The Role of Radiation Therapy in Hodgkin's Lymphoma

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ABSTRACT

Hodgkin's lymphoma is one of the early success stories in oncology. Radiation therapy has been a very effective treatment for several decades. Treatement strategies continue to evolve, with the majority of patients now receiving combined modality treatment. The excellent results in early stage disease and the presence of long-term, treatment-related complications have compelled investigators to try to identify optimal minimal treatment. Treatment for advanced stage disease control continues to be primarily directed at improving disease outcomes. Recent results of combined modality trials using dose intense and dose escalating chemotherapy regimens have been encouraging.

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INTRODUCTION

Curative therapy for Hodgkin's lymphoma (HL) is truly one of the success stories of oncology. Approximately 7,400 cases are diagnosed in the United States each year, and unlike the incidence of non-Hodgkin's lymphoma, the incidence of HL has remained relatively stable.[1] Approximately 80% of all patients will be cured, primarily due to improvements in radiation therapy (RT) and combination chemotherapy over the past 40–50 years. Unlike most other malignancies, HL continues to have a high likelihood for cure even after one or more relapses.

HISTORY

In 1832, Thomas Hodgkin described the clinical history and postmortem findings of two patients with massive enlargement of lymph nodes and spleens in an article entitled "On some morbid appearances of the exorbent glands and spleen."[2] His report went largely unnoticed until 1856 when Samuel Wilks described this same process.[3] Wilks initially believed his findings to be original until a contemporary of Hodgkin, Richard Bright, brought Hodgkin's article to his attention. In 1865, Wilks published his findings in further detail and labeled this entity "Hodgkin's disease."[4]

EARLY RADIATION TREATMENT

Only a few years after Roentgen reported his discovery of x-rays in 1895, Pusey at the University of Illinois in Chicago reported dramatic nodal responses in two patients with HL treated with RT.[5] Several similar reports followed; however, suboptimal equipment and techniques as well as lack of knowledge of the disease process prevented curative treatment. Gilbert, a Swiss radiotherapist, was the first to describe patterns of spread of HL to adjacent, normal-appearing nodal groups. He adapted his treatment techniques in an attempt to include both gross disease and the adjacent clinically uninvolved lymph node regions that he suspected harbored microscopic disease. In 1931, Gilbert and Babaiantz reported an unprecedented average survival time of 4.3 years using this approach, with 7 of 15 patients still alive at the time of publication of these findings.[6] In 1950, Peters noted 5- and 10-year survival rates of 88% and 79%, respectively, in patients treated for stage I disease at the Ontario Institute of Radiotherapy between 1924 and 1942—the first clear documentation of the curative potential for RT in HL.[7]

Henry Kaplan at Stanford University, aided by the first linear accelerator, treated extended fields with higher doses in 1956. In 1962, he reported unprecedented results in regionally localized disease, comparing results of extended-field radiation therapy (EFRT) of 30–40 Gy with palliative involved-field radiation therapy (IFRT) of 4–12 Gy.[8] In 1962, Kaplan collaborated with Saul Rosenberg to conduct the first of several randomized clinical trials demonstrating the curability of stage I and II

TALKING POINTS Physicians Pharmacy Formulary Cancer Nurses

Combined modality is appropriate in most patients.

ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) is standard chemotherapy for early stage disease.

Long-term follow-up is necessary to fully evaluate a treatment modality since some treatment-related complications may not appear for 20 years or more.

Coordination of treatment between oncology services is necessary for optimal treatment results.

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HL by EFRT and the potential curability of stage III disease with total nodal irradiation (TNI). HL, an almost uniformly fatal disease before 1950, had been transformed into a highly curable entity with RT by the end of the 1960s.

PATHOLOGY

Since 1965, the Rye classification[9] with its four histologic subtypes (nodular sclerosis, mixed cellularity, lymphocyte predominant, and lymphocyte depletion) has remained the standard. The only exceptions are the modest changes in the Revised European American Lymphoma (REAL) classification in 1994[10] and the World Health Organization (WHO) modifications of the REAL classification in 1999.[11] This current classification separates classic HL, including nodular sclerosis, mixed cellularity, lymphocyte depletion, and lymphocyte-rich classic, from the nodular lymphocyte predominant (NLP) subtype, which is a distinct clinicopathologic entity. Controversy exists over the etiology of NLP HL; however, outcomes of conventional HL therapeutic regimens in NLP HL have been excellent, suggesting no rationale for a change in overall therapy or the role of RT in this subset of patients.

