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SUPRADIAPHRAGMATIC EARLY STAGE HODGKIN'S DISEASE: DOES MANTLE RADIATION THERAPY STILL HAVE A ROLE?

Giovanni Frezza, Enza Barbieri, Pier Luigi Zinzani, Lucio Babini, Sante Tura**

*Istituto di Radioterapia "Luigi Galvani" and the *Istituto di Ematologia " L. e A. Seragnoli ", Università di Bologna, Italy*

ABSTRACT

Extended field radiation therapy represents the main therapeutic option in early stage Hodgkin's disease with favorable prognostic features. Its role however has recently been criticized, mainly due to the high incidence of late complications in irradiated tissues. Furthermore, surgical staging, which in the opinion of many is mandatory for proper selection of patients for radiotherapy alone, has a well-known morbidity, and splenectomy has been associated with a high risk of secondary leukemias. Lastly, the failure rate after radiotherapy only is not negligible and second-line treatment is not always successful. A review of our experience and of the recent literature has allowed us to refute these objections. The results of radiotherapy, when properly performed, are highly reliable and have been reproducible in many Institutions. Chemotherapy alone cannot yet be regarded as an alternative to radiotherapy in these patients since data reported on this issue are conflicting. Present knowledge regarding the relationship between clinical features and the risk of occult subdiaphragmatic spread allows patients with localized disease to be selected without surgical staging; the results of radiotherapy in clinically staged patients confirm this statement. Concern for the late effects in irradiated tissues is justified, and future efforts should be directed at reducing the toxicity of this treatment. Associating a short chemotherapy course with low-dose radiotherapy to involved sites could help to achieve this goal.

Key words: Hodgkin's disease, radiotherapy, chemotherapy, staging, late toxicity

Extended field radiation therapy (EF RT) was the first therapeutic modality to show that eradication of early stage Hodgkin's disease was possible,[1] and in recent years it has represented standard treatment in initial disease.[2-6] Identification of truly localized disease was aided by improved staging procedures, in particular bipedal lymphangiography[7] and staging laparotomy.[8] A better understanding of the natural history of Hodgkin's disease[9] has helped to improve treatment techniques and patient selection.

Combination chemotherapy, first applied as a treatment for advanced disease,[10] is also effective alone for early stage disease,[11] or combined with radiotherapy in poor prognosis patients.[12,13]

All these treatment modalities can achieve equivalent overall survival in selected patients.[14] Recent efforts have thus been directed toward decreasing treatment toxicity and more sharply defining groups with different prognosis in order to refine and tailor therapy.[15] There is general agreement that patients with unfavorable prognostic features, such as bulky mediastinal disease, high ESR, B symptoms, four or more sites of involvement, can achieve better results with chemotherapy followed by involved field irradiation. In most Institutions radiotherapy alone (mantle + para-aortic ± splenic irradiation) is still the treatment of choice in early stage favorable prognosis patients.[16-18]

Three main objections have been raised lately

Correspondence: dr. G. Frezza, Istituto di Radioterapia "L. Galvani", Policlinico S. Orsola, via Massarenti 9, 40138 Bologna, Italy. Tel. international +39.51.6363564; Fax. international +39.51.6364930.
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to the role of RT alone in early stage HD patients with favorable prognostic characteristics:

1) even in patients with favorable prognostic features (no systemic symptoms, small disease burden) the incidence of failures after EF RT (± spleen irradiation according to staging modalities) is no less than 20%,[19,20] and could perhaps be higher in peripheral Institutions not used to the sophisticated radiation techniques that are mandatory in HD. A variable percentage of relapsed patients can achieve a long-lasting second remission after salvage chemotherapy,[21,22] but this is not without risk since the association of full dose RT and full course CT can enhance late toxicity;

2) staging laparotomy with splenectomy is still considered by many authors to be the only way to select patients with truly localized disease;[23,24] however, surgical staging involves a certain degree of morbidity and splenectomy has recently been associated with a high incidence of secondary leukemias in HD patients, especially after combined modality treatment;[25,26]

3) in a significant number of patients supradiaphragmatic irradiation is related to severe late effects caused by radiation damage of normal tissues (heart, lung, thyroid) and to a higher incidence of secondary solid neoplasms in irradiated sites.[27-30]

This review will attempt to provide a summary and an analysis of these issues.

Radiation therapy: selection modalities and results

Approximately several thousand patients have been treated successfully with EF RT for early stage HD. The results of this therapeutic modality can thus be regarded as highly reliable provided that patients are adequately selected and treatment is correctly performed.[31] The same cannot be said of chemotherapy since very few patients have been treated with chemotherapy alone for I-II stage HD. Furthermore, patients relapsing after chemotherapy generally have a poorer prognosis than those who relapse after EF RT, because second-line treatment can induce a second remission only in a portion of them.[32-36]

In the past staging laparotomy was a thorough method for defining the progression patterns of HD. Nowadays, however, a great deal of information about the relationship between clinical features and the risk of subdiaphragmatic occult spread of HD has been acquired. Therefore surgical staging can no longer be considered mandatory for selecting patients with localized disease, since such individuals can be identified with excellent reliability on the basis of clinical characteristics at diagnosis, such as age, sex, number of involved sites, systemic symptoms. Bipedal lymphangiography, which in many centers is seldom performed and often misinterpreted, is, in our experience, still of great help in determining the presence of small disease deposits in retroperitoneal and pelvic nodes not enlarged at CT scan.[37]

The results of EF RT in clinically staged patients with localized Hodgkin's disease have been reported in a large number of series.[38,39] In none of them are disease free and overall survival significantly lower than in surgically staged patients.

