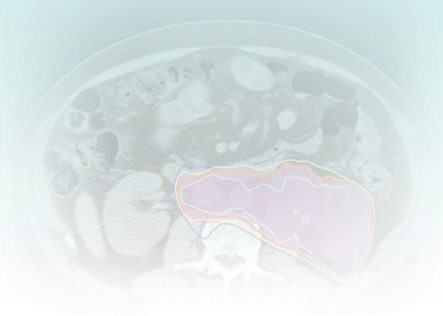
Overview



Andrea K. Ng

BASIC ISSUES IN LYMPHOMA

Significant progress had been made in recent years in the understanding of the molecular basis of lymphomagenesis, and in the diagnosis, staging, treatment, and follow-up of patients with lymphoid malignancies. The current pathological classification incorporates molecular characteristics, in addition to morphologic and clinical features in identifying distinctive subtypes of disease entities.[1] Advances in DNA microarray techniques allow improved prognostic classification of patients and provide the opportunity to develop molecularly targeted therapy for specific disease types.[2-11] More accurate staging is now available through modern medical imaging techniques and the increasing experience with functional imaging.[12]

The treatment of lymphoid malignancies had also evolved over the years. For diseases in which a high cure rate has already been achieved, the emphasis is now on treatment reduction to reduce late effects. Meanwhile, more dose-dense and dose-intense treatment, and incorporation of targeted therapy including novel agents against molecular targets or pathways, immunotherapy, and radioimmunotherapy are being used in diseases in which the cure rate is still suboptimal.

PATHOLOGICAL CLASSIFICATION

The classification of lymphoid malignancies has evolved over the past century. Previous lymphoma classification relied mainly on subtleties of morphology, cell lineage and differentiation, or clinical survival data. In 1994, the International Lymphoma Study Group published the Revised European-American Lymphoma (REAL) classification of tumors of hematopoietic and lymphatic tissues, which was later modified and updated in the World Health Organization (WHO) project.[13-15] The WHO classification combined information on morphology, immunophenotype, genetic features, and clinical features to define individual disease entity. The 2008 update provided new criteria for the recognition of some previously described neoplasms and clarified the defining criteria for others. Furthermore, it added new entities that were defined by recently discovered genetic features.[16] Despite its seeming complexity, its clinical practicality is supported by the fact that the majority of cases could be classified into one of the disease categories, that an excellent interobserver reproducibility has been demonstrated, and that the disease entities in the classification were indeed clinically distinctive, both at initial presentation and in treatment outcome.

Modern pathological classification allows researchers, pathologists, and clinicians to have a common language in diagnosing and treating different disease types and in comparing treatment results. It is anticipated that with continued progress in the field of genetic analysis, continued updating and revisions of any current classification will be necessary. Advances in the field may provide additional markers for classification, and identify new categories of disease that are not currently recognized.

MOLECULAR BASIS OF LYMPHOID MALIGNANCIES

Emerging data are now available on the origin of the malignant cells of Hodgkin's disease, the Hodgkin's Reed-Sternberg cells, and the molecular events that lead to the malignant transformation.[17-19] The nuclear factor-kappa-B (NF-κB) pathway has been implicated to play an important role in the pathogenesis of Hodgkin's disease,[20,21] and continued research in this area may provide new therapeutic targets for the disease.

Researchers have used cDNA microarray techniques to identify molecular prognostic factors for lymphoma.[2-4,6] For diffuse large B-cell lymphoma (DLBCL), using transcriptional profiling, subtypes of disease with distinct clinical outcome have been identified.[2-4,7] Genes that have been implicated in predicting treatment outcome, independent of that of the international prognostic index (IPI), include ones that regulate molecular signaling pathways and apoptotic response to treatment.[3,4] Using similar techniques, it has also been shown that the tumor microenvironment and host inflammatory response may play a key role in identifying subgroups of patients with differing prognoses in both follicular lymphoma and DLBCL.[6,22-24] Molecular prognostic factors promise to further improve risk stratification, and more importantly, provide insights into molecular pathogenesis of different subtypes of lymphoma and guide the development of novel, targeted therapy.[25]

STAGING

Improvement in imaging techniques had led to the modification of the original Ann Arbor staging classification for lymphoma, allowing incorporation of computed tomography (CT) scan results in assessing disease extent.[26] Currently, functional imaging is routinely included as part of initial lymphoma staging. The superior accuracy of fludeoxyglucose

(18F)-positron emission tomography (FDG-PET) has been shown to result in a change in the stage of 18% to 45%, and a change in management in 18% to 31% of the patients.[12] Furthermore, it has been demonstrated that incorporation of FDG-PET in radiotherapy planning resulted in modification of target volume and fields in a considerable proportion of patients.[27-30]

TREATMENT

The following is a summary of the overall treatment approaches, with a focus on the role of radiation therapy, for the three types of hematological malignancies: Hodgkin's lymphoma, non-Hodgkin's lymphoma, and plasma cell neoplasms.

Hodgkin's Lymphoma

Stages I to II Hodgkin's Lymphoma

Combined modality therapy for early-stage Hodgkin's lymphoma is associated with a cure rate of more than 90%. Currently, one of the main challenges in the management of patients with early-stage Hodgkin's lymphoma is to minimize treatment-related late complications while preserving excellent disease control. Strategies to reduce treatment, from the radiation therapy standpoint, include the use of smaller treatment fields, lower radiation doses, or elimination of radiation therapy.

Over the last several decades, radiation treatment fields for Hodgkin's lymphoma have evolved from extended-field to involved-field,[31-33] and mostly recently to involved-site/involved node radiotherapy (ISRT/INRT).[34,35] Retrospective studies have shown that ISRT/INRT as part of combined-modality therapy for early-stage Hodgkin's lymphoma did not result in any marginal misses, and yielded progression-free survival rates of more than 90%.[36,37] In the EORTC/Lymphoma Study Association (LYSA)/the Italian Lymphoma Foundation (FIL) H10 and H11 trials, INRT was adopted in both the standard and experimental arms, the results of which are pending at this time. In the ongoing German Hodgkin's Study Group (GHSG) HD17 trial for patients with early-stage disease with risk factors, the standard arm consisted of chemotherapy and involved-field radiotherapy, and the experimental arm used INRT for patients with PET-positive disease after chemotherapy.

Radiation dose deescalation from 30 Gy to 20 Gy was explored in the GHSG HD10 and HD11 trials for patients with early-stage, low-risk disease (no bulky mediastinal mass or extranodal disease, less than three nodal sites, low sedimentation rate) and high-risk disease, respectively.[38,39] In the HD10 trial, at a median follow-up of 7.5 years, there were no differences in 8-year freedom-from-treatment-failure and overall survival between 20 Gy versus 30 Gy after two to four cycles Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy.[38] This suggests that in patients with low-risk disease as per the GHSG criteria, two cycles followed by 20 Gy of radiotherapy is adequate. In the HD11 trial,[39] at a median follow-up of 82 months, there was no significant difference in 5-year freedom-from-treatment-failure rates between baseline bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) and ABVD when followed by 30 Gy of involved-field radiotherapy; however, inferiority of 20 Gy cannot be excluded after four cycles of ABVD, leading to the authors' conclusion that 30 Gy as optimal radiotherapy dose after ABVD for early-stage, unfavorable Hodgkin's lymphoma.

Randomized trials have been performed examining whether radiation therapy can be safely omitted.[40-47] The Cochrane Haematological Malignancies Group conducted a meta-analysis that included five randomized controlled trials comparing chemotherapy alone with identical chemotherapy combined with radiotherapy for patients with stages I to II Hodgkin's lymphoma.[48] The results showed that, in addition to a significant disease-control benefit favoring the combined-modality therapy approach, there was a highly significant overall survival benefit with the addition of radiation therapy (hazard ratio [HR], 0.4; $p < 0.00001$).

