Role of Radiation Therapy in Hodgkin's Lymphoma

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Abstract: Radiation therapy was the first modality that solely cured patients with Hodgkin's lymphoma (HL) as early as the 1940s. In the absence of other curative options, the radiation field in full dose was extended to encompass both involved and uninvolved sites including many normal organs. Decades later, it was evident that some of the HL survivors succumbed to radiation-related effects, mostly second solid tumors. The more recent reliance on modern chemotherapy in combination with radiation yielded further improvement in disease control and allowed a marked reduction in radiation exposure. Some oncologists even suggested that chemotherapy alone might retain the excellent results obtained with combined modality and campaigned for the exclusion of radiotherapy from the treatment program. However, analysis of randomized studies (as discussed later) supports the inclusion of reduced-field and dose radiotherapy in treatment programs for HL. Furthermore, new concerns regarding the short- and long-term safety of enhancing chemotherapy to compensate for the omission of radiotherapy favor shorter courses of chemotherapy. Short chemotherapy supplemented with mini-radiotherapy constitutes a highly effective and safe treatment of HL, particularly in early stages.

Key Words: Hodgkin's lymphoma, radiotherapy, mini-radiotherapy, chemotherapy

(*Cancer J* 2009;15: 155–160)

Radiation is probably the most effective single agent in the curative treatment of Hodgkin's lymphoma (HL). The dramatic effect of ionizing radiation on HL tumors was reported as early as 1901, a short time after Roentgen's discovery of "x-rays." Yet, during the first half of the 20th century, HL remained incurable and responses to radiotherapy were partial or brief due to limitations of antiquated technology of the time and poor clinical application. As x-ray technology and penetration improved in the 1940s and the concept of irradiating beyond the involved area was adopted, patients with early-stage HL could be cured with radiation alone—the only effective curative modality for lymphomas, that was available until the late 1960s.[1]

During the 1960s and 1970s, before the advent of chemotherapy and the use of a dual modality approach, radiation therapy (RT) alone still cured many patients, particularly in early stages. Yet, reliance on RT alone required wide extension of the radiation field and raising the dose to normal tissue tolerance levels ("radical radiotherapy"). Twenty and 30 years later, the long follow-up of the survivors disclosed an unexpected price; the incidence of morbidity and mortality of those patients with HL was significantly higher compared with the normal population. The main complications were secondary tumors (mostly breast and lung cancers).[2] There was also more than expected coronary artery disease associated with the use of radical radiotherapy.

The advent of effective and less-toxic chemotherapy regimens in the late 1970s merged with attempts to secure the cure of larger number of patients; even of those with more advanced disease. This effort translated into using full-dose combined-modality approach with full-dose chemotherapy and extended-field radiotherapy. Although this strategy indeed cured more patients, it produced a higher rate of short- and long-term complications. The ensuing reports of survivors' morbidity caused obvious alarm.

The strategic response in the 1990s was to reduce therapy for HL, although hoping to maintain the cure rate. One approach was to keep the concept of combined modality, but reduce significantly the extent of the irradiated volume, decrease the radiation dose, and at the same time also reduce the number of chemotherapy courses. Others considered radiotherapy as the only culprit causing long-term complication, and thus totally eliminated RT from the treatment regimen and consequently relied on more courses or additional combinations of chemotherapy.

These 2 conflicting strategies fostered hot debates and opinionated editorials that naturally confused and distressed new and previously treated patients with HL. Constructively, it also led to the design of several prospectively randomized studies that focused on choice between the 2 approaches described earlier.[3–5]

The advocates of the total exclusion of radiotherapy and substituting it with more chemotherapy made the following arguments:

1. Radiotherapy is the main and possibly the sole cause of the increased long-term morbidity of HL survivors.
2. Reduction in the extent and/or dose is of radiotherapy unlikely to significantly change the risk.
3. A chemotherapy alone strategy will provide an excellent outcome of disease control, that would be at least similar, if not better, than the results obtained with combined modality. If RT is omitted, the decrease in radiation-related late mortality from causes other than HL would probably result in better overall survival (OS) rates.
4. Chemotherapy alone, even if escalated or prolonged, is safe and is unlikely to result in more toxicity.
5. Even if more failures will occur without radiotherapy, salvage with higher dose chemotherapy followed by stem-cell transplantation is simple, well tolerated, and safe.

