Journal of BUON **15:** 226-234, 2010

REVIEW ARTICLE

Radiation therapy in Hodgkin's disease - decades of steady progress

L. Gocheva

University Hospital "Queen Giovanna", Institute for Specialization and Qualification of Medical Doctors, Sofia, Bulgaria

Summary

The treatment of lymphoproliferative diseases has changed dramatically during the last decades. The improved therapeutic results for this disease group are included among the most important achievements of modern oncohaematology. They are due to better disease staging, use of new markers for risk assessment, patient stratification in separate risk groups, implementation of highly effective chemotherapy (CHT), progress of targeted therapies using monoclonal antibodies, proteasome inhibitors, modern radiation therapy (RT) and supportive care. The achieved progress, especially in the treatment of Hodgkin's disease (HD), is an example of the fundamental dependence of clinical practice on the scientific achievements, mainly in the field of diagnostics and in the two pure anticancer therapeutic modalities: chemo- and radiotherapy.

The aim of this article was to discuss the basic variants of RT in the multimodal treatment of HD and the clinical experience accumulated during the last decades.

The experience gained in the area of involved field RT (IFRT) and extended field RT (EFRT), both alone or as a part of the combined-therapy protocols, is considered in detail. The role of RT is also discussed as a part of the dose-escalated CHT combined programmes for patients recurring, progressing or partially responding to treatment, carried out mainly as IFRT, total lymphoid irradiation (TLI) or total body irradiation (TBI).

Regardless of the already attained achievements of the combined treatment at the present stage of development of oncological knowledge, there is still no consensus with respect to the optimal therapy of HD in children and in adult patients. New trials addressing issues of the best modality, best RT technique, optimal dose of RT, optimal number of cycles and timing of CHT are still needed. The contemporary challenge is to optimize treatment so that it can be accomplished with the least toxicity, lowest cost, and greatest efficiency possible.

Key words: extended field radiotherapy, Hodgkin's disease, involved field radiotherapy, radiotherapy

Introduction

The treatment of lymphoproliferative diseases has been dramatically changed during the last decades. The improved therapeutic results for this disease group are included among the most important achievements of modern oncohaematology. They are due to better disease staging, use of new markers for risk assessment, stratifying patients in separate risk groups, implementing highly effective CHT, progress of the targeted therapies using monoclonal antibodies, proteasome inhibitors, modern RT and supportive care. The achieved progress, especially in the treatment of HD, is an example of the fundamental dependence of clinical practice on the scientific achievements, mainly in the field of diagnostics and in the two pure anticancer therapeutic modalities: chemo- and radiotherapy.

It is well known that in the first years of the 20th century till 1960, parallel with the advance in the classification of HD, a considerable progress was observed in the field of applied RT. Soon after the discovery of X-rays, Pusey (1902) [1] and Senn (1903) [2] reported the achieved dramatic curative effect after fractionated irradiation of large lymph node formations. The pioneered findings of Peters (1950) [3], Kaplan (1962-66) [4] and others during the 1950s of the last century

Correspondence to: Lilia Gocheva, MD. Dimitar Nestorov 120 A, app. 22, Sofia 1612, Bulgaria. Tel: +359 2 9432376, Fax: +359 2 9712600, E-mail: lgocheva2001@yahoo.co.uk

Received 17-06-2009; Accepted 16-07-2009

proved categorically the possibilities of EFRT in advanced lymphoproliferative diseases. However, parallel to the achieved success, the necessity has emerged for reducing the significant late sequelae. Not only the observed late effects in successfully RT-treated and long-survived children with HD, but also the technological progress and diagnostic possibilities led to additional modifications in RT. The restricted radiation fields, so called IFRT, found gradually broader application, which ensured more effective protection of normal tissues.

At the present stage of RT development, the extremely precise dosimetry, the computer tomography simulation, the high-energy radiation generated by linear accelerators, as well as the combination of RT with CHT in well-planned multimodal treatment, confirm its therapeutic role.

The aim of this article was to discuss the basic variants of RT application in the multimodal treatment of HD and the clinical experience accumulated during the last decades.

Radiation therapy - a basic part of treatment programmes in Hodgkin's disease

RT represents the basic part of the therapeutic programmes for HD in children and adults. The plan for the primary treatment of HD in adult patients is based on clinical stage (CS) of the disease, on the existence of B symptoms and on the size of the largest lymph node formation (Clinical Practice Guidelines in Oncology - v. 2. 2005) [5]. In children the choice of the primary therapeutic approach is determined by the higher risk of developing side effects and consequences in this age group. Applying RT in children in the volumes and doses typical for adult patients is related with disturbances in the development and growth of muscles and bones, as well as with RT-induced reactions in other organs and tissues [6]. Obviously a number of successful therapeutic approaches in children with HD have to be discussed both with respect to their effectiveness and the anticipated late morbidity.

Optimal irradiation technique requires the use of megavoltage photon beams, large fields contoured to the patient's anatomy and tumor configuration, a tumoricidal dose, multifield fractionated treatment, pretreatment simulation, and portal film verification during therapy [7]. Careful attention must be paid to every detail [8].

