual PET-positive mass of ≥2.5 cm [41••]. Although the PET-guided RT was not assessed in a randomized fashion, the study demonstrated that RT could be safely omitted in patients with PET-negative partial remission (PR). These patients had the same progression-free survival (PFS) as the patients who achieved CR after chemotherapy. The patients who received RT for PET-positive PR had a slightly, but significantly, poorer PFS. As there was no randomization to +/− RT, it cannot be determined to what extent the RT improved outcome in these patients, but with a 4-year PFS of 86 %, it seems likely to have been substantial. By using this PET-directed RT strategy, the use of RT in advanced disease was reduced to 11 % of patients compared to 70 % in the previous HD 9 study [41••, 42].

It is important to keep in mind that the need for additional RT in advanced HL is dependent on the chemotherapy regimen used. The escalated BEACOPP

regimen is a very intensive regimen, only tolerated by young and fit patients. Another quite intensive regimen, Stanford V, has RT as an integral component of the treatment [43]. This regimen features an abbreviated course of chemotherapy, increased dose intensity of the individual drugs, and a reduction in the cumulative doses. RT to 36 Gy is given to sites of initial bulky disease (≥5 cm) and macroscopic splenic disease. Around 90 % of patients treated with this regimen for advanced disease received RT, and results have been excellent in phase II or retrospective studies [43–45]. It is evident, however, that inferior results with this regimen are achieved if RT is not administered as intended in the original regimen [46, 47]. Two large randomized trials have compared the Stanford V regimen with the ABVD regimen, both given with appropriate RT [48, 49]. Seventy-five percent and 73 % of patients received RT with the Stanford V regimen and 41 and 53 % received RT with the ABVD regimen in the two trials. No difference in outcome was found except for patients with high International Prognostic Score (IPS), where Stanford V was inferior with respect to failure-free survival (FFS) [48, 49].

New drugs are being introduced in the primary treatment of HL, notably brentuximab vedotin, and, reassuringly, no added toxicity was seen when combining this drug with RT [50].

In conclusion, in advanced HL, RT to residual disease and/or initial bulk benefits some patients, depending on the chemotherapy regimen used. The percentage of patients needing RT varies from about 10 % with the intensive BEACOPP regimen, to about 40 % with ABVD, and about 80 % with the Stanford V regimen. With the additional information from PET evaluation, the number of patients needing RT may be smaller, but this has not been tested in a randomized trial.

Advanced aggressive NHL

The most common type of aggressive B cell lymphoma is diffuse large B cell lymphoma (DLBCB). In advanced DLBCL, for many years, the prevailing opinion was that "these patients relapsed in multiple different areas suggesting that adjuvant radiation therapy to the site of initial bulk disease was unlikely to benefit patients" [51]. However, this statement, which was repeated for decades, was actually based on just ten recurrences in a retrospective series from 1976 to 1986.

The treatment of DLBCL (and other B cell lymphomas) changed with the introduction of rituximab (R), which significantly improved outcome when combined with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-like chemotherapy [52–54]. An analysis of the pattern of failure in 96 patients with advanced DLBCL in CR after R-CHOP alone showed that 21 patients had isolated local recurrence, the majority from bulky (≥5 cm) sites [55]. A further 21 patients failed at both initial presenting sites and distant sites, and again the majority had initial bulky disease. Isolated distant recurrence was rare (three patients), suggesting that local control is intimately linked with distant control.

Another retrospective study included 279 patients with advanced DLBCL treated with R-CHOP, in 39 patients (23 with bulky disease (>5 cm)) supplemented by RT [56]. The authors did multivariate and matched-pair analysis in

order to try to compensate for the retrospective nature of the study, and demonstrated a significant benefit of RT. No detailed analysis of relapse location was included, but all failures in patients treated with RT occurred outside of the radiation fields.

Another retrospective study included 79 patients with advanced DLBCL achieving CR with chemotherapy, only 65 % with R-CHOP [57]. Consolidation RT was given to involved sites of disease in 38 patients. Of the patients who received RT, one patient relapsed in initially involved sites only, one at an uninvolved site, and two in both involved and uninvolved sites. Of the patients who did not receive RT, three patients relapsed in initially involved sites only, three in uninvolved sites only, and seven in both. Multivariate analysis was made in order to compensate for the retrospective nature of the study, demonstrating improved EFS with RT, but no effect on OS. However, numbers were small.

Large, prospective, randomized trials are now appearing, providing more solid data not only on different chemotherapy schedules, but also on the use of RT in advanced DLBCL.