Those who had reservations about omitting radiotherapy strongly disagreed with the above. They expected disease control rate without RT to decrease and have a negative effect on OS. They also argued that the modern reduction in both extent and dose of radiation that was designed for the setting of combined-modality treatment (as opposed to radiation alone of the past) would markedly reduce or eliminate the radiation-related long-term toxicity. At the same time, the associated reduction in chemotherapy will further enhance the short- and long-term safety profile of the combined therapy program. This approach will also reduce markedly the need for salvage therapy with high-dose therapy and autologous stem-cell transplantation that causes not only physical and psychologic trauma to these

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ISSN: 1528-9117/09/1502-0155

TABLE 1. Randomized Studies that Compared Combined Modality With Chemotherapy Alone

	Stage	Treatment Arms	EFS or FFP (%)	*P*	OS	*P*	Comments
CCG 5942 (501 pts)	I–IV (I–II 68%)	COPP/ABV × 4–6	85*	0.02*	3 yr	NS	No-RT arm closed early (relapses)
		Same + IF 21 Gy	93*				
Mumbai (251 pts)	I–IV (I–II 55%)	ABVD × 6	76	0.01	8 yr	0.02	
		ABVD × 6 + IF 30 Gy	88				
EORTC/GELA H9F (489 pts)	I–II favorable	EBVP × 6	69	0.001	4 yr	NA	No-RT arm closed early (relapses)
		EBVP × 6 + IF 20 Gy	85				
		EBVP × 6 + IF 36 Gy	88				
NCIC/ECOG HD6 (276 pts)	I–II unfavorable, but no B, or bulky	ABVD × 4–6	88	0.004	5 yr	NS	Designed for OS evaluation at 12 yr
		ABVD × 2 + STLI	95				
MSKCC (152 pts)	I–III A/B nonbulky	ABVD × 6	81	NS	5 yr	0.08	Not powered to detect differences <20%
		ABVD × 6 + EF/IF	86				

*Analyzed as treated.
NA indicates not available; NS, not significant.

young adults and their families, but also increases the risk of short- and long-term serious complications; mostly sterility and secondary leukemia.

Randomized Studies in Early-Stage HL Comparing Combined-Modality Therapy With Chemotherapy Alone

Several groups tested the hypothesis that chemotherapy alone could provide equivalent disease control to that achieved with combined-modality therapy. The studies from Europe,[6] Asia,[7] and North America[8–10] targeted mostly early-stage favorable and unfavorable patients and were conducted in adults, children or adolescents, or in both. In some the randomization was upfront, in others it was limited to patients who achieved a clear complete response (CR) with chemotherapy. The trials are detailed later and are summarized in Table 1.

Children Cancer Group (CCG) #5942[10]

The Children Cancer Study Group tested the role of radiation therapy in young patients (<21 years) who attained a CR with risk-adapted chemotherapy (mostly COPP/ABV, 4–6 cycles). They enrolled 829 patients into the study (68% were early-stage). Five hundred one patients who achieved a CR were then randomized to receive either low-dose (21 Gy)-involved-field radiotherapy (IFRT) or no further treatment. The accrual stopped earlier than planned because of a significantly higher number of relapses on the no-radiotherapy arm.

The 3-year event-free survival (EFS) with an intent-to-treat analysis was 92% for patients randomized to receive RT and 87% for those randomized to no further treatment ($P = 0.057$). Because 30 patients switched their treatment after randomization, an analysis "as treated" was performed and showed a 3-year EFS of 93% for those who received radiation and only 85% for those who were only observed ($P = 0.0024$). At this early analysis, no survival difference was detected.

The Tata Memorial Hospital Trial[7]

This is a large prospectively randomized study from the main cancer center in Mumbai, India of 251 patients with HL (55% early stage) who received 6 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy. Of those, only 179 patients (71%) who achieved a CR were randomized to either IFRT of 30 Gy (+10 Gy boost to bulky sites) or to no further therapy.