During the last decades the oncoradiology community has accumulated considerable experience in the field of RT, carried out in the form of IFRT or EFRT, either alone or as a part of combined-therapy protocols.

Radiation therapy alone

Involved field radiation therapy alone

Patients with favorable prognostic factors in HD may be subjected to IFRT, in which only the lymphatic chains involved are irradiated. Involved fields are simply portions of the classical radiation treatment fields. Most often this is the case in young, less than 30 year old, patients in CS IA, with involved high cervical lymph nodes, and lymphocyte predominance histology. In contrast to the results in the classical forms of HD, excellent therapeutic results are achieved in this variant both with IFRT of the involved areas and with EFRT [9-11]. For example, a patient with favorable CS IA may be subjected to unilateral irradiation of the ipsilateral cervical and preauricular lymphatic chains or to "mini mantle" technique, including bilateral irradiation of the cervical, supraclavicular, axillary plus preaurical lymphatic chains.

This group comprises also young women, who have the above mentioned favorable prognostic factors but with nodular sclerosis histology. In these patient groups IFRT achieves more than 90% 5-year freedom-from-progression (FFP) and overall survival (OS) rate [12].

When lymphocyte predominant disease is confined to epitrochlear or inguinal lymph nodes, the risk of disease elsewhere is very small, and the prognosis after IFRT only is also excellent [13]. The usual dose is 30-36 Gy.

The prognosis for patients in CS I and II, but with bulky mediastinal involvement, is significantly more different. The relapse-free survival (RFS) rate in this group after IFRT alone is 53% and in patients without or with small mediastinal nodal involvement is 86%. The survival rate does not differ significantly even after CHT administration (88 vs. 93%). The risk of recurrence is very high and the results from the application of independent therapeutic approach, no matter whether RT or CHT, are unsatisfactory [14-17]. It is inadmissible to assume a 50% risk of recurrence and hence the combined approach becomes indispensable without any alternative [18-22].

With such an approach, 36-44 Gy fractionated with daily dose of 1.5-1.8 Gy are accepted from the National Cancer Center Network (NCCN) guidelines as a tumoricidal dose [14]. The authors of the German Hodgkin's Study Group (GHSG) accept a lower total dose, of the order of 20-30 Gy, as suitable in HD [15].

Extended field radiation therapy alone

Before 1990 the irradiation of large volumes of the lymphatic chains, so called extended field RT, was a standard therapeutic approach in patients with early CS of HD. A complete response was recorded in more than

90% of the patients but unfortunately in 30% of them recurrence was observed. The majority of them might be subjected to CHT but there was a higher risk of cardiovascular problems and second neoplasm development.

A specific form of HD requiring special planning is the nonbulky form of CS IA, situated in the anterior mediastinum, with histology of nodular sclerosis. This form of HD is characterized by primary independent involvement of the mediastinum and when absence of disease dissemination is proved by detailed examinations, it is subjected to RT alone. Most authors recommend the mantle technique [23-25].

The clinical experience accumulated proves that patients with CS I and IIA, in whom unfavorable prognostic factors are absent (e.g. no massive mediastinal involvement) may be successfully cured by EFRT [26].

The big German study GHSG HD4 has subjected to EFRT patients with early CS of HD by randomizing them in two groups: the first one was subjected to 40 Gy EFRT and the second one to 30 Gy EFRT with boost of 10 Gy in involved volumes. The established 7-year RFS rate was 78% for the first group and 83% for the group with 30 Gy. The overall survival rate for both groups was 91 and 96%, respectively. These results, although not reaching statistical significance, support the low-dose EFRT [15].

The European EORTC H5F trial randomized patients with CS I and II with favorable prognostic factors, in two groups according to the performed EFRT (mantle technique and irradiation of the paraaortic area, so called subtotal lymphoid irradiation [SLI], vs. mantle technique alone); no difference was observed in OS and failure-free-survival (FFS) rate within a 15-year follow-up [27].

The large European study EORTC H6F is especially interesting in this respect. The inclusion criteria were one to two involved areas, lack of bulky mediastinal involvement, non-symptomatic disease with erythrocyte sedimentation rate (ESR) < 50 mm/h or with presence of B symptoms but with ESR <30 mm/h. The authors randomized CS I and II patients with favorable prognostic factors in two groups: with and without staging laparotomy [28]. It is known that laparotomy and splenectomy has been accepted as a routine staging procedure till 1991. The clinically staged patients were subjected to SLI, including RT of mantle technique, with irradiation of the paraaortic area and the spleen. Patients staged by laparotomy received a treatment corresponding to the pathological stage of the disease. No difference was established in the achieved OS and FFS rate for both groups. Based on this large European trial staging laparotomy was gradually removed from clinical practice.

In Stanford, 78 patients with favorable CS I and II have been randomly assigned to SLI or vinblastine, methotrexate, and bleomycin (VBM) CHT and regional RT. With a median follow-up period of 4 years, the rate of FFP was 92% (95% confidence interval/CI 88-96), for patients treated with SLI and 87% (95% CI 91-93) for patients treated with VBM and regional RT. Six of 7 patients who relapsed are alive and in remission following successful second-line therapy [30].