The MabThera International Trial (MInT) tested the addition of R to CHOP-like chemotherapy in young patients with good-prognosis stage I bulky (defined as >5 cm, >7.5 cm, or >10 cm according to the defined cutoff points of the participating cooperative groups) or stage II–IV disease [58]. RT was given to sites of primary bulky disease to a median of 36 Gy, which was well adhered to. RT could also be given to primary extranodal disease at the treating physician's discretion, but this was rarely done. Only 226 of the 823 patients were in stages III and IV, and it is not possible to tease out the results for these patients from the publication. However, the interesting point in this study from a RT perspective is the comparison which is made with the French LNH03-2B trial [59]. In the French study, young patients with age-adjusted International Prognostic Index (IPI) of 1 were randomized between R-CHOP and R plus doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone, with subsequent consolidation with methotrexate, ifosfamide, etoposide, and cytarabine (ACVBP), a dose-intense regimen with sequential consolidation with a significantly higher rate of toxic effects. No RT was given. In the French study, 208 out of 369 patients were in stages III and IV. Comparing patients with an age-adjusted IPI of 1 from the MInT study and from the LNH03-2B study, a striking difference in the outcome of patients treated with R-CHOP was found, with clearly inferior results in the LNH03-2B study. The most obvious difference between the two studies was the use of RT, which was given to 49 % of the patients from the MInT trial and none of the patients from the LNH03-2B trial. In fact, the outcome of patients treated with the intensive R-ACVBP regimen in the LNH03-2B trial was virtually identical to the outcome of patients treated with R-CHOP and RT to bulky disease in the MInT trial. Comparisons of this kind between studies are fraught with methodological problems, and the (correct) conclusion of this comparison was that a randomized study of the role of RT to bulky disease was needed.

In the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL), RT to initial bulky disease (>7.5 cm) or extralymphatic

involvement has been recommended, although this strategy had never been tested in a randomized trial. The RICOVER-60 trial tested the addition of R to CHOP in patients over 60 years [60]. A total of 656 out of 1222 patients were assigned to RT, and 417 patients received the RT according to protocol. An exploratory subgroup analysis showed no difference in event-free survival (EFS) in the R-treated groups between patients assigned to RT or no RT. To address the question of the role of RT in patients treated with 6 cycles of R-CHOP-14, the superior arm in the RICOVER-60 trial, an additional cohort of patients were treated in an amendment to the protocol, designated as RICOVER-noRTh [61••]. These patients were treated without RT and compared with patients who had received the same immunochemotherapy plus RT to bulky disease or extralymphatic involvement in the RICOVER-60 trial. A total of 164 patients were treated in the RICOVER-noRTh trial and compared to 306 patients from the RICOVER-60 trial. The patients in the RICOVER-noRTh trial were older, more often had stage III or IV disease and extralymphatic involvement, and had higher IPI-scores, but they less often had bulky disease. Only 57 % of patients with bulky disease in the RICOVER-60 cohort received RT, and 23 % of patients with bulky disease in the RICOVER-noRTh underwent unplanned RT. In intention-to-treat analyses, EFS was inferior in RICOVER-noRTh, but for this analysis, unplanned (protocol-violating) RT was counted as events. There were no significant differences in PFS and OS for patients with bulky disease, where unplanned RT was not counted as events, but there was a strong trend for worse outcome in RICOVER-noRTh. However, per-protocol analyses restricted to patients with bulky disease who were treated according to protocol revealed inferior EFS, PFS, and OS in RICOVER-noRTh compared with RICOVER-60. In a multivariable Cox model adjusted for IPI and age, bulky disease was a prognostic factor in RICOVER-noRTh but not in RICOVER-60. The conclusion of this study is that RT to bulky disease is recommended in patients treated with R-CHOP for aggressive B cell lymphomas.

The DSHNHL subsequently initiated the UNFOLDER trial to properly test in a randomized trial the addition of RT (39.6 Gy) to initial bulky disease or extralymphatic involvement in young patients with aggressive B cell lymphoma, age-adjusted IPI 1 (all) or 0 (with bulky disease ≥7.5 cm), treated with 6 cycles of R-CHOP-14 or R-CHOP-21. A planned interim analysis after 285 patients had been randomized led to the closure of the RT randomization because the results in the no RT arm were inferior and met the predefined stopping rules. The final analyses and publication of this trial are eagerly awaited.