At a median follow-up of 63 months, the 8-year EFS and OS were significantly better for the patients who received consolidation with IFRT compared with those who received ABVD alone (EFS-88% vs. 76%, $P = 0.01$; OS 100% vs. 89%, $P = 0.002$). Most relapses in the ABVD alone arm were early and systemic, whereas in the ABVD + RT arm, the relapses were late and localized.

National Cancer Institute of Canada/ECOG Trial HD-6[9]

This intergroup study included 405 patients with nonbulky stage I–II patients. They were randomized to either receive "standard therapy," namely, subtotal nodal irradiation alone for favorable patients and ABVD (2 cycles) followed by subtotal nodal irradiation for unfavorable (B, elevated ESR, ≥3 sites, age ≥40, mixed cellularity (MC) histology) patients, or to the experimental arm that consisted of 6 cycles or 4 cycles (if CR was attained after 2 cycles) of ABVD and no RT.

At a median follow-up of 4.2 years, progression-free survival with ABVD alone was significantly inferior [$P = 0.006$; hazard ratio (HR) = 2.6; 5-year progression-free survival estimates 87% vs. 93%]. At this early point, no survival difference has been detected. Although the "standard" arm that included RT alone for favorable patients is no longer considered the standard of care, the inferior performance of ABVD alone compared with standard therapy in nonbulky early stage patients cannot be ignored. At a median follow-up of 4 years no OS difference was detected. Originally, the study was statistically designed for a 12-year analysis of survival.

EORTC/GELA H9[6]

This is a large ongoing trial in favorable early-stage patients with classic HL. All patients received 6 cycles of epirubicin, bleomycin, vinblastine, and prednisone. Only patients who achieved a CR are randomized to either IFRT of 36 Gy, IFRT of 20 Gy, or to no radiation. Because of an excessive number of relapses in no radiation arm, the group closed it early. At the completion of the study, there was no difference between adding consolidation RT of 36 Gy or 20 Gy, but there was a significantly lower failure-free survival at 4 years if no radiation was added (failure-free survival of 87%, 84%, and 69%; $P = 0.001$, respectively). At only 4 years median follow-up, no survival difference was detected.

Memorial Sloan-Kettering Cancer Center Trial[8]

The Memorial Sloan-Kettering trial included 152 patients with nonbulky early-stage HL. Patients were randomized upfront to either received ABDV X6 alone or ABVD X6 followed by radiotherapy. At 60 months CR duration, freedom from progression, for

ABVD + RT versus ABVD alone are 91% versus 87% ($P = 0.61$) and 86% versus 81% ($P = 0.61$), respectively. OS was 97% with ABVD + RT vs. 90% with ABVD alone ($P = 0.08$). Although the differences between the outcome of the 2 treatment groups were not statistically significant, the study was not powered to detect differences between the treatment strategies that were smaller than 20%, because of the small number of patients and events. The superior OS ($P = 0.08$) of the ABVD + RT group is also difficult to explain and is possibly a result of the small size of this trial. The results are summarized in Table 1.

Effect of Omitting Radiation on Overall Survival

The effect of different treatment approaches used in prospectively randomized studies on OS has always been very difficult to demonstrate in HL. Therefore, disease control and early toxicity considerations often guided the evolvement of current treatment strategies.[11] There are multiple factors that explain why superior disease control on one arm of a randomized study does not necessarily translate into a statistically significant survival advantage: patients with HL commonly survive for a long time even with active disease, there are good salvage options; even if salvage fails, the patient could be maintained with disease for several years with single agents or simple RT. In most HL studies, the number of patients and the number of events especially in early-stage disease are small resulting in small differences that rarely meet "statistical significance" sacred criteria. Indeed, advantageous disease control by one treatment may be eventually tempered by its toxicity that will take more time to declare itself; this is relevant to both adding RT or enhancing chemotherapy as an alternative. Finally, most studies are reported early, often without full peer-review and detailed analysis of events and many large cooperative group studies do not have optimal follow-up and information on cause of death. It is thus may be misleading to declare an equality of 2 treatment options because they lack an OS difference and ignore the improved freedom from treatment failure even if significant.

Indeed, with one exception, all studies listed in Table 1 fail to show a significant OS advantage for the combined-modality arm even though the disease control for this approach was significantly better. The median follow-up ranged between 3 and 5 years; the median follow-up in the study showed that survival advantage to adding RT was 8 years.

