

Lymphoma

Optimal scheduling to reduce morbidity of involved field radiotherapy with transplantation for lymphomas: A Prospective Australasian Leukaemia and Lymphoma Group Study

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Summary:

This study evaluated delivery of involved field radiotherapy (IFRT) with transplantation for lymphomas timed to minimise toxicity. Patients transplanted for lymphoma had infradiaphragmatic disease irradiated pre-transplant and supradiaphragmatic disease post transplant. A total of 31 patients were studied, with a median follow-up duration of 4 years. Transplant conditioning was according to clinician preference. In all, 14 patients had pre-transplant abdominopelvic IFRT and 19 had post transplant IFRT (including three who had pre-transplant IFRT). Grade III–IV haematological toxicity from pre-transplant IFRT occurred in three patients and from post transplant IFRT in 10 patients. Pre-transplant IFRT had no effect on haematological recovery post transplant, but was associated with a trend towards increased gastrointestinal toxicity ($P=0.094$). Pneumonitis due to post transplant thoracic IFRT occurred in one patient. Two patients failed in involved sites after completion of protocol radiotherapy. One case of myelodysplasia has been reported. As sequenced in this study, IFRT was feasible and produced a low incidence of severe pulmonary and haematological toxicities. Patient selection, field size and radiotherapy dose warrant further study.

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High-dose chemotherapy (HDT), supported by autologous stem cell transplantation (AuSCT), is widely used for patients with relapsed non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD).¹ A number of avenues have been explored in an attempt to improve the results of transplantation, including the use of alternative salvage chemotherapy regimens, intensification of transplant conditioning, improved supportive care, stem cell purging and the addition of biological therapies.

Involved field radiotherapy (IFRT) is often used in conjunction with HDT and AuSCT, based on the observation that relapse commonly occurs at sites of prior disease involvement, and that the incidence of relapse in these sites may be reduced by the addition of radiotherapy.² Although no completed randomised trial has examined the impact of IFRT added to HDT and AuSCT, several retrospective series have indicated improved outcomes with this strategy.^{3–11}

Important concerns regarding the use of IFRT are its potential toxicity and the logistical constraints in integrating radiotherapy with the overall transplant programme.¹² Two notable forms of toxicity are pneumonitis and haematological toxicity. Some, but not all authors suggest that pneumonitis appears to be more common when thoracic IFRT immediately precedes HDT, whereas haematological toxicity may occur when large infradiaphragmatic volumes are irradiated following AuSCT.^{5,13–17}

We hypothesised that it might be possible to limit the incidence of severe toxicities by administering infradiaphragmatic IFRT prior to HDT to minimise the impact on haematopoietic recovery following AuSCT and giving supradiaphragmatic IFRT post transplant to reduce the risk of pneumonitis. The main aims of this study were to assess the toxicity and feasibility of integrating pre- and/or post transplant IFRT in a multicentre setting, and to examine the pattern of failure following protocol treatment.

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Patients and methods

Eligibility

This was a prospective, nonrandomised, multicentre pilot study. Patients were considered for the study if they either had persistent disease following first-line therapy or if they had relapsed after a prior complete remission (CR) for histologically confirmed HD or NHL, and were planned for HDT and AuSCT. Patients were considered eligible for the study if they were aged between 16 and 64 years and had an ECOG performance status ≤ 2 . Patients were excluded if they had prior IFRT to the involved site, known disseminated liver, lung or central nervous system involvement, mesenteric involvement requiring lateral radiotherapy fields, or any medical condition leading to an unacceptable risk from protocol treatment. Protocol eligibility was assessed jointly by the transplant clinician and radiation oncologist. All patients were registered on study prior to receiving protocol radiotherapy. The study was approved by the institutional ethics committees of all participating centres, and all patients provided written informed consent.

Transplantation

The management of the stem cell harvest, cytoreduction chemotherapy and HDT was according to the policy of the transplant clinician/institution. Cytoreduction chemotherapy was defined as chemotherapy given with the aim of reducing the tumour burden and/or testing chemotherapy-responsiveness prior to a planned HDT.