Another European trial (EORTC H7F) has subjected to a similar therapeutic approach only 5% of patients who had the most favorable prognostic factors, such as women younger than 40, CS IA, without massive lymph node involvement, with favorable histology and ESR < 50 mm/h. The 3-year overall survival rate in those 35 patients was 100%, but the FFS rate was only 82%, which is considered as rather unacceptable therapeutic result [31].

Patients with bulky mediastinal HD (mediastinal mass greater than one-third of the maximum intrathoracic diameter) are difficult to categorize by the Ann Arbor staging system and have a poor outcome when treated with single-modality therapy [14]. Several reports show that patients with bulky mediastinal disease are at greater risk for relapse after treatment with irradiation alone than after treatment with combined-modality therapy [20]. Although there is no difference in overall survival of patients treated initially with either approach, it is appropriate to accept a relapse risk as high as 50%. The general recommendation is that these patients have to be treated with combination of CHT and RT [19,32].

Regardless of the rather diverse opinions and statements concerning the applied RT techniques, during the last years some authors consider that EFRT leads to better OS and DFS compared to IFRT. This finding was validated in a metaanalysis conducted by Specht et al. based on combined data from 1974 patients with early-stage HD from 8 randomized trials [33]. It has been found that more extensive RT significantly reduces the risk of failure at 0-4, 5-9, and 10 or more years. There was a trend towards fewer HD deaths in the more extensive RT arm, although the difference was not statistically significant. Moreover, there was a slightly higher risk of death due to causes other than HD with more extensive RT, although not reaching statistical significance.

Radiation therapy as a part of combined treatment

Extended field radiation therapy as a part of combined treatment

Combined-modality therapy has become the most common form of management for patients with HD [34]. A number of randomized trials compared CHT alone with combined treatment in children with HD and did not establish any superiority of either of the applied

two therapeutic approaches [33-35]. However, there are other clinical trials that showed better therapeutic results after combined treatment, especially in patients with unfavorable prognostic factors and advanced stages of disease [36,37].

Donaldson et al. compared the therapeutic possibilities of combined treatment in children with HD at early stages [38]. In the first group of children, which was from Stanford, after pathological staging, the treatment included a EFRT or EFRT combined with CHT; in the second group the clinically staged patients, who were from St. Bartholomew's, received local irradiation in the form of the so called regional field (RFRT), including, except the involved lymphatic chains, the neighbouring lymph nodes. The achieved 10-year overall survival rate for both groups was 91%, while the RFS rate for the CS I patients in the second centre was a little lower (90 vs. 83%; p=0.18).

Table 1 illustrates similar therapeutic results for EFRT or EFRT combined with CHT, as well as after low dose IFRT and CHT. However, the toxicity varied significantly in the different therapeutic approaches.

The HD7 trial of the GHSG compared 2 cycles of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) combined with SLI vs. SLI alone [39]. Equal therapeutic response was observed in both groups but the RFS rate was 96 vs. 87%, respectively.

The trial of the Southwest Oncology Group (SWOG) compared 3 cycles of doxorubicin and vinblastine plus SLI with SLI alone. The trial was prematurely closed because of the better FFS rate in the first group (94 vs. 81%; $p < 0.001$) [40].

In the EORTC H6U trial the patients were randomized in 2 groups with and without unfavorable prognostic factors [28]. Patients with unfavorable prognosis were clinically staged and subjected to two therapeutic approaches: 3 cycles of ABVD/mantle technique/3 cycles ABVD compared to 3 cycles MOPP (nitrogen mustard, vincristine, procarbazine, prednisone)/mantle technique/3 cycles MOPP. Better therapeutic results were recorded with reduced hematological and gonadal toxicity in the first group.

The Milan Cancer Institute has carried out a randomized study with 114 patients with early stages of HD, comparing 4 cycles of ABVD plus SLI with 4 cycles of ABVD with IFRT [41]. The realized doses varied from 30 to 36 Gy, depending on treatment type - prophylactic or curative. After an average period of 87 months full therapeutic response was recorded in 100% of the first group compared with 97% of the second one. The RFS and OS rate in both groups were 97 vs. 94% and 93 vs. 94%, respectively.

The European trial EORTC H8U randomized patients with unfavorable prognostic factors to 4 cycles MOPP/ABVD plus IFRT (36-40 Gy) or to the same CHT plus SLI (36-40 Gy). The established FFS rate in both groups was 94% [42,43].

Based on the GHSG, EORTC and SWOG investigations the SLI application is no longer recommended (Table 1).