To overcome the shortfall of small studies statistical power, The Cochrane Hematological Malignancies Group recently performed a meta-analysis of all published prospective randomized comparing combined-modality therapy (CMT) in early-stage HL with chemotherapy alone. They included 5 eligible randomized controlled trials involving 1245 patients. Although the CR rate was similar in patients receiving chemotherapy alone compared with CMT, both tumor control and OS were significantly better in patients receiving CMT. The hazard ratio was 0.40 (95% CI 0.25–0.66) for tumor control and 0.41 (95% CI 0.27–0.60) for OS.[12]

Transformation From "Radical Radiotherapy" Into Tailored Mini-Radiotherapy: The Effect on Long-Term Complications

In the 1960s and 1970s, when radiotherapy was the primary, and at times the only curative modality for HL, it was used alone or with adjuvant mechlorethamine, vincristine, prednisone, and procarbazine (MOPP) for early and advanced stages. Bulky sites were covered with large radiation field margins, and occasionally even the lungs and the liver were intentionally irradiated. Even for favorable patients, the standard field was total lymphoid irradiation. Its giant size compensated for the lack of good imaging information. The dose was also maximized (the standard dose at Stanford was 44 Gy) and often treatment was given in a technique that delivered even higher doses anteriorly to the heart and breast.[13]

The IFRT that is used now in combined-modality programs is considerably smaller; the radiation is limited to the involved site and is often tailored to include only the reduced postchemotherapy volume.[14] It is estimated that in comparison with total lymphoid irradiation (TLI), the average involved field will reduce the irradiated volume by more than 80%. This is particularly relevant to irradiation of the breast, heart, and lungs. With the old indiscriminate "mantle" field radiotherapy, most of the breast tissue was irradiated. Most breast exposure resulted from the routine irradiation of the axillae and most second breast cancers indeed developed in the outer part of the breast. Yet, approximately, two third of women with early-stage HL do not require radiation of the axillae, and additional protection to the upper and medial aspects of the breast can now be provided by further reducing field size using careful computerized tomographic-based planning that usually allows for smaller mediastinal volumes, particularly after chemotherapy. We can now avoid irradiating the breast in most women and substantially reduce exposure of the heart and lungs.[15]

The large fields of the past limited the radiation technique to simple opposed anterior and posterior fields. The conversion to smaller and better defined radiation volumes allows the utilization of more conformal radiation therapy, based on better imaging, computerized planning programs, and when indicated, advanced tools such as intensity modulated radiotherapy.[16] Modern breakthroughs in radiotherapy technology that have been implemented recently in HL have already demonstrated better sparing of the heart and coronary arteries. They provide increased accuracy, avoid normal organs, and thus improve the therapeutic ratio.[17]

Recent studies clearly indicate that the risk of secondary solid tumor induction is radiation dose related. This was carefully analyzed for secondary breast and lung cancers as well as for other tumors.[18,19] Although it will take more years of careful follow-up of patients in randomized studies to display the full magnitude of risk tapering by current reduction of radiation field and dose, recent data suggest that this likely to be the case. In a recent Duke University study, 2 groups of patients with early-stage HL were treated with different radiation approaches over the same period. One group received radiotherapy alone, given to extended fields with a median dose of 38 Gy, the second group received chemotherapy followed by involved-field low-dose (median of 25 Gy) radiotherapy. Although 12 patients developed second tumors in the first group and 8 of them died, no second tumors were detected in the second group. The median follow-up was 11.7 and 8.1 years, respectively.[20] Similar observations with an even longer follow-up were made by the Yale group.[21] In the randomized study from Milan, comparing ABVD × 4 followed by subtotal lymphoid irradiation with ABVD × 4 followed by only IFRT, 3 patients developed second cancers after subtotal lymphoid irradiation and no second cancers were detected after IFRT. Median follow-up was 10 years.[22]

The European HL study groups recently introduced an additional reduction in the size of the involved radiation. The reduced size field is tailored to the involved lymph node and not the whole region where they reside as is in IFRT and is thus termed involved node radiotherapy (INRT).[23] Most importantly, for radiotherapy involving the mediastinum or the abdomen, INRT is designed according to the postchemotherapy volume that is often markedly reduced in comparison with the initial volume. Although there is no prospective randomized comparison of INRT with IFRT, a recently retrospective well-controlled comparison of sequential patients with HL treated with only 2 cycles of ABVD followed by either extended-field RT, involved field or further reduction to INRT showed similarly excellent disease

control and OS in all RT groups without any difference in in-field or marginal relapse.[24]