Radiotherapy

The intent was to irradiate all nodal (and contiguous extranodal) sites of relapsed or progressive disease, even if they achieved a CR following cytoreduction chemotherapy. Radiotherapy was limited to involved sites; however, if such radiotherapy fields were separated by 15 cm or less, they could be incorporated into a continuous volume. The volumes to be irradiated were based on sites of involvement prior to cytoreduction chemotherapy, with longitudinal field margins of 3–5 cm and radial margins of 1–2 cm. The protocol recommended a dose of 26 Gy in 13 fractions, at five fractions per week (dose modification was allowed at the discretion of the individual investigator). It was recommended that radiotherapy of the heart, lungs and spinal cord be limited wherever possible, providing known sites of disease were not shielded. All treatment was given on a linear accelerator with an energy of 6 MV or greater.

Infradiaphragmatic disease sites were irradiated prior to HDT but only after recovery from cytoreduction chemotherapy (if given), and confirmation of an adequate stem cell harvest. Patients proceeded to HDT therapy at least 1 week after completion of radiotherapy, and following resolution of radiotherapy-related toxicity. Supradiaphragmatic disease sites were irradiated as soon as practicable following recovery from AuSCT, generally by week 8 after

stem cell infusion. If significant post transplant toxicity occurred, post transplant IFRT could be deferred, modified or omitted if it was felt to pose an unacceptable risk. If supradiaphragmatic disease progression occurred during the immediate peritransplant period, patients could remain on study if the site of progression could still be encompassed in an acceptable involved field. Radiotherapy quality assurance assessment consisted of review of information provided on data forms and review of radiotherapy prescription forms and diagrams of radiotherapy fields.

Patients were reviewed weekly during IFRT for clinical toxicity assessment and performance of full blood counts. Recommended modifications of radiotherapy for toxicity were indicated in the protocol. Patients were monitored according to institutional policy during and following AuSCT, and the occurrence of toxicity was recorded according to the National Cancer Institute Common Toxicity Criteria version 2 which incorporates RTOG toxicity criteria.¹⁸ The overall response to cytoreduction chemotherapy and to the transplant/IFRT programme was classified as: CR – all clinical/radiological abnormalities resolved; CR (unconfirmed) minor residua consistent with fibrosis; partial response (PR) – 50% reduction in maximum tumour dimensions; minor response-reduction in tumour but less than PR; no change – no appreciable change in tumour dimensions. Subsequently, the date and sites of disease progression, the occurrence of second malignancy and myelodysplasia and the date and cause of death were recorded.

Statistical methods

All patients were followed to the close-out date. Overall survival and time to progression have been measured from the date of commencement of protocol treatment, that is, the date of commencement of infradiaphragmatic radiotherapy if given, or the date of commencement of transplant conditioning. Survival has been measured to the earlier of the date of death (no matter what the cause) and the close-out date, and has been censored for patients still alive at the close-out date. Time to progression has been measured to the earlier of the date of progression/relapse and the close-out date, and has been censored for patients who died progression-free and those who were alive, progression-free at the close-out date. Survival curves have been estimated using the Kaplan–Meier method.

Times to engraftment were compared using the Pitman exact test where there was no censoring, or the exact log-rank test where patients died before counts had recovered.¹⁹ One-sided tests were used for comparing patients with and without pre-transplant IFRT on the assumption that the times to engraftment would be increased by pre-transplant IFRT. For the major summary statistics, 95% confidence intervals (95% CI) have been reported. No adjustments have been made for multiple comparisons. Statistical analyses were carried out using StatXact, SPSS and S-PLUS statistical software.^{19–21}

Results

Patient characteristics

In all, 31 patients were enrolled over 3 years at five centres in the Australian states of Victoria, New South Wales and South Australia. Table 1 details patient characteristics at the time of disease progression prior to AuSCT. Note that histology prior to AuSCT differed from that at diagnosis in two patients. The histology at diagnosis was HD (12), indolent NHL (five) and aggressive NHL (14), WHO classification. The disease stage at diagnosis was I (three), II (14), III (seven), and IV (seven). All patients had either failed to achieve a CR with first-line therapy (primary failure, $n = 14$) or relapsed after first-line therapy (relapse, $n = 17$). Of the 14 patients with primary treatment failure, four had progressive disease during therapy and 10 failed to achieve CR following first-line therapy. Evidence of treatment failure prior to entry into the transplant protocol was: positive biopsy (17), unequivocal tumour enlargement (six), positive functional imaging (five) or residual clinical/radiological abnormalities inconsistent with a CR or CR (unconfirmed) (three). The median number of lines of chemotherapy prior to pre-transplant cytoreduction chemotherapy was 1 (range: 1–5). First-line therapy was cyclophosphamide, adriamycin, vincristine and prednisolone or variant (18), adriamycin, bleomycin, vinblastine, dacarbazine (10), cyclophosphamide, vincristine and prednisolone or variant (two) and chlorambucil (one). One patient had received radiotherapy as part of prior treatment.