STAGING

The Ann Arbor staging system, initiated in 1971, remains relatively intact.[12,13] In 1989, the Cotswald modifications were proposed to reflect additional prognostic factors, including bulky disease, extensive versus minimal splenic involvement, upper versus lower abdominal involvement, and designation of extralymphatic involvement, which frequently impact the role of RT.[14]

DIAGNOSIS AND WORK-UP

Staging for HL has evolved since the early days of curative RT. Early oncologists had only chest radiographs and tomograms to image supradiaphragmatic disease. The accuracy of RT was undoubtedly compromised by inadequate knowledge of the initial extent of disease. Lymphangiography, which was commonly used for staging and treatment planning in the 1970s and 1980s, was reported to have >80% sensitivity and >95% specificity.[15,16] However, lymphangiography does not image the mesenteric and internal iliac nodes, spleen, and liver. On the other hand, it can identify abnormal filling defects in normal-sized lymph nodes and can be helpful in two-dimensional design of RT fields.[16] Lymphangiography requires skill and experience to perform and interpret, and its routine use is limited to a few institutions.

Kaplan and colleagues at Stanford University[17] also pioneered much of the important work on laparotomy, which was the gold standard for subdiaphragmatic staging in the US from the late 1960s. Approximately 20–35% of clinical stage (CS) I and II disease was pathologically upstaged after laparotomy and splenectomy.[18-20] Correlation of laparotomy pathologic data with patient presentation helped to identify the risk of occult abdominal disease in clinically staged patients. Staging laparotomy is associated with major complications in 3–13% of patients.[19,21-27] The European Organization for Research and Treatment of Cancer (EORTC) H6F trial[28] reported that the 6-year overall survival rate favored the clinical staging arm (93% versus 89%, *P*=NS), despite freedom-from-progression data favoring the laparotomy arm (83% versus 78%, *P*=NS). The slightly higher mortality was attributed to laparotomy-related deaths. Whereas pathologic stage (PS) was particularly important before the emergence of combined-modality therapy (CMT) because selection of RT fields was dependent on disease extent, laparotomy is currently not routinely performed except in specific trials.[29]

Radiographic studies for staging work-up should include chest radiograph and computed tomography (CT) scans of the neck, chest, abdomen, and pelvis. CT scans rely primarily on size criteria for tumor involvement. For minimally enlarged nodes (>1 cm and <3 cm), the probability of involvement is approximately 50%; for nodes 3 cm, the probability of involvement is approximately 75%.[30] The accuracy of CT scans for evaluation of pelvic and para-aortic adenopathy is similar to that of lymphangiograms with a negative predictive value of approximately 95% and positive predictive value ranging from 20% to 65%.[15,19,31,32] Imaging of the spleen is problematic because occult involvement is common and CT accuracy has been reported to be 58%.[15] CT, however, remains the gold standard of radiographic staging and is critical when RT is used, both for determining disease extent and for planning treatment.

Optional, but often helpful, studies include gallium and positron emission tomography scans. Laboratory studies should include complete blood cell count, erythrocyte sedimentation rate (ESR), thyroid-stimulating hormone, liver and renal function tests, albumin, and β-HCG levels (in all women of child-bearing age).

Asymptomatic patients with stage I/II disease, normal complete blood cell count and lactate dehydrogenase values, and no B symptoms have a 1% probability of bone marrow involvement[33,34] and do not require a bone marrow biopsy.

The extent of staging necessary in HL varies with treatment regimen. For example, if RT is to be delivered to all sites of involvement, CT imaging must define all limits of disease at presentation. If the extent or type of therapy depends on early treatment response, reimaging with CT and/or gallium may be required after two or three cycles of chemotherapy. Specifically, the volume and dose of RT may be determined based on early response to chemotherapy.

GENERAL PROGNOSTIC FACTORS

HL comprises a heterogeneous group of patients, even within a particular stage. Prognostic factors useful in directing treatment and predicting outcome include patient-related factors such as age, sex, and performance status and disease-related factors such as stage, tumor size, location, and extent, large mediastinal mass (LMM),

histologic subclassification, systemic symptoms, and tumor markers.[13,18,35]

The EORTC has led the way in identifying important risk factors related to RT alone in early-stage disease and using them to stratify patients in their cooperative group protocols. Starting in 1982 in protocol H6,[36] the EORTC defined an early-stage unfavorable group as CS I or II with any of the following: LMM, age >50, ESR 50 mm/h, or ESR 30 mm/h with B symptoms, and 4 involved regions. The German Hodgkin's Study Group (GHSG)[37] has used similar criteria since 1988, but substituted "presence of extranodal disease" for "age >50" and used "three or more involved regions." All the patients in these early-stage unfavorable groups were treated with CMT because of their higher risk for relapse with RT alone.