The elimination of radiotherapy based on PET-response or early PET-response to chemotherapy is being explored by a number of randomized trials. In the EORTC/LYSA/FIL H10 and H11 trials, the experimental arms consisted of omission of radiation therapy for patients with complete PET response after two cycles of ABVD, compared against the standard arms of combined-modality therapy. Interim analysis results showed that in both studies, the objective of noninferiority of chemotherapy alone as compared with combined-modality therapy has not been met, and at the recommendation of an independent data monitoring committee, the experimental arms of no radiotherapy in both groups of patients were closed.[49] The United Kingdom RAPID trial compared combined-modality therapy with chemotherapy alone in early-stage patients with complete PET-response after three cycles of ABVD.[50] At a median follow up time of 48.6 months, by intent-to-treat analysis, there was no difference between the radiotherapy versus no radiotherapy. However, by per-treatment analysis, there is a significant benefit in the radiotherapy arm (3-year progression-free survival 97% versus 90.7%, $p = 0.03$). Based on these preliminary result, there appears to be a modest, approximately 7% gain in progression-free survival with the addition of radiotherapy on patients who achieved a complete PET response after chemotherapy. This slightly lower cure rate and toxicity of salvage therapy in the small proportion of patients with relapse disease needs to be weighed against the limited toxicity of modern radiotherapy. Two ongoing trials conducted by the GHSG are exploring omission of radiotherapy by PET-response, including the HD16 trial for patients with low-risk early-stage disease, and the HD17 trial for patients with early-stage disease with adverse risk factors. Results from the ongoing trials as well as mature results of completed trials are needed to confirm the safety of elimination of radiotherapy in patients with early-stage disease with complete PET response to chemotherapy.

Stages III to IV

The role of radiation therapy in patients with advanced-stage Hodgkin disease is controversial. Most of the randomized trials do not show a significant benefit with the addition of radiation therapy to chemotherapy.[51-58] However, there are subgroups of patients who may benefit from consolidative radiation therapy, namely, patients who failed to achieve a complete response to chemotherapy and those with bulky disease at presentation.[52,56,59,60] In a study from the United Kingdom, comparing irradiated versus patients who were nonirradiated with advanced-stage disease recruited on several clinical trials,[60] at a median follow-up of 6.9 years, a significantly higher progression-free survival (71% versus 86%, $p < 0.0001$) and overall survival rates (87% versus 93%, $p = 0.014$) were found in patients who received radiation therapy, despite the fact that there were significantly more patients with bulky disease and patients with partial response in the irradiated cohort.

The GHSG HD12 trial is a four-arm study for patients with bulky stage IIB and stages III to IV disease comparing two different BEACOPP variants with or without radiation therapy.[58] At a median follow-up of 69 months, there was no significant difference in 5-year FFTF between the radiotherapy or no-radiotherapy arms (90.4% versus 87%, $p = 0.08$). However,

on subgroup analysis, among patients with residual disease of >1.5 cm, there was a significantly higher (5.8%; 95% confidence interval [CI], 1.0% to 10.7%) 5-year freedom-from-treatment failure in the radiotherapy arm. However, among patients with <1.5-cm residual disease after chemotherapy, there was no significant benefit with the addition of radiotherapy even among patients with initial disease of 5 cm or greater.

In the GHSG HD15 trial,[61] patients with advanced-stage disease with complete response or with residual disease <2.5 cm after chemotherapy received no further treatment, whereas patients with residual disease of 2.5 cm or greater underwent PET scanning. Radiotherapy was administered only in patients with residual PET-avid disease, and as such only 11% of patients on this trial received radiotherapy. The planning target volume in this trial included the PET-positive residual disease with a 1.5-cm expansion. The 4-year progression-free survival of patients who achieved a complete response to chemotherapy and did not receive radiation therapy was 92.1%. It is noteworthy, however, that this excellent outcome was based on patients treated with variants of BEACOPP regimens and may not be applicable to patients treated with ABVD. In the response-adapted trials conducted by the GITIL and FIL (HD0607 and HD0801) for patients with advanced-stage Hodgkin's lymphoma, patients with complete PET-response after ABVD chemotherapy, patients were randomized to radiotherapy versus no-radiotherapy. The results of these two trials will clarify the role of consolidative radiotherapy in patients with advanced-stage Hodgkin's lymphoma with complete PET-response after ABVD chemotherapy.

Nodular Lymphocyte Predominant Hodgkin's Disease

Nodular lymphocyte predominant Hodgkin's disease (NLPHD) is a disease entity distinct from classical Hodgkin's disease based on its morphologic, immunophenotypic, and clinical characteristics.[14,62] The majority of cases of NLPHD present with stages I to II disease. Different management options exist[63-67]; however, radiation therapy alone remains the mainstay treatment for patients with localized disease. Studies have shown that as treatment fields evolved from extended- to involved-field radiation therapy, there was no significant compromise of disease control. The current recommendation is further field reduction to ISRT to 30 Gy to 36 Gy. In the setting of radiotherapy as the only treatment modality, the clinical target volume (CTV) should encompass gross disease as well as suspected subclinical disease.[34]

Patients with additional relapses tend to remain responsive to further therapy. These patients are more likely to die from treatment-related causes than from the lymphoma, which argues for limiting treatment upfront because of the indolent nature of the disease.

Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma is a heterogeneous disease. The two most common histologic subtypes are DLBCL and follicular lymphoma, accounting for three quarters of all cases of non-Hodgkin's lymphoma. The role of radiation therapy in both of these subtypes is mostly limited to patients with early-stage disease. Marginal zone lymphoma or mucosa-associated lymphoid tumor (MALT) is another subtype of non-Hodgkin's lymphoma, which is highly responsive to radiation therapy, and in patients who present with localized, early-stage disease, radiation therapy alone may be curative.

Diffuse Large B-Cell Lymphoma

Randomized trials have compared chemotherapy alone versus combined modality therapy in early-stage aggressive non-Hodgkin's lymphoma with mixed results, likely as a result of patient selection and differences in chemotherapy regimens used in the comparison arms in two of the trials. However, the most significant limitation of these trials was that they were conducted in the pre-Rituximab era.[68-71]

The current standard systemic therapy for DLBCL, which accounts for the majority of cases of aggressive non-Hodgkin's lymphoma, is rituximab, cyclophosphamide, vincristine and prednisone (R-CHOP).[72-75] Several studies have retrospectively compared irradiated versus nonirradiated patients after modern R-CHOP chemotherapy, all showing a significantly superior disease-free survival in patients who received radiotherapy compared to patients treated with chemotherapy alone.[76-79] In the largest study, from M. D. Anderson on 469 patients with DLBCL, not only a significantly higher progression-free (59% versus 82%, $p < 0.001$), but also overall survival (68% versus 91%, $p = 0.03$) rates were observed in irradiated patients. The significant benefit of radiation therapy in this study persisted on multivariable analysis, as well as on matched-pair analyses on patients with stages I to II disease and patients with stages III to IV disease, respectively, after a complete response to six to eight cycles of R-CHOP.