Role of RT

Special Consideration of Stage, Bulk, and Histologic Type of HL

Most of the discussion on the role of consolidation RT in HL focused on patients with favorable (without bulky disease and/or B symptoms) classic HL and most data from randomized studies is limited to this group of patients. Yet, other groups of patients with HL present other consideration and the data regarding the option of avoiding RT in these patients is limited.

Lymphocyte-Predominant Hodgkin's Lymphoma

Most (>75%) patients with Lymphocyte-Predominant Hodgkin's Lymphoma (LPHL) present with at an early stage; the disease is commonly limited to one peripheral site (neck, axilla, or groin) and involvement of the mediastinum is extremely rare. The treatment recommendations for LPHL differ markedly from those for classic HL. The American National Comprehensive Cancer Network guidelines, the German Hodgkin's Lymphoma Study Group, and the European Organization for Research and Treatment of Cancer (EORTC) currently recommend involved-field radiation alone as the treatment of choice for early-stage LPHL.[25] It should be emphasized that even if regional radiation fields are selected, the uninvolved mediastinum should not be irradiated, thus avoiding the site most prone for radiation-related short- and long-term side effects. Although there has not been a study that compared extended-field RT (commonly used in the past) with involved field RT, retrospective data suggest that involvedfield is adequate.[26] The radiation dose recommended is between 30 and 36 Gy with an optional additional boost of 4 Gy to a (rare) bulky site.

Unfavorable Early-Stage HL

Although different study groups slightly use definitions of favorable and unfavorable early stages, all consider bulky disease or B symptoms as unfavorable features. In this category of patients, chemotherapy is not reduced below 4 cycles and adding RT as consolidation is standard of care.

Advanced-Stage HL

Although the role of consolidation radiotherapy after induction chemotherapy remain controversial, irradiation is often added in patients with advanced stage HL who present with bulky disease or remain in uncertain complete remission after chemotherapy.[27] Retrospective studies have demonstrated that adding low-dose radiotherapy to all initial disease sites after chemotherapy induced complete response decreases the relapse rate by ~25% and significantly improves OS. Interpretation of the impact of radiation in prospective studies has been controversial.[28,29] However, a Southwest Oncology Group randomized study of 278 patients with stage III or IV Hodgkin's disease suggested that the addition of low-dose irradiation to all sites of initial disease after a complete response to mechlorethamine, Oncovin (vincristine), prednisone, bleomycin, Adriamycin (doxorubicin), and procarbazine chemotherapy improves remission duration in patients with advanced-stage disease.[30] An intention-to-treat analysis showed that the advantage of combined-modality therapy was limited to patients with nodular sclerosis. No survival differences were observed. A meta-analysis of several randomized studies demonstrated that the addition of radiotherapy to chemotherapy reduces the rate of relapse but did not show survival benefit for combined modality compared with chemotherapy alone.[31]

Recently, EORTC reported the results of a randomized study that evaluated the role of IFRT in patients with stage III/IV Hodgkin's disease who obtained a CR after MOPP/ABV.[32] Patients received 6 or 8 cycles of MOPP/ABV chemotherapy (number of cycles depended upon the response). Patients who have not obtained a CR (40% of patients) were not randomized to receive chemotherapy and received IFRT. Of the 418 patients who reached a CR 85 patients were not randomized to receive treatment for various reasons. A total of 161 patients were randomized to receive no RT and 172 patients were randomized to receive IFRT. The authors concluded that IFRT does not improve the treatment results in patients with stage III/IV Hodgkin's disease who reached a CR after 6 to 8 courses of MOPP/ABV chemotherapy. The 5-year OS rates were 91% and 85%, respectively ($P = 0.07$). The data indicated that in comparison with chemotherapy alone, there were more cases of leukemia second tumors on the CR combined modality, but surprisingly not in the large group of patients who have not achieved CR with chemotherapy and all received RT. This observation suggests that the increased mortality on the randomized RT arm is a statistical fluke resulting from small number of events. Interestingly, in partial responders after 6 cycles of MOPP/ABV, the addition of IFRT yielded OS and EFS rates that were similar to those obtained in CR to chemotherapy patients. The EORTC study has several limitations that detract from its applicability to many advanced-stage patients. First, a relatively small fraction of patients were determined to be in CR and thus eligible for randomization on the study. The regimen of MOPP/ABV X 6–8 is toxic and this regimen is no longer used in North America.[33] Second, only few patients with bulky disease were randomized on the EORTC study. Lastly, the claim that added RT caused more secondary malignancies on the combined modality has not been evident in patients with PR receiving even higher doses of RT to multiple areas after MOPP/ABV.