Several smaller studies[38-42] as well as a meta-analysis by Specht and colleagues[43] have shown that the adverse prognostic factors for CMT are similar to those for RT alone.

In advanced-stage disease, recognition of prognostic factors is important to identify those in whom an alternate treatment may improve survival rates as well as those in whom a standard approach may actually be overtreatment. A simplified scoring system based on seven factors (serum albumin <4 g/dL, hemoglobin <0.5 g/dL, male sex, age 45 or older, stage IV disease, white blood cell count 15,000/µL, and lymphocytopenia of <600/µL and/or <8% of total white blood cell count) was proposed by Hasenclever and Diehl[44] for the International Prognostic Factors Project on Advanced Hodgkin's Disease in 1998. Rates of freedom from relapse and overall survival for individual scores ranged from 84% and 89%, respectively, for a score of 0, to 42% and 56% for scores of 5 or higher.

TREATMENT PRINCIPLES AND CONCEPTS

RT and chemotherapy are effective treatment modalities, both alone and in combination. Approximately 80% of all patients with HL can expect to be cured. In a given patient several treatment options are often acceptable and yield a similar probability of survival. Treatment must therefore also be designed to minimize the likelihood of acute toxicity, relapse, and long-term treatment-related morbidity and mortality. Awareness of the important potential treatment- and disease-related complications is critical for planning treatment, as is preventing, identifying, and treating early and late complications, which may not manifest for 20 to 30 years or more after treatment.

RADIATION THERAPY

RT fields in HL encompass the clinically apparent disease and the contiguous nodal regions at risk for subclinical disease. Treatment of adjacent extranodal tissue may also be required; examples include lung irradiation in patients with an LMM or hilar adenopathy and liver irradiation in patients with extensive splenic involvement.

Radiation Treatment Volume

The standard RT fields are as follows:

Historically, an involved field (IF) has been a standard field encompassing an entire anatomic region that contains any clinical evidence of involvement. EFRT refers to the treatment of an involved field along with the contiguous clinically negative nodal regions. Specialized fields that encompass commonly involved sites include mantle and inverted Y fields. A mantle field includes the neck nodes bilaterally extending up to the tragus and/or mastoid, both supraclavicular and infraclavicular areas, both axillae, both hilae, and the entire mediastinum extending down to approximately T10. The inverted Y field includes para-aortic nodes and bilateral pelvic, inguinal, and femoral nodal regions. Not uncommonly, the spleen or splenic pedicle will be included in this field.

Field combinations frequently used in RT-alone regimens include subtotal nodal irradiation (STNI), a mantle field plus the para-aortic nodes, with or without the spleen or splenic pedicle; and total nodal irradiation (TNI) encompassing both the mantle, spleen or splenic pedicle, and inverted Y fields.

Radiation Dose

The radiation dose required to control HL is considerably less than is necessary for the more common epithelial tumors. Initially, Kaplan[45] recommended doses in the 40- to 44-Gy range based on a linear dose-response model. After Fletcher and Shukovsky[46] reviewed the data from studies of HL patients treated with the usual RT approach and typical results, they identified a sigmoid-shaped dose-response curve with a steep slope between 20 Gy and 30 Gy. This suggesting an optimal dose range above which little additional improvement could be expected and toxicity would escalate. Several other investigators verified this apparent sigmoid-shaped dose-response curve with little advantage for doses >30 Gy.[47-52]

A large tumor burden has emerged as a significant treatment factor for in-field disease recurrence, and it is a factor for which dose escalation beyond 30 Gy is recommended.[49] Conversely, 20–30 Gy has been shown to be sufficient for subclinical disease.[49,53]

Lower radiation doses have been used in CMT with excellent results. Loeffler et al[54] in 1997 reported results combining GHSG trials HD1 and an arm of HD5. The HD1 trial randomized patients with PS I or II disease with an LMM, extranodal involvement, or extensive splenic involvement to two cycles of COPP/ABVD (cyclophosphamide, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vinblastine, dacarbazine) followed by EFRT to either 40 Gy to the entire volume or 40 Gy to areas of bulky disease (>5 cm) and 20 Gy to the rest of the volume. The HD5 arm included patients with CS I and II disease with an LMM or ESR of 30 with B symptoms or ESR of 50 without B symptoms, extranodal involvement, or massive splenic disease.