The German High-Grade Non-Hodgkin's lymphoma Study Group (DSHNHL) recently published their experience on the role of radiotherapy in selected patients with DLBCL on their clinical trials.[80,81] The first report took patients with skeletal involvement and complete response to chemo from the MabThera International Trial (MInT) and RICOVER-60 trials, and found that those who received consolidative radiotherapy had a significantly improved 3-year event-free survival rate (75% versus 36%, $p < 0.001$).[81] On multivariable analysis, the addition of radiotherapy reduced the risk of an event by 70% ($p < 0.001$). In the second report, patients with bulky disease (≥7.5 cm) from the R-CHOP-14 for six arms of the RICOVER-60 trial formed the study population. It was found that compared to patients who did not receive radiotherapy, those who received radiotherapy had significantly improved event-free survival (80% versus 54%, $p = 0.001$), progression-free survival (88% versus 62%, $p < 0.001$), as well as overall survival (90% versus 65%, $p = 0.001$).[80] However, both of these studies were retrospective subgroup analyses and may be prone to selection bias. The UNFOLDER trial, also conducted by the DSHNHL randomized patients with DLBCL to R-CHOP14 versus R-CHOP 21, Patients with initial bulky disease (>7.5 cm) or extranodal involvement and complete response to chemotherapy were further randomized to receive radiotherapy versus no radiotherapy. In the most recent interim analysis, the no-radiotherapy arm was closed because of significantly inferior event-free survival results. The formal results of this trial, however, are still pending at this time.

Radiation doses used in previous trials ranged from 30 Gy to as high as 55 Gy.[82] In a prospective trial conducted by Lowry et al,[83] 640 sites of aggressive non-Hodgkin's lymphoma (81% treated with combined-modality therapy) were randomized to 30 Gy in 15 fractions versus 40 Gy to 45 Gy in 20 to 23 fractions. At a median follow-up of 5.6 years, there was no significant difference in freedom-from-local progression and overall survival rates between the two arms, suggesting the 30 Gy may be adequate in these patients after chemotherapy. However, the study did not describe the types of chemotherapy used and data on response to chemotherapy were not available.

There have been attempts to limit radiation fields in patients receiving consolidative radiotherapy for aggressive non-Hodgkin's lymphoma. Campbell et al reported on the British Columbia experience of using INRT ≤5 cm and found no difference in patterns of failure compared with a previous cohort of patients who received involved-field radiation therapy.[84] Verhappen et al recently reported on results of 67 patients

with stages I to II aggressive non-Hodgkin's lymphoma treated with INRT (64 of 67 patients received combined-modality therapy) as per the EORTC guidelines,[85] and there was only one relapse that was outside the INRT field but in the involved-field radiation therapy volume, supporting the use of more limited fields after chemotherapy in early-stage aggressive non-Hodgkin's lymphoma.

Follicular Lymphoma

About 20% to 25% of patients with follicular lymphoma present with stages I to II disease. There have been a number of retrospective series showing that radiation therapy alone is curative in 35% to 40% of cases.[86-95] Median doses of 36 Gy to 40 Gy resulted in control rates of 90% to 95%. Relapses beyond 10 years are uncommon, accounting for less than 5% of cases. In most series the radiation fields varied over time, with larger fields employed in the earlier years, and more limited fields in patients treated in the modern era. Campbell et al reported on the British Columbia experience of 95 with localized follicular lymphoma treated with INRT <5 cm alone, and found that only 1% of patients had regional-only recurrence.[96] Because more than half the patients with stages I to II disease will eventually relapse, the use of more limited radiation fields preserves the ability to effectively treat patients with recurrent disease or those who transform to a higher grade histology.

In most of the earlier retrospective series of radiotherapy alone for stages I to II follicular lymphoma, doses of 35 Gy to 40 Gy were employed. Lowry et al from the United Kingdom conducted a randomized trial on 361 sites of indolent lymphoma comparing 24 Gy in 12 fractions versus 40 Gy to 45 Gy in 20 to 30 fractions,[83] and found no differences in rates of local progression, progression-free survival, and overall survival between the two arms, suggesting that 24 Gy may be an adequate definitive dose for indolent lymphoma.

For patients with advanced-stage follicular lymphoma, several small series, which included patients with stage III disease, have reported results on the use of "central" or "comprehensive" lymphoid irradiation, with 10-year to 15-year disease-free survival of 30% to 40%.[97-99] Molecular complete responses, assessed by polymerase chain reaction techniques, have also been demonstrated after the treatment.[100] This approach of wide-field radiation therapy, however, is not widely accepted because of concerns with long-term toxicity for the treatment for an indolent disease and the ability to deliver effective salvage therapy at the time of relapse. Emerging data are available on the effectiveness of low-dose IFRT for palliation in patients with indolent lymphoma, with response rates of 80% to more than 90%.[101-107] The advantages of this approach, in addition to the high response rate, include minimal treatment toxicity, patient convenience, potential delay in need of starting systemic therapy, and the option of reirradiation if needed. However, results of the recently published FoRT trial showed that 4 Gy in 2 fractions was significantly inferior to 24 Gy in 12 fractions in patients with either follicular or marginal zone lymphoma in terms of response rates (81% versus 74.1%, $p = 0.006$), and 2-year progression-free survival rates (93.7% versus 80.4%, $p < 0.001$) in the 4 Gy-arm.[108] These findings led to the conclusion that although 4 Gy in 2 fractions remains a useful regimen in the palliative setting, 24 Gy is the standard dose for patients treated with radical intent.

MALT Lymphoma

Marginal zone B-cell lymphoma (MALT) accounts for about 8% to 10% of non-Hodgkin's lymphoma. The majority of cases are localized at presentation and tend to remain localized for long periods of time. This subtype of lymphoma is highly responsive to radiation therapy. Doses of around 30 Gy to involved nodal regions or extranodal sites will yield local control rate of close to 100%, with a chance of long-term cure in about three quarters of the patients,[109-114] although results from the United Kingdom randomized trial suggested that 24 Gy may be adequate.[83] Relapses tend to occur at other extranodal sites in which MALT lymphomas tend to occur or in a nonirradiated contralateral paired organ.[115] The likelihood of achieving a second remission in patients with limited relapses remains excellent with further local radiation therapy.

Multiple Myeloma and Plasma Cell Malignancies

Multiple myeloma at this time remains an incurable disease. However, novel agents including bortezomib and lenalidomide have been shown to be effective in the relapsed setting, and they are increasingly being adopted as first-line therapy.[116,117] Additional novel agents, including pomalidomide, a new immunomodulatory agent, and carfilzomib, an irreversible proteasome inhibitor, have shown promising antimyeloma activity in patients with refractory disease.[118,119] Finally, monoclonal antibodies are emerging as an important modality in the treatment of the disease.[120,121]

The current role of radiation therapy in the management of multiple myeloma is therefore largely limited to palliation, in patients with painful bony lesions, nerve root or cord compression, or lytic lesions in a weight-bearing bone at risk for pathological fractures. Kyphoplasty in conjunction with radiation therapy for patients with compression fracture of the vertebral bodies may provide more immediate and effective palliation.[122-124] Fractionation schemes of 30 Gy in 10 fractions or other biological equivalent doses are recommended because lower doses are associated with less durable palliation, and retreatment is often less effective.[125-129]

Solitary plasmacytoma accounts for 5% to 10% of all plasma cell dyscrasias. In patients with solitary plasmacytoma of the bone, local radiation therapy to doses of 45 Gy to 50 Gy can provide effective local control of more than 80%.[130-136] However, about half of the patients will progress to multiple myeloma at 10 years, and by 15 years, most will develop multiple myeloma. Unlike solitary plasmacytoma of the bone, extraosseous solitary plasmacytoma is associated with a lower risk of progression to multiple myeloma and has a more favorable disease-free survival.[133,135,137-139] Most series employed doses of 45 Gy to 50 Gy, which yielded local control rates of 85% to 90%.

CRITICAL REFERENCES

A full list of cited references is published online at www.expertconsult.com.