Table 1. Clinical trials comparing EFRT and IFRT alone or as a part of combined treatment in patients with favorable prognostic factors

Study	*Treatment protocol*	*Relapse-free survival (%)*	*p-value*	*Overall survival (%) (years)*	*p-value*
GHSG HD7 (617 patients)	EFRT	75		94 (5)	
	vs.				
	ABVD×2 cycles + EFRT	91	<0.001	94	NS
SWOG 9133 (326 patients)	STLI	81		96 (3)	
	vs.				
	AV×3 cycles +STLI	94	<0.001	98	NS
EORTC/GELA H7F (333 patients)	STLI	81		95 (5)	
	vs.				
	EBVP×6 cycles + IFRT	90	<0.0001	98	NS
EORTC/GELA H8F (543 patients)	STLI	80		80 (4)	
	vs.				
	MOPP/ABV×3 cycles + IFRT	99	<0.0001	99	<0.02

EFRT: extended field radiotherapy, IFRT: involved field radiotherapy, STLI: subtotal lymphoid irradiation, ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine, AV: doxorubicin, vinblastine, EBVP: etoposide, bleomycin, vinblastine, prednisone, MOPP/ABV: nitrogen mustard, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vinblastine

Involved field radiation therapy as a part of combined treatment

In HD patients with long-term survival (exceeding 15 years) after independent and obviously successful RT significant late effects and sequelae may happen. Disturbances in the growth and development of the irradiated skeleton and soft tissues, cardiovascular problems and development of secondary solid tumors are observed in children. This has created the necessity of developing programmes for combined treatment in early HD stages from the beginning of the 1990s of the last century. Such programmes include modified CHT regimens followed by RT which is applied in reduced volumes and doses. The independently administered CHT usually includes 6-10 cycles, while the combined treatment most often includes low-dose IFRT in combination with several CHT cycles. It has been established that the latter approach leads to improved FFS rate in early and advanced stages of HD [35,44-49].

A number of studies started in 1990 aimed at the assessment of the therapeutic results from several CHT cycles and low-dose IFRT in low-risk patients with favorable prognostic factors (local lymph node, absence of B symptoms or bulky mediastinal disease). The majority of treatment protocols included 2-4 CHT cycles, usually with alkylating agents, anthracyclines and bleomycin. Excellent treatment results have been reported [50].

The HD10 study of GHSG was of special interest [51]. It included reduced number of CHT cycles and reduced doses of IFRT in patients with early stages and favorable prognostic factors. Patients were randomized in 4 groups: 4 cycles of ABVD and 30 Gy IFRT; 4 cycles of ABVD and 20 Gy IFRT; 2 courses of ABVD and 30 Gy IFRT; and 2 cycles of ABVD and 20 Gy IFRT. From 1998 till 2000 486 patients were included in the 4 therapeutic approaches. The first interim analysis carried out in 2001 established full therapeutic response in 98% and only in 1% of the patients no effect or disease progression were observed. The final assessment of the long-term therapeutic results of the reduced CHT- and RT are pending.

The satisfactory results from RT in the early stages of HD led to its application in the advanced stages of the disease too. Patients in the advanced III and IV stages of HD are naturally candidates for systemic polychemotherapy and the combined approach, which has led to better therapeutic results [52]. The SWOG 7808 trial also included patients with stage III and IV disease [44]. All patients receive induction CHT with MOP-BAP (nitrogen mustard, vincristine, procarbazine, bleomycin, doxorubicin, prednisone) for 6 months. Complete responders were randomly assigned to receive either no further therapy or 20 Gy IFRT. Of 530 patients included in this trial, 61% achieved complete response. When analysis was limited to patients who actually completed the treatment, the 5-year FFS was 57% for those with no further therapy and 75% for those who received consolidation RT ($p=0.002$). However, these differences did not translate into a survival benefit for any subset of patients.

Loeffler et al. published a detailed meta-analysis of 14 studies, carried out during 1972-1988 on 1740 patients with HD [53]. The results showed improvement of 11% in the 10-year local tumor control for patients subjected to RT and CHT but without recording any improvement in the survival rate. Higher mortality was recorded in the same group due to sequelae from the treatment protocol and not to disease.

Patients with limited (I and II) and advanced (III and IV) stages with unfavorable prognostic factors (i.e. B symptoms, massive lymphadenopathy or extranodal involvement), are considered to be candidates for more aggressive treatment too. Patients in CS I and II with B symptoms represent 15-20% of all patients in these stages. Their management is similar with those having CS III and IV, the only exception being the obligatory application of consolidation RT. Two therapeutic approaches are used, including combination of CHT and low-dose IFRT: the conventional approach and the dose-escalating alternating polychemotherapy schemes. The conventional therapeutic approach is characterized by 6-8 CHT cycles. Current studies [54,55], mainly in adult patients, confirm the success of the second therapeutic approach. Modern protocols include dose-escalated alternating polychemotherapy schemes for a period from 3 to 5 months. Examples of such schemes are MOPP/ABV hybrid (nitrogen mustard, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vinblastine), Stanford V (nitrogen mustard, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisone) or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone).

When applying weekly combination of myelo- with nonmyelosuppressive CHT, suppressing the development of chemoresistance, it is obligatory to include also low-dose IFRT in order to consolidate the therapeutic effect achieved by CHT. For example, in the Stanford V CHT regimen the drugs used (doxorubicin, vinblastine, nitrogen mustard, etoposide, vincristine, bleomycin, prednisone) are administered weekly within 12 weeks, followed by IFRT with 36 Gy to the primary involved areas with size ≥ 5 cm [54]. That study included 142 patients, consolidation RT being applied in 70% of them. With an average follow-up time of 5.7 years the 12-year overall survival rate and 12-year FFS rate were 95% and 89%, respectively. The

therapeutic effect from the combined approach was especially pronounced in patients with nodular sclerosis and massive lymph node involvement. The fertility of women was preserved and no treatment-related mortality was recorded. At present this CHT regimen is being compared with the standard ABVD regimen in a large North American multicenter trial.

