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FULL PAPER

Evolution of radiation techniques in the treatment of mediastinal lymphoma: from 3D conformal radiotherapy (3DCRT) to intensity-modulated RT (IMRT) using helical tomotherapy (HT): a single-centre experience and review of the literature

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Objective: To evaluate radiation techniques and their toxicity in the treatment of Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) with mediastinal disease over a 10-year period.

Methods: Between 2003 and 2015, 173 patients with Stage I–III nodal lymphoma were treated in our institution: some of these patients were irradiated for HL or NHL with mediastinal disease. Some of the patients were treated by three-dimensional conformal radiotherapy (3DCRT), others by intensity-modulated radiotherapy (IMRT).

Results: We studied 26 males and 43 females with a median age of 26 years. The median follow-up was 43 months. 49 patients were treated by 3DCRT and 20 patients by IMRT. The median dose received by patients treated for NHL was 40 Gy (range: 36–44 Gy), and the median dose received by patients with HL was 30 Gy (range: 30–36 Gy). Between 2003 and 2006,

16 patients were treated by 3DCRT vs 0 patients by IMRT. Between 2007 and 2009, 16 patients received 3DCRT and one patient received IMRT. Between 2010 and 2015, 19 patients received IMRT, and no patients received 3DCRT. 11 of the 20 (55%) patients treated by IMRT and 35 of the 49 (71.4%) patients treated by 3DCRT experienced acute toxicity. Among the patients treated by 3DCRT, one patient experienced Grade 1 radiation pneumonitis and two patients experienced Grade 1 acute mucositis. No late toxicity was observed in patients treated by IMRT.

Conclusion: Improvement of radiation techniques for HL and NHL appears to have improved acute and late clinical safety. Longer follow-up is necessary to evaluate very late toxicity.

Advances in knowledge: Improvement of radiation techniques for HL and NHL appears to improve the tolerance.

INTRODUCTION

The treatment of Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) is challenging in terms of local control and acute and late toxicity.^{1,2} Standard treatment consists of HL combination chemotherapy followed by adjuvant radiotherapy.¹ This treatment can sometimes be responsible for severe life-threatening adverse effects, such as radiation pneumonitis, radiation-induced heart disease or second cancers.³ In this setting, improvement of radiation techniques allowing optimization of the dose to adjacent organs at risk (OARs) could reduce these risks.² We have previously published comparative dosimetric results between three-dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT).² The present study was designed to

evaluate the evolution of radiation techniques in the treatment of HL and NHL with mediastinal disease over a 10-year period, as well as early and late toxicity as a function of the type of radiation technique used.

METHODS AND MATERIALS

Patients

Between January 2003 and January 2015, 173 patients with Stage I–III nodal lymphoma were treated in our institution: 69 of these patients were irradiated for HL (64 patients) or NHL (5 patients) with mediastinal disease. Patients irradiated for HL had received doxorubicine, bleomycine, vinblastine, dacarbazine (ABVD) or bleomycin, etoposide, doxorubicine, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP) ± ABVD or doxorubicin,

cyclophosphamide, vindesine, bleomycin, prednisone (RACVBP) chemotherapy in the case of refractory disease. Patients treated for NHL had received rituximab-cyclophosphamide, vincristine, doxorubicin, prednisolone (R-CHOP) chemotherapy. Eight patients had received salvage chemotherapy. Six patients received treatment intensification after first-line chemotherapy. Positron emission tomography (PET) scan was performed in all patients before and after first-line chemotherapy.

Simulation and CT scan in treatment position

Unenhanced and contrast-enhanced CT scan was performed in the treatment position in each patient, 2 weeks before starting radiotherapy. A personalized immobilization cast was created for each patient. Positioning CT was performed under free-breathing conditions.