1. Campo E, Swerdlow SH, Harris NL, et al: The 2008 WHO classification of lymphoid neoplasms and beyond: Evolving concepts and practical applications. Blood 117:5019–5032, 2011.
4. Shipp MA, Ross KN, Tamayo P, et al: Diffuse large B-cell lymphoma outcome prediction by gene-expression profiling and supervised machine learning. Nat Med 8:68–74, 2002.
11. Tirado CA, Chen W, Garcia R, et al: Genomic profiling using array comparative genomic hybridization define distinct subtypes of diffuse large B-cell lymphoma: A review of the literature. J Hematol Oncol 5:54, 2012.
12. El-Najjar I, Barwick T, Avril N, et al: The role of FDG-PET and bone marrow examination in lymphoma staging. Ann Oncol 23(Suppl 10):x89–x91, 2012.
15. Jaffe ES: The 2008 WHO classification of lymphomas: Implications for clinical practice and translational research. Hematology Am Soc Hematol Educ Program 523–531, 2009.
16. Vardiman JW, Thiele J, Arber DA, et al: The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: Rationale and important changes. Blood 114:937–951, 2009.
24. Orsborne C, Byers R: Impact of gene expression profiling in lymphoma diagnosis and prognosis. Histopathology 58:106–127, 2011.
34. Specht L, Yahalom J, Illidge T, et al: Modern radiation therapy for Hodgkin's lymphoma: Field and dose guidelines from the international lymphoma radiation oncology group (ILROG). Int J Radiat Oncol Biol Phys 89(4):854–862, 2014.

36. Paumier A, Ghalibafian M, Beaudre A, et al: Involved-node radiotherapy and modern radiation treatment techniques in patients with Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 80:199–205, 2011.
37. Maraldo MV, Aznar MC, Vogelius IR, et al: Involved node radiation therapy: An effective alternative in early-stage Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 85:1057–1065, 2013.
38. Engert A, Plütschow A, Eich HT, et al: Reduced treatment intensity in patients with early-stage hodgkin's lymphoma. N Engl J Med 363:640–652, 2010.
39. Eich HT, Diehl V, Gorgen H, 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 28:4199–4206, 2010.
41. Picardi M, De Renzo A, Pane F, et al: Randomized comparison of consolidation radiation versus observation in bulky Hodgkin's lymphoma with post-chemotherapy negative positron emission tomography scans. Leuk Lymphoma 48:1721–1727, 2007.
46. Wolden SL, Chen L, Kelly KM, et al: Long-term results of CCG 5942: A randomized comparison of chemotherapy with and without radiotherapy for children with Hodgkin's lymphoma—a report from the Children's Oncology Group. J Clin Oncol 30:3174–3180, 2012.
47. Meyer RM, Gospodarowicz MK, Connors JM, et al: ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. N Engl J Med 366:399–408, 2012.
48. Herbst C, Rehan FA, Brillant C, et al: Combined modality treatment improves tumor control and overall survival in patients with early stage Hodgkin's lymphoma: A systematic review. Haematologica 95:494–500, 2010.
49. Andre M, Ramen O, Federico M, et al: Interim analysis of the randomized EORTC/LYSA/FIL intergroup H10 trial on early PET-scan driven treatment adaptation in stage I/II Hodgkin's lymphoma 54th ASH Annual Meeting Abstract 549, 2012.
50. Radford JA, Barrington S, Counsell N, et al: Involved field radiotherapy versus no further treatment in patients with clinical stages IA and IIA Hodgkin's lymphoma and a 'negative' PET scan after 3 cycles ABVD. Results of the UK NCRI RAPID trial. 54th ASH Annual Meeting Abstract 547, 2012.
58. Borchmann P, Haverkamp H, Diehl V, 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 29:4234–4242, 2011.
60. Johnson PW, Sydes MR, Hancock BW, et al: Consolidation radiotherapy in patients with advanced Hodgkin's lymphoma: Survival data from the UKLG LY09 randomized controlled trial (ISRCTN97144519). J Clin Oncol 28:3352–3359, 2010.
61. Engert A, Haverkamp H, Kobe C, 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 379:1791–1799, 2012.
64. Eichenauer DA, Fuchs M, Pluetschow A, et al: Phase 2 study of rituximab in newly diagnosed stage IA nodular lymphocyte-predominant Hodgkin's lymphoma: A report from the German Hodgkin Study Group. Blood 118:4363–4365, 2011.
66. Chen RC, Chin MS, Ng AK, et al: Early-stage, lymphocyte-predominant Hodgkin's lymphoma: Patient outcomes from a large, single-institution series with long follow-up. J Clin Oncol 28:136–141, 2010.
67. Biasoli I, Stamatoullas A, Meignin V, et al: Nodular, lymphocyte-predominant Hodgkin's lymphoma: A long-term study and analysis of transformation to diffuse large B-cell lymphoma in a cohort of 164 patients from the Adult Lymphoma Study Group. Cancer 116:631–639, 2010.
68. Bonnet C, Fillet G, Mounier N, et al: CHOP alone compared with CHOP plus radiotherapy for localized aggressive lymphoma in elderly patients: A study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 25:787–792, 2007.