The DSHNHL has published analyses of pooled data from 11 consecutive trials carried out both before and after the introduction of rituximab. They analyzed the outcome of patients with aggressive B cell lymphomas with skeletal involvement and concluded that RT to sites of skeletal involvement had a beneficial effect, whereas rituximab did not [62]. They also analyzed the outcome of patients with extralymphatic craniofacial involvement and concluded that RT did not improve outcome in patients treated with rituximab who achieved CR (or unconfirmed CR, as most of these patients were evaluated without PET) [63]. However, these analyses represent unplanned subgroup analyses without any a priori hypotheses and should be viewed with some reservation. Moreover, the group of extralymphatic craniofacial lymphomas is quite heterogeneous, consisting of lymphomas in the orbit (presumably extraocular, although that is not specified), paranasal sinuses, nasal cavity,

tongue (presumably the free part, as the base of tongue is part of the Waldeyer ring), remaining oral cavity, and salivary glands. Specifically, lymphomas in the Waldeyer ring (consisting of the adenoid structures in the nasopharynx, the tonsils, and the base of tongue), which is much more commonly involved, were not included since it is by definition not an extralymphatic site.

The conclusion of these studies is that with modern rituximab-containing systemic treatment for advanced aggressive B cell lymphomas, there is an effect of RT in the treatment of patients with bulky disease or extralymphatic involvement, but whether it is true for both or just for bulky disease, and which extralymphatic sites are important, are still unsettled issues.

In patients with advanced aggressive B cell lymphomas with insufficient response to systemic treatment, the role of RT to residual disease has not been examined in randomized trials in patients treated with rituximab-containing regimens and with PET response evaluation. A study by the DSHNHL is ongoing (the OPTIMAL >60 trial).

A retrospective analysis was published of four successive EORTC trials of a total of 974 patients with untreated advanced aggressive lymphomas treated with doxorubicin-based chemotherapy [64]. A total of 238 patients were in PR after eight cycles of chemotherapy, 114 were treated with RT (median dose 40 Gy), and 113 received other treatments. RT could convert a PR to a CR in half of the patients. Survival of patients obtaining a CR by salvage treatment was comparable to that of complete responders after first-line chemotherapy alone (58 % at 5 years). The conclusion of the study was that PR patient with initial low to intermediate IPI, bulky disease, or nodal disease only can be salvaged by RT. However, the study stems from a time when rituximab had not been introduced for the treatment of aggressive B cell lymphomas, and response evaluation by PET was not performed in all patients.

A positive interim or postchemotherapy PET scan is a strong negative prognostic factor in aggressive lymphomas [65, 66]. However, it is not clear if a positive PET scan can help guide the decision to deliver RT. In one study, 65 % of patients with positive postchemotherapy PET scans achieved long-term EFS after RT [67], but most of the patients were early stage. In another study, 20 patient with positive interim or postchemotherapy PET scans had a PFS 3 years after RT (36 Gy) of 85 % [68], indicating that most patients with residual FDG avidity during and after chemotherapy can be successfully treated with RT. However, the majority of these patients were early stage. A third study, on the contrary, analyzed 31 patients with mostly advanced disease who were PET-positive after chemotherapy [69]. Over half of these patients had a recurrence, and there was no difference in risk of recurrence between those who did and those who did not receive RT (median dose 30.6 Gy). In conclusion, it still remains unclear if PET can identify those who will benefit from RT.

Advanced indolent NHL

The most common type of indolent lymphoma is follicular lymphoma (FL). It most often presents with advanced disease, and although sensitive to both chemotherapy and immunotherapy with rituximab, it is incurable with

systemic treatments. In selected patients, mainly those with minimal stage III disease, total lymphoid irradiation has led to prolonged RFS in selected patients [70–73]. However, this treatment is rarely used today. Systemic immunochemotherapy is the mainstay of treatment for advanced indolent lymphoma.

Indolent lymphomas are exquisitely radiosensitive, and localized RT to very low doses can achieve excellent palliation [74, 75, 76•, 77–82]. A total dose of just 4 Gy given in two fractions achieves response rates around 90 %, most of them CRs, with a response duration of over 2 years. Importantly, this treatment has very few side effects, even in situations where relatively large treatment fields are necessary, e.g., whole abdominal irradiation, and can be repeated as necessary. The biological basis for this extreme radiosensitivity seems to be p53 induction and apoptosis [83, 84].

Conclusion

RT is one of the most effective agents available for the treatment of lymphomas. In advanced HL, RT to residual disease after chemotherapy and/or initial bulk benefits some patients, depending on the chemotherapy regimen used. In advanced aggressive NHL, most of the evidence comes from DLBCL, and in patients treated with modern immunochemotherapy, RT to initial bulky disease or extralymphatic involvement improves outcome. For both HL and aggressive NHL, RT to residual masses after systemic treatment is effective. In advanced indolent NHL, low-dose RT offers excellent palliation. The role of PET in defining patients who will benefit from the addition of RT has not been determined and needs further investigation.

