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**Supplement Article**

# XVI. Early stage Hodgkin lymphoma

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## Introduction

In early stage, Hodgkin lymphoma (HL) choice of therapy centres around the principle of maximizing cure while minimizing the late effects of treatment, particularly on risk of second cancers and cardiovascular disease, both of which undermine long-term quality of life and survival.

## Background

In the 1960s and 1970s, patients with clinical stage IA or IIA disease HL apparently confined to the thorax, axillae or neck underwent staging laparotomy with lymph node and liver biopsies and a splenectomy; if histological assessment confirmed the absence of disease below the diaphragm, wide field radiotherapy was recommended [1]. This approach led to prolonged disease-free survival in a significant number of patients and represented a major step forward.

What soon became apparent, however, was recurrence of disease outside the radiation field in some patients as a result of false negative histological assessment of biopsy specimens taken at staging laparotomy. This led to studies of adjuvant chemotherapy designed to determine whether a combined modality approach could prevent recurrence in patients with seemingly early stage HL. A clear benefit for patients receiving adjuvant treatment was observed in terms of progression-free survival (PFS), but there was no survival advantage because patients developing recurrent disease after radiotherapy alone were very efficiently salvaged by chemotherapy [2]. Furthermore, the benefit of fewer relapses after combined modality therapy was at the expense of patients receiving the highly emetogenic MOPP chemotherapy or a close variant at a time when anti-emetic medication was in its infancy. It also became evident that MOPP and its relations caused permanent azoospermia in a high proportion of men [3] and premature menopause in women [4] and, rarely, acute leukaemia or myelodysplasia in both sexes [5].

These studies highlighted the benefits of chemotherapy in terms of disease control but also showed that there were undesirable long-term consequences to treatment in addition to the immediate toxicity with which Hodgkin patients were already well acquainted. The replacement of MOPP with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) as the first-line choice of chemotherapy provided some reassurance in terms of the incidence of infertility, acute leukaemia and myelodysplasia, but the inclusion of doxorubicin in ABVD replaced these late treatment effects with cardiotoxicity [6].

The late consequences of radiotherapy in terms of increased risk of second cancers [7,8] and cardiovascular disease [9] have also become increasingly recognized over the last two decades, and this has produced a move towards smaller radiation fields and doses following chemotherapy. But are these changes sufficient to minimize the late toxicity of radiation and would it be better to abandon radiotherapy altogether in this setting and replace with chemotherapy?

## Progress in the modern era

In a paper by Meyer and colleagues [10], the results of a randomized clinical trial involving 405 patients with previously untreated, non-bulky stages IA and IIA HL are described. Trial subjects were randomly assigned to receive either 4–6 cycles of ABVD chemotherapy alone or a treatment approach incorporating sub-total nodal irradiation (STNI). For subjects allocated to the radiotherapy arm, treatment was further decided on the basis of risk profile; for those with a favourable risk profile, STNI was given alone, and for those with an unfavourable risk profile, STNI was preceded by two cycles of ABVD. The target volume of radiation in the STNI-treated group included all supra-diaphragmatic nodal stations (mantle field), the spleen and para-aortic lymph nodes with 35Gy of radiation administered in 20 fractions. The primary endpoint was overall survival at 12 years.

The trial was initiated in 1994, and this analysis was performed after a median of 11.3 years of follow-up. Overall survival was superior in the ABVD alone arm of the trial where there were 12 deaths compared with 20 deaths in the STNI arm (94% vs 87%, $p = 0.04$). Crucially, deaths in the ABVD arm included six from HL or early treatment toxicity and six from other causes (four second cancers and two cardiac). In the STNI arm, there were four deaths from HL or early treatment toxicity and 20 from other causes (10 second cancers, 2 cardiac, 3 infective and 5

other). Freedom from disease progression was 87% in the ABVD alone group and 92% in the STNI group, and the authors concluded that overall survival was better in the chemotherapy alone group because of a higher incidence of deaths from other cases in those receiving STNI.

Meyer and colleagues concede that the STNI featured in their trial is an outdated form of radiation treatment but speculate that even treatment protocols involving more modern radiotherapy approaches will also be associated with mortality due to causes other than HL. With a median follow-up of 7.5 years, 8-year results of the German Hodgkin Study Group HD10 trial showed that two cycles of ABVD and 20Gy of involved field radiotherapy (IFRT) produced an overall survival of 95% and freedom from treatment failure and event-free survival of 86% [11]. These results are almost identical to the 12-year outcomes in the ABVD alone-treated patients reported by Meyer. It is of interest, however, that despite the smaller radiation fields and dose in HD10, six patients died from a second cancer and an additional 14 patients developed a second cancer, a point that prompts Meyer and colleagues to say that an extended follow-up period is needed to properly evaluate the risks associated with less intensive radiation therapy.