Patients received two cycles of COPP/ABVD and EFRT to 30 Gy, with bulky sites receiving 40 Gy. Dose information extracted from the combination of these studies showed 4-year failure-free survival rates of 86%, 80%, and 90% (P=0.8), and overall survival rates of 93%, 94%, and 88% (P=0.5) for 20 Gy, 30 Gy, and 40 Gy, respectively. In addition, investigators at Stanford University have successfully treated children with clinical disease with doses ranging from 15 Gy to 25 Gy combined with six cycles of chemotherapy.[20]

PRINCIPLES OF COMBINED MODALITY THERAPY

The roles of RT and chemotherapy in CMT regimens are interrelated and variable. Emphasis on RT or chemotherapy as the primary modality of treatment reduces the role of the complementary modality. Both chemotherapy and RT carry dose-related toxicities, which vary with disease extent and location and the patient's age and sex. The major advantage of chemotherapy is the comprehensive scope of disease coverage. The major advantage of RT is the capability of tailoring dose and treatment volume to a particular patient and tumor presentation.

If RT is to play the predominant role in therapy and systemic treatment is to be minimized, then the RT fields must be comprehensive. If enhancement of RT efficacy is the goal, two cycles of chemotherapy may be given with definitive EFRT.

If a reduction in irradiated volume is the goal, two to four cycles of chemotherapy can be given to control subclinical disease in combination with IFRT. If four to six cycles of chemotherapy are delivered to control subclinical and small-volume disease, RT fields may be limited to bulky disease or areas of partial response.

Treatment selection has been increasingly tailored in an attempt to optimally decrease radiation dose and volume without sacrificing disease control or survival, since most normal-tissue toxicity and long-term sequelae are related to dose and volume. Any further improvement in long-term survival rates for early-stage HL will likely require treatment optimization, since the cumulative incidence of mortality due to second malignancies and other potentially treatment-related causes exceeds that of HL itself at 15–20 years after treatment.[55,56]

TREATMENT ACCORDING TO RISK CATEGORY

Low-Risk Patients

Stages I and II HL without adverse prognostic factors such as B symptoms, LMM or other bulky disease, more than three sites of involvement, or elevated ESR are considered favorable and have historically been treated with STNI alone, CMT, or chemotherapy alone. STNI has been the typical approach for this group of patients when using RT alone; relapse-free survival rates are generally between 70% and 85% and overall survival rates are approximately 85% to 95%.[18,57-64] CMT has resulted in improved relapse-free but not overall survival, due to the high likelihood of salvage after failure with RT alone.

MOPP (mechlorethamine, vincristine, procarbazine, prednisone) chemotherapy alone was compared with STNI in two randomized trials. An Italian randomized clinical trial for PS I and IIA disease reported similar relapse-free survival rates in both arms, but an inferior overall survival in the chemotherapy alone arm (93% versus 56%, P<.001), reflecting a poorer result for salvage treatments in patients receiving previous chemotherapy.[65]

The projected 10-year results of a National Cancer Institute randomized trial also comparing STNI versus MOPP for "early-stage" HL identified superior disease-free and overall survival favoring the chemotherapy-alone arm.[66] This trial, however, includes a heterogeneous group of patients at intermediate risk for recurrence (LMM and stage III) and excludes the patients with very favorable stage IA disease. Randomized trials comparing RT alone versus more effective chemotherapy such as ABVD in early-stage HL have not yet been performed. Thus, chemotherapy alone should not be considered a standard of care for adult patients at this time.

Attempts to decrease the number of cycles of chemotherapy as well as the volume and dose of RT have been the basis of several randomized trials. A Southwestern Oncology Group/Cancer and Leukemia Group B (SWOG/CALBG) trial[67] reported significant differences in failure-free survival at 3 years favoring doxorubicin and vinblastine chemotherapy for three cycles followed by EFRT versus EFRT alone (93% versus 81%, P<.001). The GSHG HD7 trial[68] further reduced chemotherapy to two cycles of ABVD followed by STNI versus STNI alone. The 2-year rate of freedom from treatment failure was 96% in the CMT arm versus 84% with STNI alone (P<.05). Short-term follow-up revealed no difference in overall survival in either the GHSG HD7 or the SWOG/CALGB trials.