69. Horning SJ, Weller E, Kim K, et al: Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group study 1484. J Clin Oncol 22:3032–3038, 2004.
70. Miller T, Leblanc M, Spier C, et al: CHOP alone compared to CHOP plus radiotherapy for early stage aggressive non-Hodgkin's lymphomas: Update of the southwest oncology group (SWOG) randomized trial. ASH Abstract No. 3024, 2001.
71. Reyes F, Lepage E, Ganem G, et al: ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma. N Engl J Med 352:1197–1205, 2005.
72. Feugier P, Van Hoof A, Sebban C, et al: Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: A study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 23:4117–4126, 2005.
73. Habermann TM, Weller EA, Morrison VA, et al: Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol 24:3121–3127, 2006.
74. Pfreundschuh M, Kuhnt E, Trumper 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 12:1013–1022, 2011.
75. Pfreundschuh M, Zwick C, Zeynalova S, et al: Dose-escalated CHOEP for the treatment of young patients with aggressive non-Hodgkin's lymphoma: II. Results of the randomized high-CHOEP trial of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL). Ann Oncol 19:545–552, 2008.
78. Phan J, Mazloom A, Medeiros LJ, et al: Benefit of consolidative radiation therapy in patients with diffuse large B-cell lymphoma treated with R-CHOP chemotherapy. J Clin Oncol 28:4170–4176, 2010.
80. Held G, Murawski N, Ziepert M, et al: Role of radiotherapy to bulky disease in elderly patients with aggressive B-cell lymphoma. J Clin Oncol 32:1112–1118, 2014.
81. Held G, Zeynalova S, Murawski N, et al: Impact of rituximab and radiotherapy on outcome of patients with aggressive B-cell lymphoma and skeletal involvement. J Clin Oncol 31:4115–4122, 2013.
82. Miller TP, Dahlberg S, Cassady JR, et al: Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med 339:21–26, 1998.
83. Lowry L, Smith P, Qian W, et al: Reduced dose radiotherapy for local control in non-Hodgkin's lymphoma: A randomised phase III trial. Radiother Oncol 100:86–92, 2011.
84. Campbell BA, Connors JM, Gascoyne RD, et al: Limited-stage diffuse large B-cell lymphoma treated with abbreviated systemic therapy and consolidation radiotherapy: Involved-field versus involved-node radiotherapy. Cancer 118:4156–4165, 2012.
85. Verhappen MH, Poortmans PM, Raaijmakers E, et al: Reduction of the treated volume to involved node radiation therapy as part of combined modality treatment for early stage aggressive non-Hodgkin's lymphoma. Radiother Oncol 109:133–139, 2013.
95. Guadagnolo BA, Li S, Neuberg D, et al: Long-term outcome and mortality trends in early-stage, Grade 1-2 follicular lymphoma treated with radiation therapy. Int J Radiat Oncol Biol Phys 64:928–934, 2006.
96. Campbell BA, Voss N, Woods R, et al: Long-term outcomes for patients with limited stage follicular lymphoma: Involved regional radiotherapy versus involved node radiotherapy. Cancer 116:3797–3806, 2010.
101. Martin NE, Ng AK: Good things come in small packages: Low-dose radiation as palliation for indolent non-Hodgkin's lymphomas. Leuk Lymphoma 50:1765–1772, 2009.
107. Russo AL, Chen YH, Martin NE, et al: Low-dose involved-field radiation in the treatment of non-Hodgkin's lymphoma: Predictors of response and treatment failure. Int J Radiat Oncol Biol Phys 86:121–127, 2013.
108. Hoskin PJ, Kirkwood AA, Popova B, et al: 4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): A randomised phase 3 non-inferiority trial. Lancet Oncol 15:457–463, 2014.
114. Tsai HK, Li S, Ng AK, et al: Role of radiation therapy in the treatment of stage I/II mucosa-associated lymphoid tissue lymphoma. Ann Oncol 18:672–678, 2007.
115. Goda JS, Massey C, Kuruvilla J, et al: Role of salvage radiation therapy for patients with relapsed or refractory Hodgkin's lymphoma who failed autologous stem cell transplant. Int J Radiat Oncol Biol Phys 84:e329–e335, 2012.
117. Richardson PG, Weller E, Lonial S, et al: Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood 116:679–686, 2010.
124. Kasperk C, Haas A, Hillengass J, et al: Kyphoplasty in patients with multiple myeloma a retrospective comparative pilot study. J Surg Oncol 105:679–686, 2012.
128. Stolting T, Knauerhase H, Klautke G, et al: Total and single doses influence the effectiveness of radiotherapy in palliative treatment of plasmacytoma. Strahlenther Onkol 184:465–472, 2008.
129. Rades D, Douglas S, Veninga T, et al: Prognostic factors for local control and survival in patients with spinal cord compression from myeloma. Strahlenther Onkol 188:628–631, 2012.
134. Knobel D, Zouhair A, Tsang RW, et al: Prognostic factors in solitary plasmacytoma of the bone: A multicenter Rare Cancer Network study. BMC Cancer 6:118, 2006.
136. Suh YG, Suh CO, Kim JS, et al: Radiotherapy for solitary plasmacytoma of bone and soft tissue: Outcomes and prognostic factors. Ann Hematol 91:1785–1793, 2012.