The German study on HD used dose-escalation and accelerated combined modality treatment, with BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) plus IFRT in the areas of primary bulky or residual lymphadenopathy [55]. A 3-arm randomized study [55] compared COPP (cyclophosphamide, vincristine, procarbazine, prednisone)/ABVD plus IFRT, BEACOPP plus IFRT and escalated doses of BEACOPP plus IFRT. RT was delivered to 70% of the patients from the 3 arms. The 5th interim analysis [55] on 1180 patients (average follow-up time of 36 months) established 83 vs. 88 vs. 91% 5-year overall survival rate for the 3 arms (all p-values non significant). Higher hematological toxicity was recorded in the last group -3% lethal toxicity, 100% infertility in men, 100% infertility and premature menopause in women aged over 25 years.

The achieved early therapeutic results from the conventional and the close-intensified approaches are similar. A longer period of observation is necessary both for evaluating the effectiveness and the early and late toxicity of the dose-escalation therapeutic approach compared with the conventional one.

The debate over the role of consolidation RT after CHT in the presence of bulky disease continues. The possibilities of the positron emission tomography (PET) for identifying the patients with persisting disease after polychemotherapy will provide the possibility of determining the group of patients who will benefit from consolidation RT. However, the majority of the studies [53-55] impose categorically RT as a part of the combined therapeutic approach.

Radiation therapy in patients with Hodgkin's disease with recurrence, progressing or partially responding to chemotherapy

The role of RT as part of the high-dose combined protocols for patients with recurrence, or progressing or partially responding to treatment is of special interest. It is carried out mainly as IFRT, TLI or TBI [56-64].

The therapeutic results for the above mentioned patient groups, in whom RT has been applied, are significantly better compared with patients without RT [65-67]. For example, the achieved 3-year freedom from second treatment failure rate in patients with recurrent HD with CS I-III is 84% for those with IFRT compared to 55% without RT. The freedom from second treatment failure of patients in the same stages, in whom no primary RT has been applied, with and without consolidation RT is 82 vs. 43%, respectively (p=0.07).

Interesting results were also reported by the Memorial Sloan-Kettering Cancer Center-USA [68]. After standard induction CHT prior to bone marrow transplantation (BMT), the patients were irradiated with accelerated hyperfractionation. When in CS I they received 15 Gy IFRT (in fractions of 1.5 Gy, 2 times per day), which were followed by TLI with a dose of 20.04 Gy (in fractions of 1.67 Gy, 3 times per day). After this high-dose combined therapy a 50% 6-year freedom from second treatment failure rate was achieved.

Fractionated TBI is also a part of transplantation protocols [69]. Its place in the combined treatment is not categorically established, having in mind the fact that recurrent HD is first of all locoregional and not systemic problem.

Discussion

RT has been proved a successful therapeutic modality in the treatment of HD during the last 50 years. It is the most effective single therapeutic agent. CHT has shown similar effectiveness and the choice between them is made rather on the basis of the expected toxicity and not so much on their effectiveness. Taking into consideration the increased toxicity of the higher cumulative doses of CHT drug combinations, especially of the alkylating agents, as well as the reduced radiation-induced toxicity, preference is given to the combined therapeutic approach. The optimal sequence of CHT and RT in the combined treatment protocols is still not known. Yet, CHT is most often included at the first stage. This provides the possibility of assessing the therapeutic response achieved by the cytotoxic drugs, reducing the lymph node formations and hence applying reduced radiation fields. In rare cases RT might precede CHT in cases with respiratory tract obstructions.

Irradiation with doses of the order of 15-25 Gy in children and 20-36 Gy in adult patients is assumed to be a basic component of the combined management in both primary and alternating treatment in refractory to CHT or recurrent disease. The modern combined modality approach in children with HD achieves 85-100% RFS rate in the early stages and 70-90% in the advanced stages. The combined approach has also similar therapeutic success in adult patients.

However, at the present status of oncological know-

ledge there is still no consensus with respect to the optimal therapy of HD in children and in adult patients. New trials are still necessary, addressing issues of the best modality, best RT technique, optimal dose of RT, optimal number of cycles and timing of CHT. The contemporary challenge is to optimize treatment so that it is accomplished with the least toxicity, lowest cost, and greatest efficiency possible.