The only randomized study questioning the role of consolidation RT after CR to ABVD X 6 (the most common regimen currently used for advance-stage HL) was performed at Tata Medical Center in India.[7] The study included patients of all stages, but almost half were stages III and IV. A subgroup analysis of the advanced-stage patients showed a statistically significant improvement of both 8-year EFS and 8-year OS with added RT compared with ABVD alone (EFS 78% vs. 59%; $P < 0.03$ and OS 100% vs. 80%; $P < 0.006$).

When advanced-stage HL is treated with the new highly effective and less toxic treatment program of Stanford V, it is imperative to follow the brief chemotherapy program with IFRT to sites originally larger than 5 cm or to a clinically involved spleen.[34] When radiotherapy was fully of partially omitted on this program the results were inferior.[35]

In summary, patients in CR after full-dose chemotherapy program like MOPP/ABV may not need RT consolidation. Yet, patients with bulky disease, incomplete or uncertain CR or patients treated on brief chemotherapy programs will benefit from involved field RT to originally bulky or residual disease.

RT in Savage Programs for Refractory and Relapsed HL

High-dose therapy supported by autologous stem-cell transplantation has become a standard salvage treatment for patients who relapsed or remained refractory to chemotherapy or to combined-modality therapy. Many of the patients who enter these programs have not received prior radiotherapy or relapsed at sites outside the original radiation field. These patients could benefit from integrating radiotherapy into the salvage regimen.

Poen et al[36] from Stanford analyzed the efficacy and toxicity of adding cytoreductive (pretransplant; n = 18) or consolidative

(posttransplant; n = 6) RT to 24 of 100 patients receiving high-dose therapy. This study showed that most (69%) relapses after autologous stem cell transplantation occurred in sites known to be involved immediately before transplantation. When these sites were irradiated before transplantation, no in-field failures occurred. Although only a trend in favor of IF-RT could be shown for the entire group of transplanted patients, for patients with stages I–III freedom from relapse was significantly improved. Limiting the analysis to patients who received no prior RT also resulted in a significant advantage to IF-RT. Fatal toxicity in this series was not influenced significantly by IF-RT.

At Memorial Sloan-Kettering Cancer Center, we developed a program that integrated RT into the high-dose regimen for salvage of HD. We schedule accelerated hyperfractionated irradiation (b.i.d. fractions of 1.8 Gy each) to start after the completion of reinduction chemotherapy and stem-cell collection and before the high-dose chemotherapy and stem-cell transplantation. Patients who have not been previously irradiated received involved field RT (18 Gy in 5 days) to sites of initially bulky (>5 cm) disease and/or residual clinical abnormalities followed by TLI of 18 Gy (1.8 Gy per fraction, b.i.d.) within an additional 5 days. Patients who had prior RT received only involved-field RT (when feasible) to a maximal dose of 36 Gy. This treatment strategy has been in place since 1985 with over 350 patients treated thus far. The first generation program demonstrated the feasibility and efficacy of the high-dose combined-modality regimen resulting in an EFS of 47% for the patients receiving TLI followed by cyclophosphamide-etoposide chemotherapy.[37] The recent report of the second generation two-step high-dose chemoradiotherapy program indicated that after a median follow-up of 34 months the intent-to-treat EFS and OS were 58% and 88%, respectively. For patients who underwent transplantation, the EFS was 68%.[38] Treatment-related mortality was 3% with no treatment-related mortality over the last 8 years. The results of this treatment program in refractory patients were similar to those of relapsed patients.[39] Both groups showed favorable EFS and OS compared with most recently reported series. Recent report on quality of life and treatment-related complications of long-tem survivors of the Memorial Sloan-Kettering Cancer Center program disclosed only a small number of late complications and is highly encouraging.[40]

