

## Original Article

# Long-term Results of a Randomised Trial of Involved Field Radiotherapy vs Extended Field Radiotherapy in Stage I and II Hodgkin Lymphoma

P. J. Hoskin\*, P. Smith†, T. S. Maughan‡, D. Gilson§, C. Vernon¶, I. Syndikus||, D. C. Linch†  
On behalf of the British National Lymphoma Investigation (BNLI)

\*Mount Vernon Hospital, Northwood, Middlesex, UK; †BNLI, UCL Clinical Trials Unit, London, UK; ‡Velindre Hospital, Cardiff, UK; §Cookridge Hospital, Leeds, UK; ¶Hammersmith Hospitals NHS Trust, London, UK; ||Clatterbridge Hospital, Wirral, UK

### ABSTRACT:

Involved field (IF) radiation was compared with extended field (EF) radiation in Hodgkin lymphoma (HL) to ascertain whether reduced radiation fields would reduce the late sequelae of radiation without compromising disease control and survival. A total of 603 patients with stage I or II HL were entered into this trial; laparotomy was carried out in 380 (63%) patients. Stage I or IIA disease patients were randomised to receive IF or EF comprising a mantle or inverted Y fields alone. Stage I and IIB patients were randomised between mantle or inverted Y fields and total nodal irradiation (TNI). The dose was 35 Gy to uninvolved sites and 40 Gy to involved sites. The median follow-up of surviving patients was 25.2 years with only 3.3% lost to follow-up. The treatment failure rate at 25 years in stage IA and IIA was 44% after EF and 54% after IF ( $P = 0.01$ ); in stage I and IIB this was 80% (EF) and 82% (TNI) at 25 years. No difference in overall survival between the randomised groups was seen. The incidence of second malignancies was 21% after IF and 20% after EF with a slight excess of lung cancer in the EF group. No significant differences in the causes of death between the randomised arms have emerged. In conclusion, IF radiotherapy for stage I and IIA HL results in a 11% greater risk of relapse compared with EF but has no effect on overall survival, risk of second malignancy or cause of death at 25 years. Hoskin, P. J. *et al.* (2005). *Clinical Oncology* 17, 47–53

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### Introduction

The introduction of wide-field irradiation for the treatment of localised Hodgkin lymphoma (HL) resulted in a proportion of patients being cured of their disease [1,2]. The addition of adjuvant chemotherapy further improved the disease control without improving overall survival [3,4].

The long-term follow-up of patients treated with radiotherapy has revealed a number of late sequelae including second malignancies [5–7] and cardiac disease [8–10]. In a British National Lymphoma Investigation (BNLI) study of young adult patients with HL, who achieved a continuing complete remission after first-line therapy, the mortality exceeded that expected in the general

population by over 5% at 20 years [11]. In another review of favourable risk patients the treatment-related mortality exceeded that due to the HL after 12–15 years [12]. In an analysis of 5519 patients with HL treated in the UK, the incidence of second malignancies, in excess of those expected in the general population was still rising at 15 years and approaching 1% per annum [6]. These data indicate that the assessment of any therapeutic strategy used in HL must be based on very long-term and complete follow-up to take into account the late effects of the therapy used.

We report here the results of a randomised trial conducted by the BNLI between 1970 and 1979, which addressed the role of limited field (LF) radiation vs more extended field (EF) radiotherapy in stage I and stage II HL. The aim of this trial was to try and reduce the late sequelae of radiation, particularly second malignancies, by reducing the radiation field size. No such reduction in second malignancies was observed.

Author for correspondence: Dr P. J. Hoskin, Mount Vernon Cancer Centre, Rickmansworth Road, Northwood, Middlesex HA6 2RN, UK. Tel: +44-1923-844533; Fax: +44-1923-844167; E-mail: peterhoskin@nhs.co.uk

## Materials and Methods

### Patients

All patients over the age of 15 years with stage I and II HL were eligible for this trial with no upper age limit. The diagnosis was confirmed at a central review by the BNLI histopathology panel. Staging was based on clinical examination, full blood count, unilateral bone marrow biopsy, liver function tests, chest X-ray and abdominal lymphangiography. This trial pre-dated the use of routine staging computed tomography (CT). Staging laparotomy was optional and was carried out in 380 patients (63%). Patient characteristics are shown in Table 1. The two arms of the trial were well balanced for age, sex, histological subtype, mediastinal involvement and number of sites involved. There were a non-significantly higher number of patients who had a laparotomy in the EF arm (67%) compared with the LF arm (59%). All patients were followed up at 6-monthly intervals for 5 years from time of entry into the trial and subsequently at yearly intervals. Any patient in whom no information had been received for 2 years was deemed to be lost to follow-up after checking the national cancer and death registries.