Table 1 Characteristics of patients at progression prior to transplant

	Total
Total cases	31
<i>Histology</i>	
Hodgkin's disease ^a	11
Non-Hodgkin's lymphoma	20
Diffuse large B cell	13
Mantle cell	1
Burkitt's lymphoma	1
T-cell (Lennert's lymphoma)	1
Follicular (grade I/II)	4
Median age (range)	46 (18–66)
<i>Relapse stage^b</i>	
I	4
II	20
III	4
IV	3
B-symptoms present	7
Bulk disease present	11
LDH elevated	11
Median time to first chemotherapy failure (months)	3.4 (0.2–71)
Regimens of chemotherapy prior to salvage therapy: median (range)	1 (1–5)
Previous radiotherapy given	1

^aSeven nodular sclerosis, four mixed cellularity.

^bStage based on disease extent at the time of progression leading to the transplant.

Treatment at progression

In all, 27 patients received one to two cytoreduction chemotherapy regimens prior to their transplant. Four patients with primary failure did not receive salvage chemotherapy. Regimens used were: dexamethasone, cytarabine, cis- (or carbo-) platin (nine), etoposide, cytarabine, cisplatin (five), BCNU/etoposide/cytarabine/melphalan (mini-BEAM) variants (three), ifosfamide-based (three), other (10). Of these patients, 16 showed a response: CR or CRu (five), PR (10) and minor response (one). Four patients had stable disease and in seven cases response was not formally assessed.

High-dose chemotherapy regimens were BEAM (14), cyclophosphamide, BCNU, etoposide (CBV) (six), busulphan, etoposide, cyclophosphamide (four), lomustine, cytarabine, cyclophosphamide, etoposide (two), busulphan, melphalan (two), total body irradiation (TBI), cyclophosphamide, etoposide (one) and BCNU, etoposide, melphalan (one). One patient progressed in distant sites during infradiaphragmatic radiotherapy and did not proceed to transplantation.

Details of radiotherapy

In all, 14 patients had radiotherapy to the abdomen and/or pelvis prior to their transplant (Table 2). Three of these also subsequently received supradiaphragmatic IFRT following AuSCT. All patients with follicular lymphoma (FL) had radiotherapy only to subdiaphragmatic sites. The median dose (range) to lymph node fields was 30 Gy (21–39.6 Gy) with only one patient receiving less than 26 Gy and one patient in excess of 30 Gy. If subdiaphragmatic fields are described in terms of a standard inverted-Y field, 10 patients had one limb of the inverted-Y, one patient had two limbs and three patients had a full inverted-Y. One patient did not complete radiotherapy because of disease progression in distant sites. The median time from the end of pre-transplant IFRT to the commencement of HDT was 2.7 weeks (range 0.9–8.3 weeks).

Supradiaphragmatic radiation was given in 19 patients, three of whom had also received pre-transplant subdiaphragmatic IFRT. In all, 10 of 11 patients with HD received supradiaphragmatic radiotherapy. The median time from stem cell infusion to commencement of IFRT was 8 weeks (4.1–14.9 weeks). The median dose was 26 Gy (range: 7.5–33 Gy). Two patients received less than 26 Gy and nine patients received 30 Gy or more. One patient had IFRT to the mediastinum alone, three to the neck and/or axilla alone and 15 patients had IFRT to the neck and/or axilla plus mediastinum. For one patient, the transplant clinician elected to withhold radiotherapy after the patient was registered on study.

Acute radiotherapy-related toxicity

There were no radiotherapy-related deaths. Grade III–IV radiotherapy-related toxicity occurred in four of 14 patients who had pre-transplant subdiaphragmatic radiotherapy and 11 of 19 who had post transplant supradiaphragmatic radiation (Table 3). Two of the three cases with grade III

Table 2 Radiotherapy administration according to histology and area irradiated

Histology	Total <i>n</i>	Subdiaphragmatic		Supradiaphragmatic		Both ^a <i>n</i>	<i>n</i>
		<i>n</i>	Median dose Gy (range)	<i>n</i>	Median dose Gy (range)		
Aggressive NHL	16	6	30 (21–39.6)	7	26 (26–30)	2	1
FL	4	4	30 (30–31.2)	0	NA	0	0
HD	11	1	27	9	26 (7.5–33)	1	0

NHL = non-Hodgkin's lymphoma; FL = follicular lymphoma; HD = Hodgkin's disease; NA = not applicable.