SUMMARY

Treatment results of favorable early-stage HL (FFTF over 90%) with CMT that includes short-course ABVD and reduced-dose IFRT set a high standard to challenge. At the same time, the trials that attempted to omit radiotherapy in favorable patients who obtained a CR with chemotherapy had thus far inferior outcome for chemotherapy alone. Thus, chemotherapy alone should be given only in the context of a clinical research trial or to highly selected individuals with contraindications to combined modality. Functional imaging may allow the identification of CR patients in whom treatment could possibly be further reduced, but is still experimental. The data available thus far do not support the omission of RT even in PET-negative patients.[41]

REFERENCES

1. Kaplan HS. Clinical evaluation and radiotherapeutic management of Hodgkin's disease and the malignant lymphomas. *N Engl J Med.* 1968;278: 892–899.
2. Boice JD Jr. Second cancer after Hodgkin's disease—the price of success? *J Natl Cancer Inst.* 1993;85:4–5.
3. Longo DL. Hodgkin's disease: the sword of Damocles resheathed. *Blood.* 2004;104:3418.
4. Yahalom J. "Don't throw out the baby with the bathwater"—on optimizing cure and reducing toxicity in Hodgkin's lymphoma. *J Clin Oncol*. 2006;24: 544–548.
5. DeVita VT Jr. Hodgkin's disease—clinical trials and travails. *N Engl J Med.* 2003;348:2375–2376.
6. Noordijk E, Thomas J, Ferme 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* 2005; 21(suppl 1):Abstract 6506.
7. 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.* 2004;22:62–68.
8. 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) versus ABVD alone for stages I, II, and IIIA nonbulky Hodgkin's disease. *Blood.* 2004;104:3483–3489.
9. 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.* 2005;23:4634–4642.
10. 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.* 2002;20:3765–3771.
11. Specht L, Gray RG, Clarke MJ, et al. Influence of more extensive radiotherapy and adjuvant chemotherapy on long-term outcome of early-stage Hodgkin's disease: a meta-analysis of 23 randomized trials involving 3,888 patients. International Hodgkin's Disease Collaborative Group. *J Clin Oncol.* 1998;16:830–843.
12. Rehan F, Brillant C, Schiltz H, et al. Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin's lymphoma [abstract]. *Blood.* 2007;110:2320.
13. Kaplan H. The radical radiotherapy of Hodgkin's disease. *Radiology.* 1962; 78:553–561.
14. Yahalom J. Changing role and decreasing size: current trends in radiotherapy for Hodgkin's disease. *Curr Oncol Rep.* 2002;4:415–423.
15. Yahalom J. Favorable early-stage Hodgkin's lymphoma. *J Natl Compr Canc Netw.* 2006;4:233–240.
16. Goodman KA, Toner S, Hunt M, et al. Intensity modulated radiation therapy in the treatment of lymphoma involving the mediastinum. *Int J Radiat Oncol Biol Phys.* 2005;62:198–206.
17. Girinsky T, Pichenot C, Beaudre A, et al. Is intensity-modulated radiotherapy better than conventional radiation treatment and three-dimensional conformal radiotherapy for mediastinal masses in patients with Hodgkin's disease, and is there a role for beam orientation optimization and dose constraints assigned to virtual volumes? *Int J Radiat Oncol Biol Phys*. 2006;64:218–226.
18. Travis LB, Gospodarowicz M, Curtis RE, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. *J Natl Cancer Inst.* 2002;94:182–192.
19. Travis LB, Hill D, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin's disease. *JAMA.* 2003; 290:465–475.
20. Koontz B, Kirkpatrick J, Clough R, et al. Combined modality therapy versus radiotherapy alone for treatment of early stage Hodgkin's disease: cure versus complications. *J Clin Oncol.* 2006;24:605–611.
21. Salloum E, Doria R, Schubert W, et al. Second solid tumors in patients with Hodgkin's disease cured after radiation or chemotherapy plus adjuvant low-dose radiation. *J Clin Oncol.* 1996;14:2435–2443.
22. 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.* 2004;22:2835–2841.
23. 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.* 2006;79:270–277.
24. Campbell BA, Voss N, Pickles T, et al. Involved-nodal radiation therapy as a component of combination therapy for limited-stage Hodgkin's lymphoma: a question of field size. *J Clin Oncol.* 2008;26:5170–5174.
25. Hoppe RT, Advani RH, Ambinder RF, et al. Hodgkin's disease/lymphoma. *J Natl Compr Canc Netw.* 2008;6:594–622.
26. Schlembach PJ, Wilder RB, Jones D, et al. Radiotherapy alone for lymphocyte-predominant Hodgkin's disease. *Cancer J.* 2002;8:377–383.
27. Prosnitz LR, Wu JJ, Yahalom J. The case for adjuvant radiation therapy in advanced Hodgkin's disease. *Cancer Invest.* 1996;14:361–370.
28. Yahalom J, Ryu J, Straus DJ, et al. Impact of adjuvant radiation on the patterns and rate of relapse in advanced-stage Hodgkin's disease treated with alternating chemotherapy combinations. *J Clin Oncol.* 1991;9:2193–2201.
29. Brizel DM, Winer EP, Prosnitz LR, et al. Improved survival in advanced Hodgkin's disease with the use of combined modality therapy [see comments]. *Int J Radiat Oncol Biol Phys.* 1990;19:535–542.
30. Fabian C, Mansfield C, Dahlberg S, et al. Low-dose involved field radiation