Compliance with Ethical Standards

Conflict of Interest
Lena Specht has received compensation from Takeda for service as an advisory board member and principal investigator.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Hoppe RT, Horning SJ, Rosenberg SA. The concept, evolution and preliminary results of the current Stanford clinical trials for Hodgkin's disease. Cancer Surv. 1985;4:459–75.

2. Specht L, Gray RG, Clarke MJ, Peto R. Influence of more extensive radiotherapy and adjuvant chemotherapy on long-term outcome of early-stage Hodgkin's disease: a meta-analysis of 23 randomized trials involving 3,888

patients. International Hodgkin's Disease Collaborative Group. J Clin Oncol. 1998;16:830–43.
3. Yahalom J, Varsos G, Fuks Z, Myers J, Clarkson BD, Straus DJ. Adjuvant cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy after radiation therapy in stage I low-grade and intermediate-grade non-Hodgkin lymphoma. Results of a prospective randomized study. Cancer. 1993;71:2342–50.
4. Aleman BM, van den Belt-Dusebout AW, de Bruin ML, van't Veer MB, Baaijens MH, de Boer JP, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood. 2007;109:1878–86.
5. Cutter DJ, Schaapveld M, Darby SC, Hauptmann M, van Nimwegen FA, Krol AD, et al. Risk of valvular heart disease after treatment for Hodgkin lymphoma. J Natl Cancer Inst. 2015;107, djv008.
6. Daniels LA, Krol AD, Schaapveld M, Putter H, Jansen PM, Marijt EW, et al. Long-term risk of secondary skin cancers after radiation therapy for Hodgkin's lymphoma. Radiother Oncol. 2013;109:140–5.
7. de Bruin ML, Sparidans J, van't Veer MB, Noordijk EM, Louwman MW, Zijlstra JM, et al. Breast cancer risk in female survivors of Hodgkin's lymphoma: lower risk after smaller radiation volumes. J Clin Oncol. 2009;27:4239–46.
8. de Bruin ML, Dorresteijn LD, van't Veer MB, Krol AD, van der Pal HJ, Kappelle AC, et al. Increased risk of stroke and transient ischemic attack in 5-year survivors of Hodgkin lymphoma. J Natl Cancer Inst. 2009;101:928–37.
9. de Bruin ML, Burgers JA, Baas P, van't Veer MB, Noordijk EM, Louwman MW, et al. Malignant mesothelioma after radiation treatment for Hodgkin lymphoma. Blood. 2009;113:3679–81.
10. Dores GM, Metayer C, Curtis RE, Lynch CF, Clarke EA, Glimelius B, et al. Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. J Clin Oncol. 2002;20:3484–94.
11. Dores GM, Curtis RE, van Leeuwen FE, Stovall M, Hall P, Lynch CF, et al. Pancreatic cancer risk after treatment of Hodgkin lymphoma. Ann Oncol. 2014;25:2073–9.
12. Hodgson DC, Gilbert ES, Dores GM, Schonfeld SJ, Lynch CF, Storm H, et al. Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma. J Clin Oncol. 2007;25:1489–97.
13. Mauch P, Ng A, Aleman B, Carde P, Constine L, Diehl V, Dinshaw K, Gospodarowicz M, Hancock S, Hodgson D, Hoppe R, Liang R, Loeffler M, Specht L, Travis LB, Wirth A, Yahalom J. Report from the Rockefellar Foundation Sponsored International Workshop on reducing mortality and improving quality of life in long-term survivors of Hodgkin's disease: July 9–16, 2003, Bellagio, Italy. Eur J Haematol Suppl 2005; 68–76.
14. Morton LM, Dores GM, Curtis RE, Lynch CF, Stovall M, Hall P, et al. Stomach cancer risk after treatment for Hodgkin lymphoma. J Clin Oncol. 2013;31:3369–77.
15. Morton LM, Gilbert ES, Stovall M, van Leeuwen FE, Dores GM, Lynch CF, et al. Risk of esophageal cancer following radiotherapy for Hodgkin lymphoma. Haematologica. 2014;99:e193–6.
16. Swerdlow AJ, Cooke R, Bates A, Cunningham D, Falk SJ, Gilson D, et al. Breast cancer risk after supradiaphragmatic radiotherapy for Hodgkin's lymphoma in England and Wales: a National Cohort Study. J Clin Oncol. 2012;30:2745–52.
17. Travis LB, Curtis RE, Glimelius B, Holowaty E, van Leeuwen FE, Lynch CF, et al. Second cancers among long-term survivors of non-Hodgkin's lymphoma. J Natl Cancer Inst. 1993;85:1932–7.
18. Travis LB, Gospodarowicz M, Curtis RE, Clarke EA, Andersson M, Glimelius B, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J Natl Cancer Inst. 2002;94:182–92.
19. Travis LB, Hill D, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, et al. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. J Natl Cancer Inst. 2005;97:1428–37.
20. Travis LB, Ng AK, Allan JM, Pui CH, Kennedy AR, Xu XG, et al. Second malignant neoplasms and cardiovascular disease following radiotherapy. J Natl Cancer Inst. 2012;104:357–70.
21. van Leeuwen FE, Klokman WJ, Stovall M, Dahler EC, van't Veer MB, Noordijk EM, et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. J Natl Cancer Inst. 2003;95:971–80.
22. van Nimwegen FA, Schaapveld M, Janus CP, Krol AD, Raemaekers JM, Kremer LC, et al. Risk of diabetes mellitus in long-term survivors of Hodgkin lymphoma. J Clin Oncol. 2014;32:3257–63.
23. van Nimwegen FA, Schaapveld M, Janus CP, Krol AD, Petersen EJ, Raemaekers JM, et al. Cardiovascular Disease After Hodgkin Lymphoma Treatment: 40-Year Disease Risk. JAMA Int Med. 2015;175:1007–17.
24. Koh ES, Tran TH, Heydarian M, Sachs RK, Tsang RW, Brenner DJ, et al. A comparison of mantle versus involved-field radiotherapy for Hodgkin's lymphoma: reduction in normal tissue dose and second cancer risk. Radiat Oncol. 2007;2:13.
25. Maraldo MV, Brodin NP, Vogelius IR, Aznar MC, Munck Af RP, Petersen PM, et al. Risk of developing cardiovascular disease after involved node radiotherapy versus mantle field for Hodgkin lymphoma. Int J Radiat Oncol Biol Phys. 2012;83:1232–7.
26. Maraldo MV, Brodin P, Aznar MC, Vogelius IR, Munck Af RP, Petersen PM, et al. Doses to carotid arteries after modern radiation therapy for Hodgkin lymphoma: is stroke still a late effect of treatment? Int J Radiat Oncol Biol Phys. 2013;87:297–303.
27. Maraldo MV, Brodin NP, Aznar MC, Vogelius IR, Munck Af RP, Petersen PM, et al. Estimated risk of cardiovascular disease and secondary cancers with modern highly conformal radiotherapy for early-stage mediastinal Hodgkin lymphoma. Ann Oncol. 2013;24:2113–8.