Definition of target volumes

Baseline CT and PET scans before chemotherapy were merged with the treatment position CT scan. Contouring was performed with Eclipse® software (Varian® Medical System, Palo Alto, CA) for all treatment plans. The clinical target volume (CTV) was always delineated by the same radiation oncologist. The CTV

receiving a dose of 30 Gy corresponded to the initial lymph-node invasion contoured for “involved-field” (IF) radiotherapy with the following modifications: cervical nodes as far as the larynx were included in the target volume only when they were invaded. Right and left supraclavicular nodes were included in the target volume when the mediastinum was invaded. The lower limit of the mediastinal field was not less than the lower limit of invasion. When a residual tumour mass was present on the evaluation CT or PET scan at the end of chemotherapy, a 6–10-Gy boost was delivered to this residual CTV. The PTV was determined by adding 10 mm margins to the CTV. The following OARs were delineated: spinal cord, left and right lungs, oesophagus, trachea, thyroid, left and right breasts and origin of the left and right coronary arteries.

In all cases the patients received If radiotherapy; the boost to residual mass was realized with margins of 1 cm. The dose per fraction was 2 Gy in all cases. The total doses are given in Table 1.

The dose was prescribed in point International Commission on Radiation Units and Measurements for the 3D planning and the coverage of PTV by the 95% isodose was respected.

Table 1. Patient characteristics

Characteristics	3DCRT	Tomotherapy
Median age	25 (17–61)	27 (16–46)
Male	21 (43%)	5 (25%)
Female	28 (57%)	15 (75%)
Histology		
Hodgkin lymphoma	47 (98%)	17 (85%)
Non-Hodgkin lymphoma	2 (2%)	3 (15%)
Chemotherapy		
3 ABVD	10 (20.5%)	1 (5%)
4 ABVD	23 (47%)	6 (30%)
6 ABVD	12 (24.5%)	2 (10%)
6 EBVP	1 (2%)	0
2 BEACOPP 2 ABVD	0	6 (30%)
4 BEACOPP	1 (2%)	2 (10%)
6 R-BEACOPP	0	1 (5%)
6 R-CHOP	1 (2%)	1 (5%)
4 R-ACVBP	1 (2%)	1 (5%)
Irradiation		
At the dose of 20 Gy	0	1 (5%)
At the dose of 30 Gy	17 (34%)	10 (50%)
At the dose of 30 Gy + 6 Gy boost to residual disease on the CT	29 (58%)	6 (30%)
At the dose of 40 Gy	3 (6%)	2 (10%)
At the dose of 44 Gy	0 (0%)	1 (5%)

3DCRT, three-dimensional conformal radiotherapy; ABVD, doxorubicine, bleomycine, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicine, cyclophosphamide, vincristine, procarbazine and prednisone; EBVP, epirubicin, bleomycine, vinblastine, prednisone; R-ACVBP, rituximab-doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; R-BEACOPP, rituximab, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; R-CHOP, rituximab, cyclophosphamide, vincristine, doxorubicin, prednisolone.

Treatment planning

Three-dimensional conformal radiation therapy

3DCRT plans were performed with Eclipse (Varian Medical System) as a standard reference for comparison. They consisted of two fields one anterior and one posterior each of energy superior to 6 MV. The calculation model was the Eclipse analytic anisotropic algorithm « AAA » equivalent to superposition/convolution models.

Helical tomotherapy

Tomotherapy plans were calculated on the Tomotherapy Hi-Art® workstation (Tomotherapy Incorporated, Madison, WI) with a superposition/convolution algorithm. Collimator width was 2.5 cm, pitch was 0.287 and the maximum modulation factor was set to 3. Priorities were assigned to each OAR for inverse planning as follows:

- contralateral lung; ipsilateral lung; heart; ipsilateral breast; contralateral breast; parotides; and spinal cord
- for bilateral or midline target volumes: left lung; right lung; heart; left breast; right breast; parotids; and spinal cord.

The doses to OARs were previously published by Pernin et al² and respected the recommendations of Société Française de Radiothérapie Oncologique.

Follow-up

All patients were examined at weekly visits throughout the duration of radiation therapy. Radiation-related adverse effects were classified according to the Common Terminology Criteria for Adverse Events version 3.0. All patients were followed for 5 years alternately by a haematologist and the radiation oncologist. Follow-up consisted of clinical examination, routine blood tests including thyroid stimulating hormone (TSH), annual CT scan and mammography or annual breast MRI in young female patients.