References

1. Pusey WA. Cases of sarcoma and of Hodgkin's disease treated by exposure to X-rays: A preliminary report. JAMA 1902; 38: 166-169.
2. Senn N. Therapeutical value of roentgen ray in the treatment of pseudoleukemia. New York Med J 1903; 77: 665-668.
3. Peters MV. A study in survival of Hodgkin's disease treated radiologically. Am J Roentgenol 1950; 63: 299-311.
4. Kaplan HS. The radical radiotherapy of regionally localized Hodgkin's disease. Radiology 1962; 78: 553-561.
5. Clinical Practice Guidelines in Oncology - v. 2. 2005, www.esmo.org/referenceGuidelines/html/MCR9.htm
6. Donaldson S, Kaplan H. Complications of treatment of Hodgkin's disease in children. Cancer Ther Rep 1982; 66: 977-989.
7. Hoppe R. Hodgkin's lymphoma. In: Halperin E, Carlos P, Brady L (Eds): Principles and Practice of Radiation Oncology: Hodgkin's Disease. Philadelphia: Lippincott Williams & Wilkins, 2004, pp 1721-1739.
8. Mendenhall N, Hoppe R, Prosnitz L et al. Principles of radiation therapy in Hodgkin's disease. In: Mauch P, Armitage J, Diehl V et al (Eds): Hodgkin's disease. Philadelphia: Lippincott Williams &Wilkins, 1999, pp 337-376.
9. Russel K, Hoppe R, Colby T et al. Lymphocyte predominant Hodgkin's disease: clinical presentation and results of treatment. Radiother Oncol 1984; 1: 197-205.
10. Surciffe S, Gospodarowich M, Bergsagel D et al. Prognostic groups for management of localized Hodgkin's disease. J Clin Oncol 1985; 3: 393-401.
11. Donaldson S, Link M. Combined modality treatment with low-dose radiation and MOPP chemotherapy for children with Hodgkin's disease. J Clin Oncol 1987; 5: 742-749.
12. Tubiana M, Henry-Amar M, Carde P et al. Toward comprehensive management tailored to prognostic factors of patients with clinical stage I and II in Hodgkin's disease. The EORTC Lymphoma Group controlled clinical trials: 1964-1987. Blood 1989; 73: 47-56.
13. Bodis S, Henry-Amar M, Bos J et al. Late relapse in early-stage Hodgkin's disease patients enrolled on European Organization for Research and Treatment of Cancer protocols. J Clin Oncol 1993; 11: 225-232.
14. Hoppe R, Cosset J, Santoro A et al. Treatment of unfavorable prognosis stage I-II Hodgkin's disease. In: Mauch P, Armitage J, Diehl V et al (Eds): Hodgkin's disease. Philadelphia: Lippincott Williams Willkins, 1999, pp 459-482.
15. Duhmke E, Franklin J, Freundschuh M et al. Low-dose radiation is sufficient for the noninvolved extended-field treatment in favorable early-stage Hodgkin's disease: long-term results of randomized trial of radiotherapy alone. J Clin Oncol 2001; 19: 2905-2914.
16. Longo D, Russo A, Duffey P et al. Treatment of advanced-stage massive mediastinal Hodgkin's disease: the case for combined modality treatment. J Clin Oncol 1991; 9: 227-235.
17. Bonadonna G, Valagussa P, Santoro A. Prognosis of bulky Hodgkin's disease treated with chemotherapy alone or combined with radiotherapy. Cancer Surv 1985; 4: 439-458.
18. Mauch P, Goodman R, Hellman S. The significance of mediastinal involvement in early stage Hodgkin's disease. Cancer 1978; 42: 1039-1045.
19. Behar R, Horning S, Hoppe R. Hodgkin's disease with bulky mediastinal involvement: effective management with combined modality therapy. Int J Radiat Oncol Biol Phys 1993; 25: 771-776.
20. Hoppe R, Coleman C, Cox R et al. The management of stage I-II Hodgkin's disease with irradiation alone or combined modality therapy: the Stanford experience. Blood 1982; 59: 455-465.
21. Hoppe R. The management of bulky mediastinal Hodgkin's disease. Hematol Oncol Clin North Am 1989; 3: 265-276.
22. Leopold K, Canellos G, Rosenthal D et al. Stage IA-IIB Hodgkin's disease: staging and treatment of patients with large mediastinal adenopathy. J Clin Oncol 1989; 7: 1059-1065.
23. Mauch P, Connors J, Pavlovsky S et al. Treatment of favourable prognosis stage I-II Hodgkin's disease. In: Mauch P, Armitage J, Diehl V et al. (Eds): Hodgkin's disease. Philadelphia: Lippincott Williams &Wilkins, 1999, pp 435-458.
24. Diehl V, Franclin J, Sextro M et al. Clinical presentation and treatment of lymphocyte predominance Hodgkin's disease. In: Mauch P, Armitage J, Diehl V et al (Eds): Hodgkin's disease. Philadelphia: Lippincott Williams &Wilkins, 1999, pp 563-584.
25. Wirth A, Chao M, Corry J et al. Mantle irradiation alone for clinical stage I-II Hodgkin's disease: long-term follow-up and analysis of prognostic factors in 261 patients. J Clin Oncol 1999; 17: 230-240.
26. Maity A, Goldwein J, Lange B et al. Mediastinal masses in children with Hodgkin's disease. An analysis of the Children's Hospital of Philadelphia and the Hospital of the University of Pennsylvania experience. Cancer 1992; 69: 2755-2760.
27. Carde P, Burgers JM, Henry-Amar M et al. Clinical stages I and II Hodgkin's disease: A specifically tailored therapy according to prognostic factors. J Clin Oncol 1988; 6: 239-252.
28. Carde P, Hagenbeek A, Hayat M et al. Clinical staging versus laparotomy and combined modality with MOPP versus ABVD in early-stage Hodgkin's disease: the H6 twin randomized trials from the European Organization for Research and Treatment of Cancer Lymphoma Cooperative Group. J Clin Oncol 1993; 11: 2258-2272.
29. Carde P, Noordijk E, Hagenbeek A et al. Superiority of EBVP chemotherapy in combination with involved field irradiation over subtotal nodal irradiation in favorable clinical stage I-II Hodgkin's disease: the EORTC-GPMC H7F-randomized trial. Proc Am Soc Clin Oncol 1997; 16: 13 (abstr).
30. Horning S, Hoppe R, Mason J et al. Stanford-Kaiser Permanent G1 study for clinical stage I to IIA Hodgkin's disease: subtotal lymphoid irradiation versus vinblastine, methotrexate, and bleomycin chemotherapy and regional irradiation. J Clin Oncol 1997; 15: 1736-1744.
31. Noordijk E, Corde P, Mandard A et al. Preliminary results of the EORTC-GPMC controlled clinical trial H7 in early stage Hodgkin's disease: EORTC Lymphoma Cooperative Group. Groupe Pierre et Marie-Curie. Ann Oncol 1994; 5: 107-112.
32. Longo D, Russo A, Duffey P et al. Treatment of advanced-stage