REFERENCES

1. Campo E, Swerdlow SH, Harris NL, et al: The 2008 WHO classification of lymphoid neoplasms and beyond: Evolving concepts and practical applications. Blood 117:5019–5032, 2011.
2. Alizadeh AA, Eisen MB, Davis RE, et al: Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 403:503–511, 2000.
3. Rosenwald A, Wright G, Chan WC, et al: The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med 346:1937–1947, 2002.
4. Shipp MA, Ross KN, Tamayo P, et al: Diffuse large B-cell lymphoma outcome prediction by gene-expression profiling and supervised machine learning. Nat Med 8:68–74, 2002.
5. Savage KJ, Monti S, Kutok JL, et al: The molecular signature of mediastinal large B-cell lymphoma differs from that of other diffuse large B-cell lymphomas and shares features with classical Hodgkin's lymphoma. Blood 102:3871–3879, 2003.
6. Dave SS, Wright G, Tan B, et al: Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. N Engl J Med 351:2159–2169, 2004.
7. Lossos IS: Diffuse large B cell lymphoma: From gene expression profiling to prediction of outcome. Biol Blood Marrow Transplant 14:108–111, 2008.
8. Korenberg MJ, Farinha P, Gascoyne RD: Predicting survival in follicular lymphoma using tissue microarrays. Methods Mol Biol 377:255–268, 2007.
9. Iqbal J, d'Amore F, Hu Q, et al: Gene arrays in lymphoma: Where will they fit in? Curr Hematol Malig Rep 1:129–136, 2006.
10. Chetaille B, Bertucci F, Finetti P, et al: Molecular profiling of classical Hodgkin's lymphoma tissues uncovers variations in the tumor microenvironment and correlations with EBV infection and outcome. Blood 113:2765–3775, 2009.
11. Tirado CA, Chen W, Garcia R, et al: Genomic profiling using array comparative genomic hybridization define distinct subtypes of diffuse large B-cell lymphoma: A review of the literature. J Hematol Oncol 5:54, 2012.
12. El-Najjar I, Barwick T, Avril N, et al: The role of FDG-PET and bone marrow examination in lymphoma staging. Ann Oncol 23(Suppl 10):x89–x91, 2012.
13. Harris NL, Jaffe ES, Stein H, et al: A revised European-American classification of lymphoid neoplasms: A proposal from the International Lymphoma Study Group. Blood 84:1361–1392, 1994.
14. Harris NL, Jaffe ES, Diebold J, et al: World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: Report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol 17:3835–3849, 1999.
15. Jaffe ES: The 2008 WHO classification of lymphomas: Implications for clinical practice and translational research. Hematology Am Soc Hematol Educ Program 523–531, 2009.
16. Vardiman JW, Thiele J, Arber DA, et al: The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: Rationale and important changes. Blood 114:937–951, 2009.
17. Rajewsky K, Kanzler H, Hansmann ML, et al: Normal and malignant B-cell development with special reference to Hodgkin's disease. Ann Oncol 8(Suppl 2):79–81, 1997.
18. Marafioti T, Hummel M, Foss HD, et al: Hodgkin and Reed-Sternberg cells represent an expansion of a single clone originating from a germinal center B-cell with functional immunoglobulin gene rearrangements but defective immunoglobulin transcription. Blood 95:1443–1450, 2000.
19. Stein H, Marafioti T, Foss HD, et al: Down-regulation of BOB.1/OBF.1 and Oct2 in classical Hodgkin disease but not in lymphocyte predominant Hodgkin disease correlates with immunoglobulin transcription. Blood 97:496–501, 2001.
20. Hinz M, Lemke P, Anagnostopoulos I, et al: Nuclear factor kappaB-dependent gene expression profiling of Hodgkin's disease tumor cells, pathogenetic significance, and link to constitutive signal transducer and activator of transcription 5a activity. J Exp Med 196:605–617, 2002.
21. Bargou RC, Emmerich F, Krappmann D, et al: Constitutive nuclear factor-kappaB-RelA activation is required for proliferation and survival of Hodgkin's disease tumor cells. J Clin Invest 100:2961–2969, 1997.
22. Monti S, Savage KJ, Kutok JL, et al: Molecular profiling of diffuse large B-cell lymphoma identifies robust subtypes including one characterized by host inflammatory response. Blood 105:1851–1861, 2005.
23. Kiaii S, Clear AJ, Ramsay AG, et al: Follicular lymphoma cells induce changes in T-cell gene expression and function: Potential impact on survival and risk of transformation. J Clin Oncol 31:2654–2661, 2013.
24. Orsborne C, Byers R: Impact of gene expression profiling in lymphoma diagnosis and prognosis. Histopathology 58:106–127, 2011.
25. Iqbal J, Liu Z, Deffenbacher K, et al: Gene expression profiling in lymphoma diagnosis and management. Best Pract Res Clin Haematol 22:191–210, 2009.
26. Lister TA, Crowther D, Sutcliffe SB, et al: Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 7:1630–1636, 1989.
27. Terezakis SA, Schoder H, Kowalski A, et al: A prospective study of FDG-PET with CT coregistration for radiation treatment planning of lymphomas and other hematologic malignancies. Int J Radiat Oncol Biol Phys 89(2):376–383, 2014.
28. Terezakis SA, Hunt MA, Kowalski A, et al: [(1)(8)F]FDG-positron emission tomography coregistration with computed tomography scans for radiation treatment planning of lymphoma and hematologic malignancies. Int J Radiat Oncol Biol Phys 81:615–622, 2011.
29. Hutchings M, Loft A, Hansen M, et al: Clinical impact of FDG-PET/CT in the planning of radiotherapy for early-stage Hodgkin's lymphoma. Eur J Haematol 78:206–212, 2007.
30. Girinsky T, Ghalibafian M, Bonniaud G, et al: Is FDG-PET scan in patients with early stage Hodgkin's lymphoma of any value in the implementation of the involved-node radiotherapy concept and dose painting? Radiother Oncol 85:178–186, 2007.
31. Ferme C, Eghbali H, Meerwaldt JH, et al: Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. N Engl J Med 357:1916–1927, 2007.
32. Engert A, Schiller P, Josting A, et al: Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: Results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. J Clin Oncol 21:3601–3608, 2003.
33. Bonadonna G, Bonfante V, Viviani S, et al: ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: Long-term results. J Clin Oncol 22:2835–2841, 2004.
34. Specht L, Yahalom J, Illidge T, et al: Modern radiation therapy for Hodgkin's lymphoma: Field and dose guidelines from the international lymphoma radiation oncology group (ILROG). Int J Radiat Oncol Biol Phys 89(4): 854–862, 2014.
35. Girinsky T, van der Maazen R, Specht L, et al: Involved-node radiotherapy (INRT) in patients with early Hodgkin's lymphoma: Concepts and guidelines. Radiother Oncol 79:270–277, 2006.
36. Paumier A, Ghalibafian M, Beaudre A, et al: Involved-node radiotherapy and modern radiation treatment techniques in patients with Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 80:199–205, 2011.
37. Maraldo MV, Aznar MC, Vogelius IR, et al: Involved node radiation therapy: An effective alternative in early-stage Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 85:1057–1065, 2013.
38. Engert A, Plütschow A, Eich HT, et al: Reduced treatment intensity in patients with early-stage hodgkin's lymphoma. N Engl J Med 363:640–652, 2010.
39. Eich HT, Diehl V, Gorgen H, 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 28:4199–4206, 2010.
40. Straus DJ, Portlock CS, Qin J, et al: Results of a prospective randomized clinical trial of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) followed by radiation therapy (RT) vs. ABVD alone for stages I, II and IIIA non bulky Hodgkin's disease. Blood 104(12):3483–3489, 2004. [Epub 2004 Aug 17].
41. Picardi M, De Renzo A, Pane F, et al: Randomized comparison of consolidation radiation versus observation in bulky Hodgkin's lymphoma with post-chemotherapy negative positron emission tomography scans. Leuk Lymphoma 48:1721–1727, 2007.
42. Noordijk EM, Thomas J, Fermé C, et al: First results of the EORTC-GELA H9 randomized trials: The H9-F trial (comparing 3 radiation dose levels) and H9-U trial (comparing 3 chemotherapy schemes) in patients with favorable or unfavorable early stage Hodgkin's lymphoma (HL). J Clin Oncol 23:6505a, 2005.
43. Nachman JB, Sposto R, Herzog P, et al: Randomized comparison of low-dose involved-field radiotherapy and no radiotherapy for children with Hodgkin's disease who achieve a complete response to chemotherapy. J Clin Oncol 20:3765–3771, 2002.
44. Meyer RM, Gospodarowicz MK, Connors JM, et al: Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. J Clin Oncol 23:4634–4642, 2005.
45. Laskar S, Gupta T, Vimal S, et al: Consolidation radiation after complete remission in Hodgkin's disease following six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy: Is there a need? J Clin Oncol 22:62–68, 2004.
46. Wolden SL, Chen L, Kelly KM, et al: Long-term results of CCG 5942: A randomized comparison of chemotherapy with and without radiotherapy for children with Hodgkin's lymphoma—a report from the Children's Oncology Group. J Clin Oncol 30:3174–3180, 2012.
47. Meyer RM, Gospodarowicz MK, Connors JM, et al: ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. N Engl J Med 366:399–408, 2012.
48. Herbst C, Rehan FA, Brillant C, et al: Combined modality treatment improves tumor control and overall survival in patients with early stage Hodgkin's lymphoma: A systematic review. Haematologica 95:494–500, 2010.
49. Andre M, Ramen O, Federico M, et al: Interim analysis of the randomized EORTC/LYSA/FIL intergroup H10 trial on early PET-scan driven treatment adaptation in stage I/II Hodgkin's lymphoma 54th ASH Annual Meeting Abstract 549, 2012.