But we must not forget the effects of chemotherapy. The main late toxicity associated with ABVD is cardiac because of the effects of doxorubicin. The cardiotoxicity of doxorubicin is dependent on cumulative dose [6], but even in those patients receiving doses below the ceiling of 450–500 mg/m$^2$ usually considered 'safe' in clinical practice, there is clear evidence of increased cardiac mortality in Hodgkin survivors. In a paper describing risk of death from myocardial infarction in more than 7000 survivors of HL [12], the peak incidence was 15–19 years after treatment and remained statistically significantly increased at 20–24 years. Risk factors associated with death from myocardial infarction in this study were exposure to anthracycline drugs and supra-diaphragmatic radiotherapy.

It is clear therefore that in HL, successful elimination of disease is not the only variable associated with long-term survival. It is self-evident that long-term survival will be non-existent or severely limited in the absence of effective therapy, but if we are to optimize long-term survival, we also have to recognize the impact of toxicity. In general, early treatment toxicity for HL has a minor impact on survival, but second cancers and cardiovascular disease erode long-term survival in patients where the primary disease was eliminated years earlier. In this respect, both radiotherapy and chemotherapy are implicated, and our focus should be on designing therapies capable of maximizing cure and minimizing late toxicity and testing these in clinical trials.

So how do we go about this? One approach is the sequential and careful assessment of treatment reduction in a particular sub-group of patients. This is exemplified by the German Hodgkin Study Group in their HD10 trial [11] where a standard of care based on minimal combined modality treatment in patients identified as having 'favourable' pre-treatment characteristics has been established. Another is by using magnitude of response measured by positron emission tomography (PET) after initial cycles of chemotherapy in a broader grouping of early stage patients to determine the type and extent of subsequent treatment, and this approach is being evaluated by a number of groups.

In the UK National Cancer Research Institute Randomised Phase III Trial to Determine the Role of FDG-PET Imaging in Clinical Stages IA/IIA Hodgkin's Disease (RAPID) trial [13], patients with stages IA and IIA HL and no mediastinal bulk received three cycles of ABVD followed by a PET scan. If this was 'positive' at central review, a fourth cycle of ABVD and IFRT was given. Patients with a 'negative' PET scan were randomized between no further treatment (NFT) and IFRT. With 420 PET negative patients randomized and after 60 months median follow-up, eight progressions and eight deaths (three with progression; one from HL) have occurred in the IFRT arm and 20 progressions and four deaths (two with progression; none from HL) in the NFT arm; five deaths in the IFRT arm occurred in patients who received no radiotherapy. A 3-year PFS was 94.6% (95% confidence interval: 91.5, 97.7) and 90.8% (86.9, 94.8) in the IFRT and NFT arms, respectively, with an absolute risk difference of −3.8 (−8.8, 1.3).

This study did not demonstrate non-inferiority of the two approaches in PFS based on a designated difference of −7 percentage points; although the measured difference was −3.8 percentage points, the 95% confidence interval included a possible difference of up to −8.8 percentage points. Nevertheless, the results of RAPID how that patients who are PET negative after chemotherapy have a very good outcome with or without consolidation radiotherapy and they present an opportunity to take a more individualized approach to the treatment of early stage HL. For patients where salvage treatment might be challenging or impossible because of age or co-morbidity and primary disease control is paramount, combined modality treatment remains a good choice. For others, such as the young, where late radiation toxicity is of greater concern, three cycles of ABVD followed by observation if PET 'negative' offers almost as good a chance of cure and no risk of RT induced second cancers [7,8] _ENREF_10 or cardiac disease [9].

The EORTC/LYSA H10 trial [14] has also investigated a PET response adapted approach in stages IA/IIA HL. Patients with favourable (H10F) or unfavourable (H10U) pre-treatment characteristics were randomized between standard treatment [ABVD plus involved node radiotherapy (INRT)] and treatment based on the PET result after two cycles of ABVD. In the PET directed arm, PET 2



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'negative' patients received a further two (H10F) or four (H10U) cycles of ABVD and the PET 2 'positive', escalated BEACOPP [15] plus INRT. Interim analysis performed after a median of 1.1 years of follow-up showed that in the H10F PET 'negative' group, 1-year PFS was 100.0% in the ABVD plus INRT arm and 94.9% in the ABVD only arm (HR 9.36, $p = 0.017$). In the H10U group, corresponding 1-year PFS values were 97.3% and 94.7% (HR 2.42, $p = 0.026$). On the basis of the statistical design, the authors concluded futility and chemotherapy, only treatment for PET 'negative' patients was halted. It can be argued, however, that both the H10 and RAPID trials show a similar result; RT after initial chemotherapy marginally improves the PFS over chemotherapy alone but at the expense of irradiating all PET 'negative' patients, most of whom are already cured. Clearly, long-term survival and cause of death data will be required for a full evaluation of this strategy, but as pointed out by Meyer and colleagues, this will become a mandatory requirement in future trials of therapy in limited stage HL.