^aSubdiaphragmatic and supradiaphragmatic radiotherapy administered.

Table 3 Incidence of grade III and IV radiotherapy-related toxicities

	III	IV	% Grade III or IV (%)
<i>Pre-AuSCT subdiaphragmatic IFRT (n = 14)^a</i>			
Neutropenia	1	1	14
Thrombocytopenia	1	0	7
Raised bilirubin	1	0	7
<i>Post-AuSCT supradiaphragmatic IFRT (n = 19)^b</i>			
Neutropenia	4	0	21
Thrombocytopenia	3	0	16
Anaemia	3	0	16
Pneumonitis	1	0	5
Nausea	1	0	5
Fatigue/lethargy	3	0	16

^aFour patients had one grade III or IV toxicity.

^bFour patients had two grade III toxicities. A total of 11 patients (58% of 19) had at least one grade III toxicity.

anaemia following supradiaphragmatic radiation had grade II anaemia at the time of commencing radiotherapy. Three patients needed treatment to be interrupted or suspended because of toxicity. Treatment interruption occurred in one case due to thrombocytopenia (grade III), and radiotherapy was ceased prematurely in two cases due to nausea and vomiting/weight loss (grade III) and thrombocytopenia (grade III). There was no apparent relationship between the occurrence of grade III–IV toxicity and the IFRT field size as reflected in number of limbs of the inverted-Y or the inclusion of the mediastinum. Only one patient developed pneumonitis (grade III) following supradiaphragmatic radiation. This patient had conditioning with lomustine, etoposide, ara-C and cyclophosphamide and had radiotherapy fields including the mediastinum and axilla.

Post transplant toxicity

Post transplant gastrointestinal toxicity, and the time to haemopoietic recovery were assessed. Recombinant human granulocyte colony stimulating factor was used from the day following stem cell infusion in 76% of cases. For the groups that did and did not receive pre-transplant abdomino pelvic IFRT, the median times to a neutrophil count $>0.5 \times 10^9/l$ were 10 and 13 days, respectively ($P=0.97$), and the median times to a platelet count $>20 \times 10^9/l$ were 14 and 16 days, respectively ($P=0.83$). The incidence of grade III–IV gastrointestinal toxicity was 31% for patients who had pre-transplant IFRT (three

patients with grade III and one patient with grade IV) and 6% for patients who did not (one patient with grade III) ($P=0.094$). Conditioning regimens used for the four patients with grade III–IV GIT toxicity were BEAM (1) and CBV (3). There was no apparent relation between the number of limbs of the inverted-Y irradiated and the occurrence of GIT toxicity post transplant.

Late toxicity

At the time of analysis one case of myelodysplasia had been diagnosed 2.7 years following transplant. This patient's prior treatment included cyclophosphamide, mitozantrone, vincristine, prednisolone, etoposide, ara-C and cisplatin and BEAM conditioning with radiotherapy to para-aortic nodes, neck and axilla. No case of acute myeloid leukaemia or solid tumour had been diagnosed. Other late toxicities that have been reported included persistent pulmonary symptoms in six patients at nine or 12 months (grade I: 5, grade II: 1).

Survival and time to progression

The duration of follow-up from the date of commencement of protocol treatment to the close-out date ranged from 2.7 to 5.4 years with a median of 4.0 years. In all, 10 patients died before the close-out date. Causes of death were progressive disease in nine patients and transplant-related toxicity (sepsis) in one. An estimated 74% (95% CI 56–87%) of patients survived 1 year following commencement of protocol treatment and 71% (95% CI 53–84%) survived 3 years. A total of 12 patients experienced disease progression before the close-out date. An estimated 73% (95% CI 55–86%) of patients were progression-free 1 year following commencement of protocol treatment and 67% (95% CI 48–81%) at 3 years.