massive mediastinal Hodgkin's disease: the case for combined modality treatment. J Clin Oncol 1991; 9: 227-235.
33. Specht L, Gray R, Clarke R 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.
34. Connors J, Jahalom J, Noordijk E et al. Principles of combined-modality therapy in Hodgkin's disease. In: Mauch P, Armitage J, Diehl V et al (Eds): Hodgkin's disease. Philadelphia: Lippincott Williams &Wilkins, 1999, pp 395-408.
35. Hutchinson R, Fryer C, Davis P et al. MOPP or radiation in addition to ABVD in the treatment of pathologically staged advanced Hodgkin's disease in children: results of the Children's Cancer Group Phase III trial. J Clin Oncol 1998; 16: 897-906.
36. Yahalom J, Ryi J, Straus D 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.
37. Weiner M, Lewenthal B, Breht M et al. Randomized study of intensive MOPP-ABVD with or without low-dose total-nodal radiation therapy in the treatment of stages IIB, IIIA2, IIIB, and IV Hodgkin's disease in pediatric patients: a Pediatric Oncology Group study. J Clin Oncol 1997; 15: 2769-2779.
38. Donaldson S, Whitaker S, Plowman P et al. Stage I-II pediatric Hodgkin's disease: long-term follow-up demonstrates equivalent survival rates following different management schemes. J Clin Oncol 1990; 8: 1128-1137.
39. Sieber M, Franklin J, Tesch H et al. Two cycles of ABVD plus extended field radiotherapy is superior to radiotherapy alone in early stage Hodgkin's disease: Results of the German Hodgkin's Lymphoma Study Group (GHSG) Trial HD7. Blood 2002; 100: 93a, 341 (abstr).
40. Press O, LeBlank M, Lichter A et al. Phase III randomized intergroup trial of subtotal lymphoid irradiation for stage IA to IIA Hodgkin's disease. J Clin Oncol 2001; 19: 4238-4244.
41. Bonfante V, Viviani S, Devizzi L. Ten-year experience with ABVD plus radiotherapy: subtotal nodal (CTNI) vs. involved field (IFRT) irradiation in early-stage HD. Proc Am Soc Clin Oncol 2001; 20: 1120a (abstr).
42. Hagenbeek A, Eghbali H, Ferme C et al. Three cycles of MOPP/ABV hybrid and involved - field irradiation is more effective than subtotal nodal irradiation in favorable supradiaphragmatic clinical stages I-II Hodgkin's disease; preliminary results of the EORTC-Gela H9-F randomized trial in 543 patients. Blood 2000; 96: A 575 (abstr).
43. Carde P, Noordijk E, Hagenbeek A et al. Superiority of EBVP chemotherapy in combination with involved field irradiation over subtotal nodal irradiation in favorable clinical stage I-II Hodgkin's disease: the EORTC-GPMC H7F-randomized trial. Proc Am Soc Clin Oncol 1997; 16: 13 (abstr).
44. Fabian C, Mansfield C, Dahlberg S et al. Low-dose involved field radiation after chemotherapy in advanced Hodgkin's disease: a Southwest Oncology Group randomized study. Ann Intern Med 1994; 120: 903-912.
45. Hudson M, Greenwald C, Thompson C. Efficacy and toxicity of multiagent chemotherapy and low-dose involved field radiotherapy in children and adolescents with Hodgkin's disease. J Clin Oncol 1993; 11: 100-108.
46. Hunger S, Link M, Donaldson S. ABVD/MOPP and low-dose involved-field radiotherapy in pediatric Hodgkin's disease: the Stanford experience. J Clin Oncol 1994; 12: 2160-2166.
47. Nachman J, 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.
48. Schellong E. The balance between cure and late effects in childhood Hodgkin's lymphoma: the experience of the German-Austrian Study-Group since 1978. German-Austrian Pediatric Hodgkin's Disease Study-Group. Ann Oncol 1996; 7: 67-72.
49. Schellong E, Potter R, Bramswig J et al. High cure rates and reduced long-term toxicity in pediatric Hodgkin's disease: the German-Austrian Multicenter Trial DAL-HD-90. Clin Oncol 1999; 17: 3736-3744.
50. Landman-Parver J, Pacquement H, Leblanc T et al. Localized childhood Hodgkin's disease response adapted chemotherapy with etoposide, bleomycin, vinblastine and prednisone before low-dose radiation therapy - results of the French Society of Pediatric Oncology Study MDH 90. J Clin Oncol 2000; 18: 1500-1507.
51. Diehl V, Brillant C, Engert A et al. Investigating reduction of combined modality treatment intensity in early stage Hodgkin's lymphoma. Interim analysis of a randomized trial of the German Hodgkin Study Group (GHSG). J Clin Oncol 2005; 23: 6506 (abstr).
52. Salloum E, Doria R, Farber L et al. Combined modality therapy in previously untreated patients with advanced Hodgkin's disease: a 24-year follow up study. Cancer J Sci Amer 1995; 2: 267-273.
53. Loeffler M, Brosteann O, Hasenclever D et al. Meta-analysis of chemotherapy versus combined modality treatment trials in Hodgkin's disease. International Database in Hodgkin's disease overview Study Group. J Clin Oncol 1998; 16: 818-829.
54. Horning S, Hoppe R, Advani R et al. Efficacy and late effects of Stanford V chemotherapy and radiotherapy in untreated Hodgkin's disease: mature data in early and advanced stage patients. Blood 2004; 104: 308 (abstr).
55. Diehl V, Franklin J, Pfreundschuh M et al. Standard and increased dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. N Engl J Med 2003; 348: 286-2395.
56. Canellos G, Horwich A. Management of recurrent Hodgkin's disease. In: Mauch P, Armitage J, Diehl V et al (Eds): Hodgkin's disease. Philadelphia: Lippincott Williams &Wilkins, 1999, pp 507-520.
57. Roach M, Kapp D, Rosenberg S et al. Radiotherapy with curative intent: an option in selected patients relapsing after radiotherapy for early-stage Hodgkin's disease. J Clin Oncol 1990; 8: 623-629.
58. Specht L, Horwich A, Ashley S. Salvage of relapse of patients with Hodgkin's disease in clinical stage I or II who were staged with laparotomy and initially treated with radiotherapy alone: a report from the international database on Hodgkin's disease. Int J Radiat Oncol Biol Phys 1994; 30: 805-811.
59. Perry A, Penicer A, Watts M et al. Peripheral blood stem cell versus autologous bone marrow transplantation for Hodgkin's disease: equivalent survival outcome in a single-centre matched-pair analysis. Br J Haematol 1999; 105: 280-287.
60. Brice P, Bouabdallah R, Moreau P et al. Prognostic factors for survival after high-dose therapy and autologous stem cell transplantation for patients with relapsing Hodgkin's disease: analysis of 280 patients from the French registry. Societe Francaise de Greffe de Moelle. Bone Marrow Transplant 1997; 20: 21-26.