50. Radford JA, Barrington S, Counsell N, et al: Involved field radiotherapy versus no further treatment in patients with clinical stages IA and IIA Hodgkin's lymphoma and a 'negative' PET scan after 3 cycles ABVD. Results of the UK NCRI RAPID trial. 54th ASH Annual Meeting Abstract 547, 2012.
51. Pavlovsky S, Santarelli MT, Muriel FS, et al: Randomized trial of chemotherapy versus chemotherapy plus radiotherapy for stage III-IV A & B Hodgkin's disease. Ann Oncol 3:533–537, 1992.
52. Fabian CJ, Mansfield CM, Dahlberg S, et al: Low-dose involved field radiation after chemotherapy in advanced Hodgkin disease. A Southwest Oncology Group randomized study. Ann Intern Med 120:903–912, 1994.
53. Diehl V, Loeffler M, Pfreundschuh M, et al: Further chemotherapy versus low-dose involved-field radiotherapy as consolidation of complete remission after six cycles of alternating chemotherapy in patients with advance Hodgkin's disease. German Hodgkins' Study Group (GHSG). Ann Oncol 6:901–910, 1995.
54. Loeffler M, Brosteanu O, Hasenclever D, et al: Meta-analysis of chemotherapy versus combined modality treatment trials in Hodgkin's disease. International Database on Hodgkin's Disease Overview Study Group. J Clin Oncol 16:818–829, 1998.
55. Ferme C, Sebban C, Hennequin C, et al: Comparison of chemotherapy to radiotherapy as consolidation of complete or good partial response after six cycles of chemotherapy for patients with advanced Hodgkin's disease: Results of the groupe d'etudes des lymphomes de l'Adulte H89 trial. Blood 95:2246–2252, 2000.
56. Aleman BM, Raemaekers JM, Tirelli U, et al: Involved-field radiotherapy for advanced Hodgkin's lymphoma. N Engl J Med 348:2396–2406, 2003.
57. Diehl V, Haverkamp H, Mueller R, et al: Eight cycles of BEACOPP escalated compared with 4 cycles of BEACOPP escalated followed by 4 cycles of BEACOPP baseline with or without radiotherapy in patients in advanced stage Hodgkin's lymphoma (HL): Final analysis of the HD12 trial of the German Hodgkin Study Group (GHSG). J Clin Oncol 27:Abstract 8544, 2009.
58. Borchmann P, Haverkamp H, Diehl V, 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 29:4234–4242, 2011.
59. Aleman BM, Raemaekers JM, Tomisic R, et al: Involved-field radiotherapy for patients in partial remission after chemotherapy for advanced Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 67:19–30, 2007.
60. Johnson PW, Sydes MR, Hancock BW, et al: Consolidation radiotherapy in patients with advanced Hodgkin's lymphoma: Survival data from the UKLG LY09 randomized controlled trial (ISRCTN97144519). J Clin Oncol 28:3352–3359, 2010.
61. Engert A, Haverkamp H, Kobe C, 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 379:1791–1799, 2012.
62. Anagnostopoulos I, Hansmann ML, Franssila K, et al: European Task Force on Lymphoma project on lymphocyte predominance Hodgkin disease: Histologic and immunohistologic analysis of submitted cases reveals 2 types of Hodgkin disease with a nodular growth pattern and abundant lymphocytes. Blood 96:1889–1899, 2000.
63. Savage KJ, Skinnider B, Al-Mansour M, et al: Treating limited-stage nodular lymphocyte predominant Hodgkin's lymphoma similarly to classical Hodgkin's lymphoma with ABVD may improve outcome. Blood 118:4585–4590, 2011.
64. Eichenauer DA, Fuchs M, Pluetschow A, et al: Phase 2 study of rituximab in newly diagnosed stage IA nodular lymphocyte-predominant Hodgkin's lymphoma: A report from the German Hodgkin Study Group. Blood 118:4363–4365, 2011.
65. Diehl V, Sextro M, Franklin J, et al: Clinical presentation, course, and prognostic factors in lymphocyte-predominant Hodgkin's disease and lymphocyte-rich classical Hodgkin's disease: Report from the European Task Force on Lymphoma Project on Lymphocyte-Predominant Hodgkin's Disease. J Clin Oncol 17:776–783, 1999.
66. Chen RC, Chin MS, Ng AK, et al: Early-stage, lymphocyte-predominant Hodgkin's lymphoma: Patient outcomes from a large, single-institution series with long follow-up. J Clin Oncol 28:136–141, 2010.
67. Biasoli I, Stamatoullas A, Meignin V, et al: Nodular, lymphocyte-predominant Hodgkin's lymphoma: A long-term study and analysis of transformation to diffuse large B-cell lymphoma in a cohort of 164 patients from the Adult Lymphoma Study Group. Cancer 116:631–639, 2010.
68. Bonnet C, Fillet G, Mounier N, et al: CHOP alone compared with CHOP plus radiotherapy for localized aggressive lymphoma in elderly patients: A study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 25:787–792, 2007.
69. Horning SJ, Weller E, Kim K, et al: Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group study 1484. J Clin Oncol 22:3032–3038, 2004.
70. Miller T, Leblanc M, Spier C, et al: CHOP alone compared to CHOP plus radiotherapy for early stage aggressive non-Hodgkin's lymphomas: Update of the southwest oncology group (SWOG) randomized trial. ASH Abstract No. 3024, 2001.
71. Reyes F, Lepage E, Ganem G, et al: ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma. N Engl J Med 352:1197–1205, 2005.
72. Feugier P, Van Hoof A, Sebban C, et al: Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: A study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 23:4117–4126, 2005.
73. Habermann TM, Weller EA, Morrison VA, et al: Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol 24:3121–3127, 2006.
74. Pfreundschuh M, Kuhnt E, Trumper 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 12:1013–1022, 2011.
75. Pfreundschuh M, Zwick C, Zeynalova S, et al: Dose-escalated CHOEP for the treatment of young patients with aggressive non-Hodgkin's lymphoma: II. Results of the randomized high-CHOEP trial of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL). Ann Oncol 19:545–552, 2008.
76. Dorth JA, Prosnitz LR, Broadwater G, et al: Radiotherapy dose-response analysis for diffuse large B-cell lymphoma with a complete response to chemotherapy. Radiat Oncol 7:100, 2012.
77. Marcheselli L, Marcheselli R, Bari A, et al: Radiation therapy improves treatment outcome in patients with diffuse large B-cell lymphoma. Leuk Lymphoma 52:1867–1872, 2011.
78. Phan J, Mazloom A, Medeiros LJ, et al: Benefit of consolidative radiation therapy in patients with diffuse large B-cell lymphoma treated with R-CHOP chemotherapy. J Clin Oncol 28:4170–4176, 2010.
79. Shi Z, Das S, Okwan-Duodu D, 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 86:569–577, 2013.
80. Held G, Murawski N, Ziepert M, et al: Role of radiotherapy to bulky disease in elderly patients with aggressive B-cell lymphoma. J Clin Oncol 32:1112–1118, 2014.
81. Held G, Zeynalova S, Murawski N, et al: Impact of rituximab and radiotherapy on outcome of patients with aggressive B-cell lymphoma and skeletal involvement. J Clin Oncol 31:4115–4122, 2013.
82. Miller TP, Dahlberg S, Cassady JR, et al: Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med 339:21–26, 1998.
83. Lowry L, Smith P, Qian W, et al: Reduced dose radiotherapy for local control in non-Hodgkin's lymphoma: A randomised phase III trial. Radiother Oncol 100:86–92, 2011.
84. Campbell BA, Connors JM, Gascoyne RD, et al: Limited-stage diffuse large B-cell lymphoma treated with abbreviated systemic therapy and consolidation radiotherapy: Involved-field versus involved-node radiotherapy. Cancer 118:4156–4165, 2012.
85. Verhappen MH, Poortmans PM, Raaijmakers E, et al: Reduction of the treated volume to involved node radiation therapy as part of combined modality treatment for early stage aggressive non-Hodgkin's lymphoma. Radiother Oncol 109:133–139, 2013.
86. Soubeyran P, Eghbali H, Bonichon F, et al: Localized follicular lymphomas: Prognosis and survival of stages I and II in a retrospective series of 103 patients. Radiother Oncol 13:91–98, 1988.
87. Taylor RE, Allan SG, McIntyre MA, et al: Low grade stage I and II non-Hodgkin's lymphoma: Results of treatment and relapse pattern following therapy. Clin Radiol 39:287–290, 1988.
88. Lawrence TS, Urba WJ, Steinberg SM, et al: Retrospective analysis of stage I and II indolent lymphomas at the National Cancer Institute. Int J Radiat Oncol Biol Phys 14:417–424, 1988.
89. Vaughan Hudson B, Vaughan Hudson G, MacLennan KA, et al: Clinical stage 1 non-Hodgkin's lymphoma: Long-term follow-up of patients treated by the British National Lymphoma Investigation with radiotherapy alone as initial therapy. Br J Cancer 69:1088–1093, 1994.
90. Pendlebury S, el Awadi M, Ashley S, et al: Radiotherapy results in early stage low grade nodal non-Hodgkin's lymphoma. Radiother Oncol 36:167–171, 1995.
91. Mac Manus MP, Hoppe RT: Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University. J Clin Oncol 14:1282–1290, 1996.
92. Gospodarowicz M, Lippuner T, Pintilie M: 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 45:217a, 1999.
93. Wilder RB, Jones D, Tucker SL, et al: Long-term results with radiotherapy for Stage I-II follicular lymphomas. Int J Radiat Oncol Biol Phys 51:1219–1227, 2001.
94. Eich HT, Heimann M, Stutzer H, et al: Long-term outcome and prognostic factors in early-stage nodal low-grade non-Hodgkin's lymphomas treated with radiation therapy. Strahlenther Onkol 185:288–295, 2009.
95. Guadagnolo BA, Li S, Neuberg D, et al: Long-term outcome and mortality trends in early-stage, Grade 1-2 follicular lymphoma treated with radiation therapy. Int J Radiat Oncol Biol Phys 64:928–934, 2006.