Sites of disease failure

Four patients had a component of failure within or adjacent to the planned irradiated fields, in one case solely in a prior site of disease. One patient progressed during the interval between AuSCT and the commencement of IFRT. This patient had bilateral cervical lymphadenopathy, and achieved a CR to cytoreduction chemotherapy in this area prior to AuSCT. The relapse occurred in the neck shortly before the planned commencement of neck irradiation. Following radiotherapy this site achieved a CR, but the patient subsequently relapsed in a distant site. Another

patient relapsed in the lung adjacent to a site of bulky mediastinal disease, with possible lung involvement prior to the transplant. Only two patients clearly failed within an irradiated field following completion of planned radiotherapy. Both patients had primary refractory HD and minimal or no response to cytoreduction chemotherapy, and relapsed in sites receiving doses of 26 and 30 Gy. In all, 11 patients had a component of failure in distant sites, and in eight cases relapse was confined to distant sites. Five patients failed in out-of-field nodal sites, one on the same side of the diaphragm, three on the opposite side of the diaphragm and one on both sides of the diaphragm. No patient relapsed solely in an unirradiated lymph node group adjacent to the irradiated field. Eight patients failed in extranodal sites – two with HD in contiguous lung, and six with NHL in distant extranodal sites. The time of relapse was during infradiaphragmatic radiation (1), in the interval between AuSCT and planned post transplant radiotherapy (1), and after completion of all protocol therapy (10).

Discussion

Several lines of evidence support the use of IFRT with AuSCT for lymphomas:^{2,22–24} (1) relapse following AuSCT most commonly occurs at sites of prior disease involvement in HD, aggressive NHL and follicular NHL,^{3,6,14,15,25–29} (2) relapse of lymphoma appears to be less common in sites receiving IFRT following AuSCT for HD and NHL,^{3,6,8,15,30} (3) radiotherapy alone can salvage 25–50% of selected patients with HD after failure of initial chemotherapy,^{31–42} (4) in series with short follow-up, IFRT has been reported to salvage some transplant failures for both HD and NHL^{17,27,43} and (5) several retrospective series have demonstrated improved failure-free survival with the addition of IFRT to AuSCT for HD and NHL.^{3–8,11} In two studies, the improvement in progression-free survival associated with the use of IFRT was significant on multivariate analysis.^{9,10} Furthermore, in a recent report from the US Autologous Blood and Marrow Transplant Registry, multivariate analysis demonstrated that patients who received radiotherapy experienced a reduced relative risk of death.¹¹

Nonetheless, the optimal method and timing of IFRT with AuSCT remains to be defined. The potential advantages of pre-transplant IFRT are a reduction in haematological toxicity, avoidance of irradiating bone marrow containing recently infused stem cells and additional debulking prior to HDT. The potential advantages of post transplant IFRT are the potential to reduce the risks of pneumonitis, veno-occlusive disease (VOD) and gastrointestinal toxicity, no delay in delivering HDT, and the ability to tailor the radiotherapy dose according to the response to the transplant.^{2,12} The present study is the first to prospectively evaluate the feasibility and toxicity of a flexible strategy that integrates IFRT at potentially the most favourable time to minimise toxicity – that is, pre- and/or post transplant, according to the region being irradiated. We have shown this strategy to be feasible in a multicentre setting. Only two patients were unable to

complete planned radiotherapy, and only two others required a treatment interruption due to toxicity. The median interval between pre-transplant IFRT and transplantation was 2.7 weeks, and only one case of systemic progression occurred between the commencement of pre-transplant IFRT and AuSCT.

It is recognised that the delivery of post transplant IFRT may be limited by the development of cytopenias.^{9,17,44–46} Lumbar and pelvic radiotherapy in particular produces the greatest marrow insult, and it is difficult to irradiate large infradiaphragmatic volumes following transplantation because of limiting haematological toxicity.¹⁷ In a recent prospective trial in which IFRT was to be given post transplant, approximately one-quarter of transplanted patients did not receive IFRT due to haematological toxicity.⁴⁶ In our study, the haematological toxicity of pre-transplant IFRT was less frequent than that of post transplant IFRT, despite the former generally encompassing larger areas of active marrow in the lumbar spine and pelvis, and no patient had to cease pre-transplant radiotherapy due to toxicity.

A concern is the potential for pre-transplant abdominal radiotherapy to increase the risk of post transplant gastrointestinal toxicity. Although cases of VOD, enteritis and gastritis have been reported when transplantation has been preceded by abdominal radiotherapy, it is not clear whether the incidence is greater than in nonirradiated patients.^{5,6,8,14,15} We compared the incidence of grade III–IV gastrointestinal toxicity in patients who received pre-transplant IFRT and those who did not, and found a trend to a higher rate of toxicity. However, due to the small number of events, this observation needs to be evaluated in a larger cohort of patients. Overall, our data suggest that it may be preferable to give large-field infradiaphragmatic radiotherapy prior to transplantation. Pre-transplant radiation should be given after cytoreduction chemotherapy and after progenitor cell harvest is complete, to minimise adverse effects on bone marrow reserve.