28. Maraldo MV, Jorgensen M, Brodin NP, Aznar MC, Vogelius IR, Petersen PM, et al. The impact of involved node, involved field and mantle field radiotherapy on estimated radiation doses and risk of late effects for pediatric patients with Hodgkin lymphoma. Pediatr Blood Cancer. 2014;61:717–22.

29.•• Eich HT, Diehl V, Gorgen H, Pabst T, Markova J, Debus J, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. J Clin Oncol. 2010;28:4199–206.

Large randomized trial of radiation dose to unfavourable HL.

30. Engert A, Plutschow A, Eich HT, Lohri A, Dorken B, Borchmann P, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. N Engl J Med. 2010;363:640–52.

31. Hoskin PJ, Kirkwood AA, Popova B, Smith P, Robinson M, Gallop-Evans E, et al. 4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial. Lancet Oncol. 2014;15:457–63.

32.•• Lowry L, Smith P, Qian W, Falk S, Benstead K, Illidge T, et al. Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: a randomised phase III trial. Radiother Oncol. 2011;100:86–92.

Large randomized trial of radiation dose to aggressive and indolent NHL.

33.•• Illidge T, Specht L, Yahalom J, Aleman B, Berthelsen AK, Constine L, et al. Modern radiation therapy for nodal non Hodgkin lymphoma - target definition and dose guidelines from the International Lymphoma Radiation Oncology Group (ILROG). Int J Radiat Oncol Biol Phys. 2014;89:49–58.

Guidelines for modern RT for nodal NHL.

34.•• Specht L, Yahalom J, Illidge T, Berthelsen AK, Constine LS, Eich HT, et al. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the international lymphoma radiation oncology group (ILROG). Int J Radiat Oncol Biol Phys. 2014;89:854–62.