## Future directions

Current research in the field is evaluating semi-objective methods for interpreting PET images in an effort to reduce error introduced by visual reporting and improve the discrimination between PET 'negative' and 'positive'. In addition, integration of PET result after initial treatment with tumour-based characteristics might allow better identification of 'poor risk' patients requiring chemotherapy followed by radiotherapy and 'good risk' patients who have an excellent prognosis after chemotherapy alone. Additionally, the new CD30-targeted agent, brentuximab vedotin [16], might find a role in the treatment of early stage HL by replacing or reducing exposure to chemotherapy and radiotherapy. Trials exploring all these possibilities are currently in development.

## Conclusions

The treatment of early stage HL has evolved considerably over the last four decades; from extended field radiotherapy alone to combined modality approaches through to less chemotherapy combined with smaller fields of radiotherapy and finally to individualized approaches based on PET response-based assessments. This progress has been made as a result of performing carefully designed clinical trials, a fact that highlights the importance of continuing to design and undertake these as we strive to optimize outcomes for this group of patients.

## References


1. Kaplan HS. The radical radiotherapy of regionally localized Hodgkin's disease. *Radiology* 1962; **78**(4): 553–61. PubMed PMID: 14453744.
2. Anderson H, Deakin DP, Wagstaff J, *et al*. A randomised study of adjuvant chemotherapy after mantle radiotherapy in supradiaphragmatic Hodgkin's disease PS IA-IIB: a report from the Manchester lymphoma group. *Br J Cancer* 1984; **49**(6): 695–702. PubMed PMID: PMC1976842.
3. Whitehead E, Shalet SM, Blackledge G, Todd I, Crowther D, Beardwell CG. The effects of Hodgkin's disease and combination chemotherapy on gonadal function in the adult male. *Cancer* 1982; **49**(3): 418–422.
4. van der Kaaij MAE, Heutte N, Meijnders P, *et al.* Premature ovarian failure and fertility in long-term survivors of Hodgkin's lymphoma: a European Organisation for Research and Treatment of Cancer Lymphoma Group and Groupe d'Étude des Lymphomes de l'Adulte cohort study. *J Clin Oncol* 2012; **30**(3): 291–299.
5. Boivin J-F, Hutchison GB, Zauber AG, *et al.* Incidence of second cancers in patients treated for Hodgkin's disease. *J Natl Cancer Inst* 1995; **87**(10): 732–741.
6. Von Hoff DD, Layard MW, Basa P, *et al.* Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med* 1979; **91**(5): 710–7.
7. Deniz K, O'Mahony S, Ross G, Purushotham A. Breast cancer in women after treatment for Hodgkin's disease. *Lancet Oncol* 2003; **4**(4): 207–214.
8. Travis LB, Gospodarowicz M, Curtis RE, *et al.* Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. *J Natl Cancer Inst* 2002; **94**(3): 182–192.
9. Galper SL, Yu JB, Mauch PM, *et al*. Clinically significant cardiac disease in patients with Hodgkin lymphoma treated with mediastinal irradiation 2011 2011-01-13 00:00:00. pp. 412-8
10. Meyer RM, Gospodarowicz MK, Connors JM, *et al*. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. *N Engl J Med* 2012; **366**(5): 399–408. PubMed PMID: 22149921. Epub 2011/12/14. eng.
11. Engert A, Plütschow A, Eich HT, *et al*. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *New Engl J Med* 2010; **363**(7): 640–52. PubMed PMID: 20818855.
12. Swerdlow AJ, Higgins CD, Smith P, *et al.* Myocardial infarction mortality risk after treatment for Hodgkin disease: a collaborative British cohort study. *J Natl Cancer Inst* 2007; **99**(3): 206–214.
13. Radford J, Illidge T, Counsell N, *et al.* Results of a trial of PET directed therapy for early stage Hodgkin's lymphoma. *New Engl J Med* 2015; **372**: 1598–1607.
14. Raemaekers JMM, André MPE, Federico M, *et al.* Omitting radiotherapy in early positron emission tomography–negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol* 2014; **32**(12): 1188–1194.
15. Engert A, Diehl V, Franklin J, *et al.* Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. *J Clin Oncol* 2009; **27**(27): 4548–4554.
16. Younes A, Gopal AK, Smith SE, *et al*. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol* 2012; **30**(18): 2183–2189. PubMed PMID: 22454421. PubMed Central PMCID: 3646316. Epub 2012/03/29. eng. N=2483




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