It is uncertain whether the delivery of IFRT prior to autologous transplantation is the primary risk factor for the development of pneumonitis. Putative risk factors identified to date include the administration of thoracic radiotherapy within 3 months prior to HDT, radiotherapy doses exceeding 30 Gy and the type and dose of chemotherapy utilised in the HDT regimen (ie carmustine, etoposide, melphalan).^{5,13–16,47–49} There is pre-clinical evidence that the sequence of chemotherapy and thoracic radiotherapy may be important in determining the risk of pneumonitis, which may be lower when IFRT follows chemotherapy rather than the reverse.^{50–52} Taken together, we elected in our trial, to administer supradiaphragmatic IFRT following the AuSCT and not to stipulate the conditioning regimen used. In our series, pneumonitis was uncommon after post transplant mediastinal IFRT, and fatal or severe pneumonitis was not observed.

A number of other late toxicities have been reported following IFRT and AuSCT, including myelodysplasia/leukaemia, solid tumours and unpredictable spinal cord or cardiac injury.^{12,53,54} Although IFRT has been considered a risk factor for myelodysplasia, transplant conditioning regimens and the extent of prior treatment may also be

factors.^{12,55} It is also unclear whether the timing of IFRT is important, and whether TBI confers a different risk to IFRT. To date, one case of myelodysplasia has been reported in the present study, but longer follow-up is needed to determine the incidence of second malignancy.

An exploratory analysis of pattern of failure was undertaken. In most reports, when radiotherapy has not been used, local failure occurred as a component of the majority of relapses following AuSCT. In the present study, local failure occurred in only four of 12 cases of progression, and in only two did this occur after completion of protocol radiotherapy. These local failures were associated with primary refractory disease, unresponsive to cytoreduction chemotherapy. The protocol recommended a dose of 26 Gy, based on the dose used in the Parma study and with the aim of minimising the risk of radiotherapy toxicity.⁶ This dose was in fact exceeded for several patients, based on the clinical judgement of individual clinicians. Radiotherapy dose–response data in the relapse setting are difficult to interpret given the heterogeneity of most series. Data from studies of first-line therapy suggest that the optimal dose of IFRT depends on histology, disease bulk and the response to chemotherapy, and it is reasonable to assume that patients undergoing AuSCT with bulky or refractory disease require higher radiotherapy doses to achieve local control.^{56–58} The optimal dose of IFRT with AuSCT requires study in larger series of patients.

The optimal irradiated volume is also uncertain. Some investigators have used total nodal radiotherapy prior to AuSCT for HD, on the assumption that any nodal site is at risk of relapse.²³ In the Parma study, IFRT was given to sites of disease greater than 5 cm.⁶ However, in that study, unirradiated patients with nonbulky relapse (ie less than 5 cm) had a preponderance of failures occurring in sites of prior disease, providing a rationale for including nonbulky disease sites within the IFRT field. Relapses may also occur at sites that were not involved prior to transplantation, but were involved at a previous relapse or at diagnosis.⁸ In another study, it is suggested that adjacent uninvolved sites are at risk of failure when involved fields are strictly confined to known sites of HD in a transplant setting.⁵⁹ In the present series, we found that relapse in adjacent sites occurred in the lung in the presence of extensive mediastinal disease, but we found no cases of isolated adjacent nodal failure.

This was a pilot study intended in part to establish the safety of IFRT, and patients are likely to have been selected on the basis of perceived need for radiotherapy. No log of potential study candidates was maintained, so is not possible to establish a denominator for the study population, or to assess the degree of selection for the study. Hence, outcomes such as freedom from progression and survival must be interpreted with caution due to possible unrecognised selection biases.

This series is one of only a few detailed prospective studies of the incorporation of IFRT with AuSCT for lymphomas, and is the first to report flexible timing of IFRT delivery to minimise toxicity. Our data demonstrate that this is a well-tolerated approach and in Australia a larger prospective study has been initiated evaluating

in-field control rates and pattern of failure following AuSCT using this IFRT strategy.

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