Guidelines for modern RT for HL.

35.•• Yahalom J, Illidge T, Specht L, Hoppe RT, Li YX, Tsang R, et al. Modern radiation therapy for extranodal lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys. 2015;92:11–31.

Guidelines for modern RT for extranodal NHL.

36. NCCN Clinical Practice Guidelines in Oncology, Non-Hodgkin's Lymphomas Version 2.2015.

37.• Aleman BM, Raemaekers JM, Tirelli U, Bortolus R, van't Veer MB, Lybeert ML, et al. Involved-field radiotherapy for advanced Hodgkin's lymphoma. N Engl J Med. 2003;348:2396–406.

Large randomized trial of RT in advanced NHL before the rituximab era.

38.• Aleman BM, Raemaekers JM, Tomisic R, Baaijens MH, Bortolus R, Lybeert ML, et al. Involved-field radiotherapy for patients in partial remission after chemotherapy for advanced Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys. 2007;67:19–30.

Analysis of patients in PR after non rituximab treatment for advanced NHL.

39. Johnson PW, Radford JA, Cullen MH, Sydes MR, Walewski J, Jack AS, et al. Comparison of ABVD and Alternating or hybrid multidrug regimens for the treatment of advanced Hodgkin's lymphoma: results of the United Kingdom Lymphoma Group LY09 Trial (ISRCTN97144519). J Clin Oncol. 2005;23:9208–18.

40. Borchmann P, Haverkamp H, Diehl V, Cerny T, Markova J, Ho AD, et al. Eight cycles of escalated-dose BEACOPP compared with four cycles of escalated-dose BEACOPP followed by four cycles of baseline-dose BEACOPP with or without radiotherapy in patients with advanced-stage Hodgkin's lymphoma: final analysis of the HD12 trial of the German Hodgkin Study Group. J Clin Oncol. 2011;29:4234–42.

41.•• Engert A, Haverkamp H, Kobe C, Markova J, Renner C, Ho A, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. Lancet. 2012;379:1791–9.

Large randomized trial in advanced HL in the PET era.

42. Engert A, Diehl V, Franklin J, Lohri A, Dorken B, Ludwig WD, et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. J Clin Oncol. 2009;27:4548–54.

43. Horning SJ, Hoppe RT, Breslin S, Bartlett NL, Brown BW, Rosenberg SA. Stanford V and radiotherapy for locally extensive and advanced Hodgkin's disease: mature results of a prospective clinical trial. J Clin Oncol. 2002;20:630–7.

44. Advani R, Ai WZ, Horning SJ. Management of advanced stage Hodgkin lymphoma. J Natl Compr Canc Netw. 2006;4:241–7.

45. Edwards-Bennett SM, Jacks LM, Moskowitz CH, Wu EJ, Zhang Z, Noy A, et al. Stanford V program for locally extensive and advanced Hodgkin lymphoma: the Memorial Sloan-Kettering Cancer Center experience. Ann Oncol. 2010;21:574–81.

46. Chisesi T, Bellei M, Luminari S, Montanini A, Marcheselli L, Levis A, et al. Long-term follow-up analysis of HD9601 trial comparing ABVD versus Stanford V versus MOPP/EBV/CAD in patients with newly diagnosed advanced-stage Hodgkin's lymphoma: a study from the Intergruppo Italiano Linfomi. J Clin Oncol. 2011;29:4227–33.

47. Gobbi PG, Levis A, Chisesi T, Broglia C, Vitolo U, Stelitano C, et al. ABVD versus modified Stanford V versus MOPPEBVCAD with optional and limited radiotherapy in intermediate- and advanced-stage Hodgkin's lymphoma: final results of a multicenter randomized trial by the Intergruppo Italiano Linfomi. J Clin Oncol. 2005;23:9198–207.

48. Gordon LI, Hong F, Fisher RI, Bartlett NL, Connors JM, Gascoyne RD, et al. Randomized phase III trial of

ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). J Clin Oncol. 2013;31:684–91.