Toxicity

Late toxicity of supradiaphragmatic RT is not negligible and has recently raised great concern, since HD patients are generally young and a great percentage of them could experience long survival after treatment (Table 1). Late effects of RT on the heart, which may appear ten or more years after mediastinal irradiation, have recently been reported by many authors. A 3.1% incidence of acute myocardial infarction was observed in 409 patients who received supradiaphragmatic RT at the *Gustave Roussy Institute* in Paris.[40] One hundred thirty-two patients treated for HD in the same period but not submitted to mediastinal irradiation did not present any late cardiac complications. At the *Joint Center for Radiation Therapy* the incidence of acute pericarditis in 509 patients treated with thoracic RT for HD was 3.6%, and 1.6% of all the patients died of acute myocardial infarction. The late cardiac effects of RT are not limited to coronary artery and pericardial damage, but include valvular thickening[41] and abnormalities of conduction tissue.[42] The risk of late heart sequelae is especially high in children and

Table 1. Treatment-related complications after curative therapy for Hodgkin's disease.

Potentially fatal	
	acute myelomonocytic leukemia
	diffuse high-grade non Hodgkin's lymphoma
	solid tumors (mostly lung and breast cancer)
	overwhelming bacterial sepsis after splenectomy
Serious	
	myocardial damage from radiation and anthracyclines
	lung fibrosis from radiation plus bleomycin
	sterility in men and women
	opportunistic infections
Minor	
	chemical or clinical hypothyroidism
	long-term alteration of lymphocyte function

young adults (8% actuarial risk of acute myocardial infarction according to Hancock), since the latency of cardiac complications can be very long.

In our experience no late cardiac complications were observed in patients who received less than 40 Gy to the heart.[43] It is not possible to conclude, however, that lower doses are safe, given the long latency of late cardiac complications and the ever increasing employment of antracycline-based chemotherapy in combined modality treatment.

Many authors have proposed reducing RT doses markedly in HD patients.[44] The improvement of imaging techniques can actually help in delineating radiation fields more accurately than in the past, and the flat aspect of the last part of the dose-response curve in HD suggests that increasing the dose above 36 Gy is not likely to enhance significantly local control.[45] This reduction could decrease the risk of late heart complications, but a prospective randomized study is necessary to evaluate whether the cure rate would be jeopardized.

Thyroid dysfunction and lung capacity impairment due to supradiaphragmatic RT are seldom clinically significant in adult patients and should not determine the choice of treatment. The high incidence of secondary neoplasms in patients treated for HD is well known.[46,47] Alkylating drugs are associated, especially after combined modality treatment, with a high rate of secondary leukemias. RT plays a main role in determining secondary solid neoplasms that arise in irradiated sites. Patients treated with mantle RT present a significantly higher incidence of lung and breast cancer. The frequency of the latter is inversely related to the age of the patient at diagnosis (relative risk <15 years: 136; 15-24 years: 19; 24-29 years: 7; >30 years: 0.7 according to Hancock).

Future perspectives

The mortality rate of patients treated for early stage HD is still higher than that observed in the normal population, due to treatment related complications. The main goal for the future will therefore be to reduce treatment toxicity without impairing the excellent cure rate achieved in recent years. A decrease in the rate of complications will be the result of a better integration of RT and CT (no alkylating drugs, lower number of CT courses, reduction of dose and volume of irradiation).

Several experiences in pediatric HD patients (Table 2) suggest that a significant reduction of the therapeutic load is possible without sacrificing excellent results.[48,49] Preliminary results from a similar approach in adult patients are promising.[50] Due to the protracted latency of late complications, a longer follow-up is necessary to determine whether this approach will significantly reduce the complication rate.

Table 2. Chemotherapy (CT) and low-dose involved field radiation therapy (LDIF) in early stage Hodgkin's disease in children.

Institution	AIEOP	SFOP
Clinical stage	I, IIa	I, IIa
N. patients	158	238
Median follow-up	4 yrs.	6 yrs.
Chemotherapy	ABVDx3	ABVDx4
LDIF RT (cGy)	2000-2500	2000
FFR	95.3%	89%
OS	99%	92%

Conclusions

Extended field radiation therapy still represents the treatment of choice for early stage adult HD patients without unfavorable prognostic characteristics, and the standard approach against which new treatment strategies should be tested.

The selection of patients for RT alone does not require surgical staging, since the well-known correlations between clinical features and occult subdiaphragmatic spread allow patients with a low risk of subclinical involvement of retroperitoneal nodes and abdominal organs to be identified with good reliability.

The incidence of RT failures in clinically staged patients is low, and a large number of relapsed patients will achieve a durable second remission after salvage chemotherapy.

Supradiaphragmatic RT is, however, related to severe late damage in irradiated organs, especially the heart, and to a measurable incidence of secondary solid neoplasms in irradiated sites. These two complications are of special concern for young patients, in whom they have been reported to occur more frequently.

Chemotherapy alone is not, in our opinion, a reliable alternative option in these patients. Data reported in the recent literature on this issue are conflicting, and too few patients have been treated with this approach to draw any firm conclusions. The therapeutic scheme most often employed has been MOPP, and the late toxicity of this regimen is different but not milder than that of RT. Lastly, the chances of a second remission in patients relapsing after chemotherapy are poorer.

Our goal should be a significant reduction of late treatment-related complications in early stage HD patients. This could probably be best achieved by a short non-alkylating, non-cardiotoxic chemotherapy course associated with low-dose RT to involved sites.

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