61. Sweetenham J, Taghipour G, Milligan D et al. High-dose therapy and autologous stem cell rescue for patients with Hodgkin's disease in first relapse after chemotherapy: results from the EBMT. Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant 1997; 20: 745-752.
62. Roach M, Kapp D, Rosenberg S et al. Radiotherapy with curative intent: an option in selected patients relapsing after radiotherapy for early-stage Hodgkin's disease. J Clin Oncol 1990; 8: 623-629.
63. Armitage J, Goldstone A, Carella A et al. Role of bone marrow transplantation in Hodgkin's disease. In: Mauch P, Armitage J, Diehl V et al (Eds): Hodgkin's disease. Philadelphia: Lippincott Williams &Wilkins, 1999, pp 521-530.
64. Shamash J, Lee S, Radford J et al. Patterns of relapse and subsequent management following high-dose chemotherapy with autologous haematopoietic support in relapsed or refractory Hodgkin's lymphoma: a two centre study. Ann Oncol 2000; 11: 715-719.
65. Mundt A, Sibley G, Williams S et al. Patterns of failure following high-dose chemotherapy and autologous bone marrow transplantation with involved field radiotherapy for relapsed/refractory Hodgkin's disease. Int J Radiat Oncol Biol Phys 1995; 33: 261-270.
66. Pezner R, Nademanee A, Niland J et al. Involved field radiation therapy for Hodgkin's disease autologous bone marrow transplantation regimens. Radiother Oncol 1995; 34: 23-29.
67. Poen J, Hoppe R, Horning S. 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. Int J Radiat Oncol Biol Phys 1996; 36: 3-12.
68. Yahalom J, Gulati S, Toja M et al. Accelerated hyperfractionated total-body-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.
69. Nademanee A, O'Donnel M, Snyder D et al. High-dose chemotherapy with or without total body irradiation followed by autologous bone marrow and/or peripheral blood stem cell transplantation for patients with relapsed and refractory Hodgkin's disease: results in 85 patients with analysis of prognostic factors. Blood 1995; 85: 1381-1390.