49. Hoskin PJ, Lowry L, Horwich A, Jack A, Mead B, Hancock BW, et al. Randomized comparison of the stanford V regimen and ABVD in the treatment of advanced Hodgkin's lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group Study ISRCTN 64141244. J Clin Oncol. 2009;27:5390–6.
50. Kumar A, Yahalom J, Schoder H, Caron P, Drullinsky P, Gerecitano JF, et al. Safety and early efficacy in an ongoing pilot study of brentuximab vedotin and AVD chemotherapy followed by 30 Gray involved site radiotherapy for newly diagnosed, early stage, unfavorable risk Hodgkin lymphoma. Blood. 2014;124:3085.
51. Shipp MA, Klatt MM, Yeap B, Jochelson MS, Mauch PM, Rosenthal DS, et al. Patterns of relapse in large-cell lymphoma patients with bulk disease: implications for the use of adjuvant radiation therapy. J Clin Oncol. 1989;7:613–8.
52. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346:235–42.
53. Habermann TM, Weller EA, Morrison VA, Gascoyne RD, Cassileth PA, Cohn JB, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol. 2006;24:3121–7.
54. Pfreundschuh M, Trumper L, Osterborg A, Pettengell R, Trneny M, Imrie K, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol. 2006;7:379–91.
55. Shi Z, Das S, Okwan-Duodu D, Esiashvili N, Flowers C, Chen Z, et al. Patterns of failure in advanced stage diffuse large B-cell lymphoma patients after complete response to R-CHOP immunochemotherapy and the emerging role of consolidative radiation therapy. Int J Radiat Oncol Biol Phys. 2013;86:569–77.
56. Phan J, Mazloom A, Medeiros LJ, Zreik TG, Wogan C, Shihadeh F, et al. Benefit of consolidative radiation therapy in patients with diffuse large B-cell lymphoma treated with R-CHOP chemotherapy. J Clin Oncol. 2010;28:4170–6.
57. Dorth JA, Prosnitz LR, Broadwater G, Diehl LF, Beaven AW, Coleman RE, et al. Impact of consolidation radiation therapy in stage III-IV diffuse large B-cell lymphoma with negative post-chemotherapy radiologic imaging. Int J Radiat Oncol Biol Phys. 2012;84:762–7.
58. Pfreundschuh M, Kuhnt E, Trumper L, Osterborg A, Trneny M, Shepherd L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. Lancet Oncol. 2011;12:1013–22.
59. Recher C, Coiffier B, Haioun C, Molina TJ, Ferme C, Casasnovas O, et al. Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial. Lancet. 2011;378:1858–67.
60. Pfreundschuh M, Schubert J, Ziepert M, Schmits R, Mohren M, Lengfelder E, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol. 2008;9:105–16.
61.•• Held G, Murawski N, Ziepert M, Fleckenstein J, Poschel V, Zwick C, et al. Role of radiotherapy to bulky disease in elderly patients with aggressive B-cell lymphoma. J Clin Oncol. 2014;32:1112–8.

Analysis of amendment to large randomized trial, omitting RT to bulky disease.

62. Held G, Zeynalova S, Murawski N, Ziepert M, Kempf B, Viardot A, et al. Impact of rituximab and radiotherapy on outcome of patients with aggressive B-cell lymphoma and skeletal involvement. J Clin Oncol. 2013;31:4115–22.
63. Murawski N, Held G, Ziepert M, Kempf B, Viardot A, Hanel M, et al. The role of radiotherapy and intrathecal CNS prophylaxis in extralymphatic craniofacial aggressive B-cell lymphomas. Blood. 2014;124:720–8.
64. Moser EC, Kluin-Nelemans HC, Carde P, Meerwaldt JH, Tirelli U, Aleman BM, et al. Impact of involved field radiotherapy in partial response after doxorubicin-based chemotherapy for advanced aggressive non-Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys. 2006;66:1168–77.
65. Cashen AF, Dehdashti F, Luo J, Homb A, Siegel BA, Bartlett NL. 18F-FDG PET/CT for early response assessment in diffuse large B-cell lymphoma: poor predictive value of international harmonization project interpretation. J Nucl Med. 2011;52:386–92.
66. Spaepen K, Stroobants S, Dupont P, Vandenberghe P, Thomas J, de Groot T, et al. Early restaging positron emission tomography with (18)F-fluorodeoxyglucose predicts outcome in patients with aggressive non-Hodgkin's lymphoma. Ann Oncol. 2002;13:1356–63.
67. Dorth JA, Chino JP, Prosnitz LR, Diehl LF, Beaven AW, Coleman RE, et al. The impact of radiation therapy in patients with diffuse large B-cell lymphoma with positive post-chemotherapy FDG-PET or gallium-67 scans. Ann Oncol. 2011;22:405–10.
68. Halasz LM, Jacene HA, Catalano PJ, Van den Abbeele AD, LaCasce A, Mauch PM, et al. Combined modality treatment for PET-positive non-Hodgkin lymphoma: favorable outcomes of combined modality treatment for patients with non-Hodgkin lymphoma and positive interim or postchemotherapy