RESULTS

This series comprised 26 males and 43 females with a median age of 26 years (range: 16–61 years). The overall median follow-up was 43 months, the median follow-up in the patient group treated by 3DCRT was 46 months and the median follow-up in the patient group treated by IMRT (helical tomotherapy) was 10 months. Patients treated for HL had received 3–6 cycles of ABVD in 54 cases, 2 cycles of BEACOPP, followed by 2 cycles of ABVD in 6 cases, 4–6 cycles of BEACOPP in 3 cases and 6 cycles of EBVP in 1 case. Patients treated for B-cell NHL had received six cycles of R-CHOP in two cases, four cycles of R-ACVBP in four cases and six cycles of R-BEACOPP in one case. Eight patients had received salvage chemotherapy. Six patients had received treatment intensification after first-line chemotherapy. PET scan was performed in all patients before and after first-line chemotherapy. Patient characteristics and treatments are presented in Table 1.

49 patients were treated by 3DCRT and 20 patients were treated by IMRT. The median dose received by patients treated for NHL was 40 Gy (range: 36–44 Gy) and the median dose received by patients treated for HL was 30 Gy (range: 30–36 Gy).

Between 2003 and 2006, 16 patients were treated by 3DCRT vs 0 patients treated by IMRT. Between 2007 and 2009, 16 patients

were treated by 3DCRT vs 1 patient treated by IMRT. Between 2010 and 2015, 19 patients were treated by IMRT, while no patients were treated by 3DCRT.

Local control was 100% in presented series; 8.6% (one patient treated with IMRT and five patients with 3DCRT) recurrence was observed in irradiated volumes treated with chemotherapy.

11 of the 20 (55%) patients treated by IMRT and 35 of the 49 (71.4%) patients treated by 3DCRT experienced acute toxicity. Nine patients treated by IMRT and 21 patients treated by 3DCRT experienced Grade 1 radiation dermatitis. Seven patients treated by IMRT and 24 patients treated by 3DCRT experienced Grade 1 dysphagia. One patient treated by IMRT vs seven patients treated by 3DCRT experienced Grade 2 dysphagia. Among the patients treated by 3DCRT, one patient experienced Grade 1 radiation pneumonitis and two patients experienced Grade 1 acute mucositis (Tables 2 and 3).

No late toxicity was observed in patients treated by tomotherapy.

Three patients treated by 3DCRT experienced late toxicity [radiation pneumonitis, myocardial infarction (but in a patient also treated by anthracyclines) and hypothyroidism]. One patient presented disease progression after 3DCRT. Five cases of recurrence were observed in the 3DCRT group. One death was observed in the 3DCRT group, but it was not related to the initial disease or treatment.

One patient treated for HL by chemotherapy followed by radiotherapy at a dose of 30 Gy to the mediastinum presented disease progression 1 month after the completion of radiotherapy. The first mediastinal irradiation was delivered by intensity-modulated tomotherapy and the second irradiation delivered 30 Gy by 3DCRT. No major events were observed during radiotherapy. Late toxicity could not be analysed in this patient owing to death from disease progression seven months after the completion of the second mediastinal irradiation.

The choice and the evolution from 3DCRT to IMRT using tomotherapy could be explained with our previous findings.² The conformity index was better with tomotherapy (1.4) than with 3DCRT (2.9) ($p = 0.01$). The homogeneity index was also better on tomotherapy plans ($p = 0.03$) (Table 4). The observed high doses in the lungs and heart were reduced using tomotherapy (Table 5). Tomotherapy allowed a reduction of the maximum dose and a reduction of V_{15Gy} and V_{20Gy} for the right breast only ($p = 0.03$).²

DISCUSSION

The present study is realized to evaluate the evolution in our clinical practice, as well to evaluate the toxicity of both treatments “in the real life”. This study has shown that the optimal dose distribution and the reduction of high doses at the OAR changes our clinical attitude, and the choice is mostly to use high conformal radiotherapy techniques such as IMRT; in this case, helical tomotherapy.

Management of lymphoma raises a number of challenges in terms of efficacy and safety in view of the prognosis of this disease and the age of the patients concerned. Our study

Table 2. Acute toxicity

Radiotherapy technique	Overall rates <i>n</i> (%)	Radiodermatitis <i>n</i> (%)	Mucositis <i>n</i> (%)	Dysphagia <i>n</i> (%)	Pneumonitis <i>n</i> (%)
3DCRT	35 (71.4%)	Grade 1: 21 (42.8%)	Grade 1: 2 (4%)	Grade 1: 24 (48.9%) Grade 2: 7 (14.2%)	Grade 1: 1 (2%)
IMRT (tomotherapy)	11 (55%)	Grade 1: 9 (45%)	0	Grade 1: 7 (35%) Grade 2: 1 (5%)	0

3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

confirmed the evolution from 3DCRT to IMRT with reduction of the early and late side effects. Obviously, long-term follow-up is needed to confirm these results.