after chemotherapy in advanced Hodgkin's disease. *Ann Intern Med.* 1994; 120:903–912.
31. Loeffler M, Brosteanu O, Hasenclever D, et al. Meta-analysis of chemotherapy versus combined modality treatment trials in Hodgkin's disease. Inter national Database on Hodgkin's Disease Overview Study Group [see comments]. *J Clin Oncol.* 1998;16:818–829.
32. Aleman BM, Raemaekers JM, Tirelli U, et al. Involved-field radiotherapy for advanced Hodgkin's lymphoma. *N Engl J Med.* 2003;348:2396–2406.
33. Duggan DB, Petroni GR, Johnson JL, et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. *J Clin Oncol.* 2003;21:607–614.
34. Horning SJ, Hoppe RT, Breslin S, et al. Stanford V and radiotherapy for locally extensive and advanced Hodgkin's disease: mature results of a prospective clinical trial. *J Clin Oncol.* 2002;20:630–637.
35. Chisesi T, Federico M, Levis A, et al. ABVD versus stanford V versus MEC in unfavourable Hodgkin's lymphoma: results of a randomised trial. *Ann Oncol.* 2002;13(suppl 1):102–106.
36. Poen JC, Hoppe RT, Horning SJ. High-dose therapy and autologous bone marrow transplantation for relapsed/refractory Hodgkin's disease: the impact of involved field radiotherapy on patterns of failure and survival [see comments]. *Int J Radiat Oncol Biol Phys.* 1996;36:3–12.
37. Yahalom J, Gulati SC, Toia M, et al. Accelerated hyperfractionated total-lymphoid irradiation, high-dose chemotherapy, and autologous bone marrow transplantation for refractory and relapsing patients with Hodgkin's disease. *J Clin Oncol.* 1993;11:1062–1070.
38. Moskowitz CH, Nimer SD, Zelenetz AD, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin's disease: analysis by intent to treat and development of a prognostic model. *Blood.* 2001;97:616–623.
39. Moskowitz CH, Kewalramani T, Nimer SD, et al. Effectiveness of high dose chemoradiotherapy and autologous stem cell transplantation for patients with biopsy-proven primary refractory Hodgkin's disease. *Br J Haematol.* 2004; 124:645–652.
40. Goodman KA, Riedel E, Serrano V, et al. Long-term effects of high-dose chemotherapy and radiation for relapsed and refractory Hodgkin's lymphoma. *J Clin Oncol.* 2008;26:5240–5247.
41. Yahalom J. Omitting radiotherapy after attaining FDG PET-negative status following chemotherapy alone for Hodgkin's lymphoma: a randomized study caveat. *Leuk Lymphoma.* 2007;48:1667–1669.