96. Campbell BA, Voss N, Woods R, et al: Long-term outcomes for patients with limited stage follicular lymphoma: Involved regional radiotherapy versus involved node radiotherapy. Cancer 116:3797–3806, 2010.
97. Jacobs JP, Murray KJ, Schultz CJ, et al: Central lymphatic irradiation for stage III nodular malignant lymphoma: Long-term results. J Clin Oncol 11:233–238, 1993.
98. De Los Santos JF, Mendenhall NP, Lynch JW, Jr: 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 38:3–8, 1997.
99. Ha CS, Kong JS, Tucker SL, et al: Central lymphatic irradiation for stage I-III follicular lymphoma: Report from a single-institutional prospective study. Int J Radiat Oncol Biol Phys 57:316–320, 2003.
100. Ha CS, Tucker SL, Lee MS, et al: The significance of molecular response of follicular lymphoma to central lymphatic irradiation as measured by polymerase chain reaction for t(14;18)(q32;q21). Int J Radiat Oncol Biol Phys 49:727–732, 2001.
101. Martin NE, Ng AK: Good things come in small packages: Low-dose radiation as palliation for indolent non-Hodgkin's lymphomas. Leuk Lymphoma 50:1765–1772, 2009.
102. Ganem G, Lambin P, Socie G, et al: Potential role for low dose limited-field radiation therapy (2 x 2 grays) in advanced low-grade non-Hodgkin's lymphomas. Hematol Oncol 12:1–8, 1994.
103. Girinsky T, Guillot-Vals D, Koscielny S, 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 51:148–155, 2001.
104. Haas RL, Poortmans P, de Jong D, et al: High response rates and lasting remissions after low-dose involved field radiotherapy in indolent lymphomas. J Clin Oncol 21:2474–2480, 2003.
105. Sawyer EJ, Timothy AR: Low dose palliative radiotherapy in low grade non-Hodgkin's lymphoma. Radiother Oncol 42:49–51, 1997.
106. Luthy SK, Ng AK, Silver B, et al: Response to low-dose involved-field radiotherapy in patients with non-Hodgkin's lymphoma. Ann Oncol 19:2043–2047, 2008.
107. Russo AL, Chen YH, Martin NE, et al: Low-dose involved-field radiation in the treatment of non-Hodgkin's lymphoma: Predictors of response and treatment failure. Int J Radiat Oncol Biol Phys 86:121–127, 2013.
108. Hoskin PJ, Kirkwood AA, Popova B, et al: 4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): A randomised phase 3 non-inferiority trial. Lancet Oncol 15:457–463, 2014.
109. Schechter NR, Portlock CS, Yahalom J: Treatment of mucosa-associated lymphoid tissue lymphoma of the stomach with radiation alone. J Clin Oncol 16:1916–1921, 1998.
110. Fung CY, Grossbard ML, Linggood RM, et al: Mucosa-associated lymphoid tissue lymphoma of the stomach: Long term outcome after local treatment. Cancer 85:9–17, 1999.
111. Tsang RW, Gospodarowicz MK, Pintilie M, et al: Stage I and II MALT lymphoma: Results of treatment with radiotherapy. Int J Radiat Oncol Biol Phys 50:1258–1264, 2001.
112. Hitchcock S, Ng AK, Fisher DC, et al: Treatment outcome of mucosa-associated lymphoid tissue/marginal zone non-Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 52:1058–1066, 2002.
113. Isobe K, Kagami Y, Higuchi K, et al: A multicenter phase II study of local radiation therapy for stage IEA mucosa-associated lymphoid tissue lymphomas: A preliminary report from the Japan Radiation Oncology Group (JAROG). Int J Radiat Oncol Biol Phys 69:1181–1186, 2007.
114. Tsai HK, Li S, Ng AK, et al: Role of radiation therapy in the treatment of stage I/II mucosa-associated lymphoid tissue lymphoma. Ann Oncol 18:672–678, 2007.
115. Goda JS, Massey C, Kuruvilla J, et al: Role of salvage radiation therapy for patients with relapsed or refractory Hodgkin's lymphoma who failed autologous stem cell transplant. Int J Radiat Oncol Biol Phys 84:e329–e335, 2012.
116. Raab MS, Podar K, Breitkreutz I, et al: Multiple myeloma. Lancet 374:324–339, 2009.
117. Richardson PG, Weller E, Lonial S, et al: Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood 116:679–686, 2010.
118. Jakubowiak AJ, Dytfeld D, Griffith KA, et al: A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. Blood 120:1801–1809, 2012.
119. Siegel DS, Martin T, Wang M, et al: A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. Blood 120:2817–2825, 2012.
120. Lonial S, Vij R, Harousseau JL, et al: Elotuzumab in combination with lenalidomide and low-dose dexamethasone in relapsed or refractory multiple myeloma. J Clin Oncol 30:1953–1959, 2012.
121. de Weers M, Tai YT, van der Veer MS, et al: Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. J Immunol 186:1840–1848, 2011.
122. Dudeney S, Lieberman IH, Reinhardt MK, et al: Kyphoplasty in the treatment of osteolytic vertebral compression fractures as a result of multiple myeloma. J Clin Oncol 20:2382–2387, 2002.
123. Huber FX, McArthur N, Tanner M, et al: Kyphoplasty for patients with multiple myeloma is a safe surgical procedure: Results from a large patient cohort. Clin Lymphoma Myeloma 9:375–380, 2009.
124. Kasperk C, Haas A, Hillengass J, et al: Kyphoplasty in patients with multiple myeloma a retrospective comparative pilot study. J Surg Oncol 105:679–686, 2012.
125. Adamietz IA, Schober C, Schulte RW, et al: Palliative radiotherapy in plasma cell myeloma. Radiother Oncol 20:111–116, 1991.
126. Alcorn S, Mauch P, Ng A, et al: Predictors of symptomatic failure after palliative radiation therapy for multiple myeloma. Int J Radiat Oncol Biol Phys 75:S503–S504, 2009.
127. Rades D, Hoskin PJ, Stalpers LJ, et al: Short-course radiotherapy is not optimal for spinal cord compression due to myeloma. Int J Radiat Oncol Biol Phys 64:1452–1457, 2006.
128. Stolting T, Knauerhase H, Klautke G, et al: Total and single doses influence the effectiveness of radiotherapy in palliative treatment of plasmacytoma. Strahlenther Onkol 184:465–472, 2008.
129. Rades D, Douglas S, Veninga T, et al: Prognostic factors for local control and survival in patients with spinal cord compression from myeloma. Strahlenther Onkol 188:628–631, 2012.
130. Frassica DA, Frassica FJ, Schray MF, et al: Solitary plasmacytoma of bone: Mayo Clinic experience. Int J Radiat Oncol Biol Phys 16:43–48, 1989.
131. Dimopoulos MA, Goldstein J, Fuller L, et al: Curability of solitary bone plasmacytoma. J Clin Oncol 10:587–590, 1992.
132. Liebross RH, Ha CS, Cox JD, et al: Solitary bone plasmacytoma: Outcome and prognostic factors following radiotherapy. Int J Radiat Oncol Biol Phys 41:1063–1067, 1998.
133. Liebross RH, Ha CS, Cox JD, et al: Clinical course of solitary extramedullary plasmacytoma. Radiother Oncol 52:245–249, 1999.
134. Knobel D, Zouhair A, Tsang RW, et al: Prognostic factors in solitary plasmacytoma of the bone: A multicenter Rare Cancer Network study. BMC Cancer 6:118, 2006.
135. Ozsahin M, Tsang RW, Poortmans P, et al: Outcomes and patterns of failure in solitary plasmacytoma: A multicenter Rare Cancer Network study of 258 patients. Int J Radiat Oncol Biol Phys 64:210–217, 2006.
136. Suh YG, Suh CO, Kim JS, et al: Radiotherapy for solitary plasmacytoma of bone and soft tissue: Outcomes and prognostic factors. Ann Hematol 91:1785–1793, 2012.
137. Wax MK, Yun KJ, Omar RA: Extramedullary plasmacytomas of the head and neck. Otolaryngol Head Neck Surg 109:877–885, 1993.
138. Michalaki VJ, Hall J, Henk JM, et al: Definitive radiotherapy for extramedullary plasmacytomas of the head and neck. Br J Radiol 76:738–741, 2003.
139. Dagan R, Morris CG, Kirwan J, et al: Solitary plasmacytoma. Am J Clin Oncol 32:612–617, 2009.