In the previous purely dosimetric study, the mean doses delivered to the PTV 30 Gy were equivalent with 3DCRT and tomotherapy with significantly improved V_{90} and V_{95} . We also reported that no significant difference in terms of mean dose to the right breast and left breast was observed between 3DCRT and tomotherapy, but, as expected, V_4 was higher with tomotherapy than with 3DCRT.² In our first study used to evaluate the impact of IF tomotherapy on coverage of target volumes and sparing of OARs we demonstrated improvement of the conformity index and homogeneity index for PTV 30 Gy.² The dosimetric study also demonstrated dosimetric advantages of tomotherapy in terms of cardiac protection, particularly in patients with anterior mediastinal lymph-node invasion. Tomotherapy allowed better sparing of breast, lung and healthy tissue volumes exposed to high doses.²

Several studies in the 1960s demonstrated the curative value of radiotherapy in these haematological malignancies.³ The treatment of aggressive B-cell lymphomas has been escalated over the past decade with the arrival of immunotherapy.

Up until the 2000s, standard treatment consisted of CHOP combination chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisone). The addition of rituximab to CHOP for the treatment of B-cell lymphoma improved overall survival.⁴ The RICOVER 60 trial (24493716)⁵ then studied addition of radiotherapy in bulky stage large B-cell lymphoma. In this trial, following chemotherapy with R-CHOP, radiotherapy delivered 36 Gy by an IF technique to initially invaded lymph nodes. The radiotherapy arm was found to be superior in terms of overall survival and progression-free survival.

An inverse rationale has been adopted for HL in order to achieve dose de-escalation.^{6–9} The trial H15⁹ decided to compare eight

cycles of escalated BEACOPP, six cycles of escalated BEACOPP and eight cycles of non-escalated BEACOPP. Patients with a persistent mass on CT scan were further investigated by PET scan, followed by 30 Gy of irradiation in case of positive PET. This trial confirmed six cycles of escalated BEACOPP as reference chemotherapy in view of the better overall survival compared with eight cycles of escalated BEACOPP owing to the toxicity related to this regimen. PET scan played a decisive role in the indication for radiotherapy in this trial and presented a good negative-predictive value.

The toxicity of radiotherapy can be reduced by: dose reduction, volume reduction and optimization by the use of IMRT.^{2,10}

In 2010, Arakelyan *et al*¹¹ reported the 10-year results of trial H 97E studying radiation dose de-escalation in patients with Stage 1 or 2 HL. The experimental arm received 36 Gy to the involved field and 24 Gy to adjacent fields. The experimental arm was compared with the control arm that received 40 Gy to initially IFs and 30 Gy to adjacent lymph-node fields and to a historical arm that received identical irradiation to that of the H97 E regimen. The 10-year results did not reveal any significant difference in terms of overall survival: 88.6% in the experimental arm and 97.8% in the control arm. The 10-year late toxicity rate was 0 in the experimental arm, 15.5% in the control arm and 11.1% in the historical arm ($p < 0.003$).

The involved-node (IN) radiation technique has also allowed a reduction of the target volume. The Institut Gustave Roussy team in Villejuif¹⁰ published a retrospective study including 47 patients treated between 2003 and 2010 with IN IMRT. This study concluded that the 5-year overall survival and 5-year progression-free survival were 96% and 92%, respectively. Three in-field recurrences and two out-of-field recurrences were observed in their series. In 2015, Kwon *et al*¹² demonstrated the efficacy of IN radiation therapy for large B-cell lymphoma after R-CHOP combination chemotherapy. This trial, conducted in 198 patients, compared R-CHOP combination chemotherapy only vs R-CHOP followed by IN radiation therapy, which improved overall survival and progression-free survival.

Guidelines have been defined for HL¹³ and NHL¹⁴ to standardize treatment between radiotherapy centres.