### Therapy

Patients were stratified into those with B symptoms ( $n = 61$ ) and those without B symptoms ( $n = 542$ ). There was no stratification into whether or not the patient had had a laparotomy. Patients with stage IA or IIA disease were randomised to receive either involved field radiation

( $n = 262$ ) or EF radiation ( $n = 280$ ), namely a mantle field for supra-diaphragmatic disease or an inverted Y field for infra-diaphragmatic disease, although in fact all of the stage IA and IIA patients had 'upper-half disease' and received mantle radiotherapy. The mantle field did not include an upper para-aortic strip or splenic bed field. The dose prescribed was 35 Gy in 20 daily fractions to uninvolved areas and 40 Gy in 20 daily fractions to areas containing macroscopic tumour. Patients with stage IB or IIB disease were randomised between EF, defined as mantle field ( $n = 36$ ) or inverted Y field ( $n = 3$ ) and total nodal irradiation ([TNI]; i.e. mantle plus inverted Y radiotherapy ( $n = 22$ )). The doses were again 35 Gy to uninvolved areas and 40 Gy to involved areas.

No patients in this trial received chemotherapy as part of their primary treatment, however, chemotherapy was given at relapse.

### Analysis

Complete remission (CR) was defined as the complete regression of all abnormalities attributable to the disease, maintained for at least 3 months after the end of therapy. Partial remission (PR) was defined as at least a 50% reduction of all measurable disease (product of perpendicular diameters); any response less than this was defined as a non-response (NR). Response assessment was based on clinical examination and radiography only.

Overall survival (OS) was defined as the time from randomisation to the time of last follow-up or until death from any cause. Time to treatment failure (TTF) was the time from randomisation to one of the following events: failure to achieve CR, relapse, and death from disease, with censoring of deaths not due directly to HL or immediate therapy-related complications. The censor date for this analysis was 31 December 2001 and patients known to be alive beyond this date were only accredited with survival to the censor date.

CR rates were compared using the Chi-squared test. Survival curves were calculated using the method of Kaplan and Meier with comparison by Log-rank analysis [13].

**Table 1 – Patient characteristics**

Characteristic	Involved field	Extended field	All patients
Age (years)	30 (15–77)	31 (15–78)	30 (15–78)
Sex			
Men	188 (63%)	175 (58%)	363 (60%)
Women	113 (38%)	127 (42%)	240 (40%)
Histology			
Nodular sclerosing	215 (71%)	218 (72%)	433 (72%)
Mixed cellularity	48 (16%)	46 (15%)	94 (16%)
Lymph predominantly	35 (12%)	33 (11%)	68 (11%)
Lymph depleted	3 (1%)	4 (1%)	7 (1%)
Unclassified	–	1	1
Laparotomy	179 (59%)	201 (67%)	380 (63%)
Stage			
IA	122 (41%)	143 (47%)	265 (44%)
IB	6 (2%)	2 (1%)	8 (1%)
IIA	140 (47%)	137 (45%)	277 (46%)
IIB	33 (11%)	20 (7%)	53 (9%)
Mediastinal involvement	114 (38%)	106 (35%)	220 (37%)
Number of sites			
≤2	200 (66%)	216 (72%)	416 (69%)
>2	80 (27%)	70 (23%)	150 (25%)
Unknown	21 (7%)	16 (5%)	37 (6%)

## Results

### Follow-up

A total of 603 patients were randomised in this trial and follow-up was relatively complete; at 10 years only 1.2% had been lost to follow-up and at 20 years 2.5%. At the censor date of 31 December 2001, only 20 patients (3.3%) were lost to follow-up. The median follow-up at this time was 25.2 years for surviving patients.

### Response Rates

The CR rate in patients receiving LF radiation was 92.4% compared with 94.4% in patients receiving either a mantle or inverted Y field ( $P > 0.1$ ). In patients with stage IB or IIB disease, the CR rate with either a mantle or inverted Y field was 77% compared with 55% with TNI. However, the

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