FDG-PET. Int J Radiat Oncol Biol Phys. 2012;83:e647–54.
69. Kahn ST, Flowers C, Lechowicz MJ, Hollenbach K, Johnstone PA. Value of PET restaging after chemotherapy for non-Hodgkin's lymphoma: implications for consolidation radiotherapy. Int J Radiat Oncol Biol Phys. 2006;66:961–5.
70. Cox JD, Komaki R, Kun LE, Wilson JF, Greenberg M. Stage III nodular lymphoreticular tumors (non-Hodgkin's lymphoma): results of central lymphatic irradiation. Cancer. 1981;47:2247–52.
71. De Los Santos JF, Mendenhall NP, Lynch JW. Is comprehensive lymphatic irradiation for low-grade non-Hodgkin's lymphoma curative therapy? Long-term experience at a single institution. Int J Radiat Oncol Biol Phys. 1997;38:3–8.
72. Jacobs JP, Murray KJ, Schultz CJ, Wilson JF, Goswitz MS, Stevens CW, et al. Central lymphatic irradiation for stage III nodular malignant lymphoma: long-term results. J Clin Oncol. 1993;11:233–8.
73. Murtha AD, Knox SJ, Hoppe RT, Rupnow BA, Hanson J. Long-term follow-up of patients with Stage III follicular lymphoma treated with primary radiotherapy at Stanford University. Int J Radiat Oncol Biol Phys. 2001;49:3–15.
74. Ganem G, Cartron G, Girinsky T, Haas RL, Cosset JM, Solal-Celigny P. Localized low-dose radiotherapy for follicular lymphoma: history, clinical results, mechanisms of action, and future outlooks. Int J Radiat Oncol Biol Phys. 2010;78:975–82.
75. Girinsky T, Guillot-Vals D, Koscielny S, Cosset JM, Ganem G, Carde P, et al. A high and sustained response rate in refractory or relapsing low-grade lymphoma masses after low-dose radiation: analysis of predictive parameters of response to treatment. Int J Radiat Oncol Biol Phys. 2001;51:148–55.
76.• Haas RL, Poortmans P, de Jong D, Aleman BM, Dewit LG, Verheij M, et al. High response rates and lasting remissions after low-dose involved field radiotherapy in indolent lymphomas. J Clin Oncol. 2003;21:2474–80.
Largest study of very low dose palliative RT to indolen t NHL.
77. Haas RL, Poortmans P, de Jong D, Verheij M, van der Hulst M, de Boer JP, et al. Effective palliation by low dose local radiotherapy for recurrent and/or chemotherapy refractory non-follicular lymphoma patients. Eur J Cancer. 2005;41:1724–30.
78. Johannsson J, Specht L, Mejer J, Jensen BA. Phase II study of palliative low-dose local radiotherapy in disseminated indolent non-Hodgkin's lymphoma and chronic lymphocytic leukemia. Int J Radiat Oncol Biol Phys. 2002;54:1466–70.
79. Luthy SK, Ng AK, Silver B, Degnan KO, Fisher DC, Freedman AS, et al. Response to low-dose involved-field radiotherapy in patients with non-Hodgkin's lymphoma. Ann Oncol. 2008;19:2043–7.
80. Murthy V, Thomas K, Foo K, Cunningham D, Johnson B, Norman A, et al. Efficacy of palliative low-dose involved-field radiation therapy in advanced lymphoma: a phase II study. Clin Lymphoma Myeloma. 2008;8:241–5.
81. Ng M, Wirth A, Ryan G, MacManus M, Davis S. Value of low-dose 2 × 2 Gy palliative radiotherapy in advanced low-grade non-Hodgkin's lymphoma. Australas Radiol. 2006;50:222–7.
82. Sawyer EJ, Timothy AR. Low dose palliative radiotherapy in low grade non-Hodgkin's lymphoma. Radiother Oncol. 1997;42:49–51.
83. Haas RL, de Jong D, Valdes Olmos RA, Hoefnagel CA, van den Heuvel I, Zerp SF, et al. In vivo imaging of radiation-induced apoptosis in follicular lymphoma patients. Int J Radiat Oncol Biol Phys. 2004;59:782–7.
84. Knoops L, Haas R, de Kemp S, Majoor D, Broeks A, Eldering E, et al. In vivo p53 response and immune reaction underlie highly effective low-dose radiotherapy in follicular lymphoma. Blood. 2007;110:1116–22.