Several randomized studies delivering CMT plus IFRT versus STNI alone have generally reported a statistically significant improvement in relapse-free survival in most instances, and overall survival in one trial favored CMT. A Stanford trial[69] comparing VBM (vinblastine, bleomycin, and methotrexate) followed by IFRT versus STNI alone revealed no difference in relapse-free or overall survival. The EORTC H7 trial,[70,71] in which 165 patients were randomized to either six cycles of epirubicin, bleomycin, vinblastine, and prednisone (EBVP) followed by IFRT or STNI alone, revealed a 6-year relapse-free survival of 92% for CMT versus 81% for STNI alone (P=.004), but no difference in overall survival (98% and 96%, respectively). The EORTC-GELA H8F randomized trial[72] compared less chemotherapy (three cycles of MOPP/ABV hybrid chemotherapy) followed by IFRT versus STNI alone. This trial showed a statistically significant difference in failure-free survival (99% versus 77%) as well as overall survival (99% versus 95%, P=.019) favoring CMT.

Several RT-alone trials have also been designed to decrease treatment volumes. The EORTC H5 trial[36]

randomized 198 patients with favorable prognosis and negative laparotomy results to mantle irradiation or STNI. At 6 years there was no difference in relapse-free survival or overall survival (mantle 74% and 96% versus STNI 72% and 89%, respectively). Mantle irradiation alone in selected patients has yielded differing results in subsequent trials. EORTC trial H7VF[70,71] described the results of 40 patients in a subgroup described as very favorable (CS IA, women <40 years old, nodular sclerosis or lymphocyte predominant histologies, and ESR <50 mm/h) treated with mantle irradiation alone. The 73% 6-year relapse-free survival rate was considered unacceptable for this group of patients, although overall survival was 96%. Wirth et al[73] reported a retrospective study of 261 CS I and II patients treated with mantle irradiation alone; overall survival was 73% and progression-free survival was 58%. Subset analysis revealed more acceptable results in the lymphocyte-predominant subtype with a progression-free survival rate of 81% for stage I and 78% for stage II, and an estimated progression-free survival of up to 90% for favorable stage I disease.

Backstrand and coworkers[29] recently reported results of a prospective trial using mantle irradiation alone in 87 patients with selected CS IA or PS IA or IIA disease. Patients with an LMM, hilar disease, or subcarinal adenopathy were excluded. The 5-year actuarial rates of freedom from treatment failure and overall survival were 86% and 100%, respectively. In the 43 stage I patients the rate of freedom from treatment failure was 92%, and none of the six clinically staged patients had a relapse.

Specht et al[43] in 1998 reported a meta-analysis of 23 randomized trials including both low- and intermediate-risk patients, comparing more versus less extensive RT as well as CMT versus RT alone. More extensive RT reduced the risk of treatment failure (resistant or recurrent) at 10 years by more than one third (31.3% versus 43.4%) with no difference in overall survival (77.1% versus 77.0%). The 10-year risk of failure was reduced from 32.7% to 15.8% with addition of chemotherapy; however, the improvement in overall survival again did not reach statistical significance (79.4% versus 76.5%).

Clearly, there are several excellent options for treatment of early-stage HL—including STNI in favorable patients, two cycles of chemotherapy with STNI, and two to four cycles of chemotherapy with IFRT in adults. IFRT and mantle RT alone should be reserved for very favorable patients in clinical trials.

Intermediate-Risk Patients

Intermediate-risk patients represent a group who are at 25–50% risk of relapse with STNI or TNI alone. This includes those with stage I and II HL with adverse prognostic factors including >3 sites of involvement, LMM, bulky disease, or B symptoms.[18] Patients with PS IIIA1 HL with <5 splenic nodules and no LMM may also fit into this category.

In 1977 the EORTC H5-U[36] began stratifying unfavorable subgroups in CS I and II disease. This study randomized between two arms: TNI to 40–45 Gy versus three cycles of MOPP, then mantle RT, followed by an additional three cycles of MOPP. The rate of treatment failure at 15 years in the CMT arm was 16% versus 35% for TNI; however, the overall survival was 69% in both arms. Subsequent EORTC trials for early-CS, unfavorable-prognosis HL have not had an RT-alone arm; instead, they have randomized between different chemotherapy approaches and either STNI or IFRT.

Additional randomized trials have studied CMT with varying RT volumes. A French cooperative trial,[74] carried out from 1976 through 1981, randomized patients between three cycles of MOPP, then IFRT, followed by an additional three cycles of MOPP versus the same chemotherapy with EFRT. The 6-year disease-free survival was 93% for the EFRT versus 87% for the IFRT arm (P=.15). A Milan trial randomized 136 patients with early-CS HL (stage I bulky, IB, IIA, IIA bulky, and IIAE) to four cycles of ABVD followed by STNI to 30–36 Gy or the same CT followed by IFRT. Recently updated results showed no difference in rates of freedom from progression (97% versus 94%) or overall survival (93% versus 94%) with a median follow-up of 87 months.[75] The interim analysis of the GHSG HD8 unfavorable disease trial[76] found no difference in FFTF and overall survival at 2 years between two cycles of COPP/ABVD with EFRT versus the same chemotherapy and IFRT. Preliminary results of the EORTC-GELA H8U trial[77] have also revealed no significant difference in overall survival and failure-free survival at 39 months between three arms: six cycles of MOPP/ABV plus IFRT, four cycles of MOPP/ABV plus IFRT, and four cycles of MOPP/ABV plus STNI.

Because of the high risk of treatment failure with RT alone in intermediate-stage HL, most patients should receive CMT unless there are significant contraindications to chemotherapy. The optimal amounts of chemotherapy and volume of RT are under investigation. Early results suggest that four cycles of chemotherapy and IFRT or two cycles of chemotherapy and EFRT are effective; results with two cycles of chemotherapy and IFRT are encouraging but need further follow-up.

Advanced-Stage Disease

In 1964 MOPP chemotherapy changed the perception of treatment for advanced-stage disease from primarily palliation to one with a greater than 50% of cure.[78] In 1973 Bonadonna et al[79] reported the next major advance: ABVD plus RT was slightly more effective than MOPP plus RT. MOPP was subsequently combined with ABVD in equally effective alternating cycles or hybrid regimens. Further trials have shown an equal or superior efficacy for ABVD alone, which, with its better toxicity profile, has become the standard of care.

The role of RT in advanced HL is controversial. The basis for recommending CMT is primarily the knowledge that most recurrences with chemotherapy alone are located at areas of initial involvement, and that RT enhances local

control. Several randomized clinical trials using CMT for advanced-stage disease have been reported, but most are limited by small size[80-83] or poor compliance.[84] In an attempt to overcome these problems, Loeffler et al[85] carried out a meta-analysis of 14 studies with 1,740 patients comparing CMT versus the same chemotherapy alone, and CMT versus additional cycles or an alternate regimen of chemotherapy as a substitute for RT. Although the addition of RT improved the 10-year tumor control rate versus that in the group receiving the same chemotherapy, it did not improve overall survival. Because of an increase in fatal events in the CMT group among patients with continuous complete remission, the CMT group had an inferior survival rate versus those receiving additional cycles of chemotherapy.

Cautious application of these results is required for several reasons, including problems inherent to a meta-analysis, inclusion of older trials (some starting more than 30 years ago), use of outdated RT and chemotherapy regimens, the unknown impact of quality assurance factors in RT, and a disproportionate number of more advanced cases in the group showing the most benefit from additional or alternate chemotherapy.

Encouraging early results of two dose-intense, dose-escalated regimens have recently been reported. Horning et al[86] described 5-year rates of freedom from progression and overall survival of 85% and 96%, respectively, in patients with advanced or bulky HL treated in an ECOG pilot study using the Stanford V dose-intensive CT with RT to areas of residual or bulky disease (>5 cm). The GHSG[87] reported updated results from the multicenter HD9 trial comparing COPP/ABVD (arm A) against the standard (arm B) and escalated-dose plus granulocyte-stimulating colony factor (arm C) regimens of BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), with all arms receiving IFRT to initial bulky or residual disease. Failure-free survival rates at 3 years were 70%, 79%, and 89% in arms A, B, and C, respectively (each difference, P=NS). Survival rates at 3 years in arms B and C (91% and 92%) were both significantly better than arm A (86%). Subset analysis indicated that the entire benefit, with lesser toxicity, came in younger patients, and therefore patients older than 65 should not receive BEACOPP.

CONCLUSIONS

RT continues to be an important modality in the treatment of HL. A trend toward an increased use of CMT, even in early-stage disease, has been driven by both the potential to decrease long-term complications and to increase disease-free survival. Optimization of chemotherapy and radiation dose and volume are critical in patients with HL, who have a high likelihood of long-term survival and thus are at greater risk of experiencing late complications. Meticulous attention to quality assurance and use of technological advances in both diagnostic and therapeutic radiology are necessary to realize the full potential value of RT in HL. Ongoing trials will help to further shape the evolving role of RT in HL; however, follow-up of 20 years or more is required to identify potential long-term treatment-related complications. **OS**

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