This type of IN radiation therapy has been made possible by the systematic use of PET scan in the initial staging and post-chemotherapy assessments. PET scan is more specific and more

Table 3. Late toxicity with median follow-up of 46 months for patients treated with three-dimensional conformal radiotherapy (3DCRT) and 10 months for intensity-modulated radiotherapy (IMRT) (tomotherapy group)

Radiotherapy technique	Heart	Lung	Skin
3DCRT	1 (2%)	1(2%)	0
IMRT (tomotherapy)	0	0	0

Table 4. Comparison of doses to the target volume with 30 Gy prescribed total dose

Parameters	3DCRT	Tomotherapy	<i>p</i> -value
PTV 30 Gy			
Mean Dose	30.1	30.3	NS
V ₉₀ (%)	98.1	99.9	0.03
V ₉₅ (%)	94.7	98.7	0.03
V ₁₀₀ (%)	63	52.2	NS
V ₁₀₇ (%)	1.2	0	NS
Conformity index	2.9	1.4	0.01
Homogeneity index	2.9	0.5	0.03

3DCRT, three-dimensional conformal radiotherapy; NS, non-significant; PTV, planning target volume.

sensitive than CT alone,¹⁵ allowing reduction of radiation fields. In 2007, Girinski et al¹⁶ demonstrated the major impact of fludeoxyglucose PET on delineation of IN radiation fields, as, in 36% of cases, fludeoxyglucose PET identified INs not detected by CT scan. PET was performed in all patients in our study before and after chemotherapy.

Aznar et al¹⁷ assessed the role of deep inspiration breath-hold and IMRT in patients with mediastinal HL. Their dosimetric study showed that deep inspiration breath-hold allowed a significant reduction of the dose to the heart and lung ($p < 0.001$). This study did not demonstrate any significant difference in terms of mean heart dose, heart V_{20Gy} and lung V_{20Gy}. The mean breast dose was increased with IMRT regardless of breathing technique. No second cancer was observed in patients treated by IMRT in our study. However, the follow-up of this study is too short to demonstrate this type of adverse event.

In terms of OARs, a reduction of the breast dose was observed,¹⁸ but no significant difference was observed for the mean doses to the lungs, thyroid or coronary arteries. However, the maximum OAR dose was decreased, which allowed the treatment of mediastinal lymph nodes while avoiding high heart doses.

Chelsea et al in 2015¹⁹ conducted a dosimetric study analysing the doses delivered to the lungs during mediastinal IMRT in patients treated for HL or NHL. In this study, the only clinical parameter influencing the development of radiation pneumonitis was the use of salvage chemotherapy. The other criteria were dosimetric, including mean lung dose, and volumes V₅ to V₂₀. IMRT allowed optimization on these criteria, in contrast with 3DCRT.

In the context of radiation therapy allowing lower maximum doses but higher low doses to OARs, Filippi et al, in 2015,²⁰ calculated the statistical risks of second cancers (lung, breast

Table 5. Comparison of mean and median dosimetric parameters for the heart and lungs

Parameters	3DCRT		Tomotherapy		<i>p</i> -value
	Mean	Median	Mean	Median	
Heart					
Mean dose (Gy)	11.7	8.4	9	7	0.03
Maximum dose (Gy)	30.3	30.6	30	31	NS
<i>V</i> _{4Gy} (%)	45	35.2	51.2	43.7	NS
<i>V</i> _{15Gy} (%)	36.4	26.5	24.7	13.1	0.03
<i>V</i> _{20Gy} (%)	34.1	23.1	18.6	6.6	0.01
<i>V</i> _{30Gy} (%)	16.6	0.3	3.4	0.2	NS
Lungs					
Mean dose (Gy)	9.6	8.7	9.5	11.1	NS
Maximum dose (Gy)	31.6	31.4	32.5	32.3	NS
<i>V</i> _{4Gy} (%)	42.4	35.6	62	63.8	0.03
<i>V</i> _{15Gy} (%)	28.2	26.1	24.8	27.7	NS
<i>V</i> _{20Gy} (%)	25.6	23.9	16.2	16.1	0.01
<i>V</i> _{30Gy} (%)	9.8	6.8	2.3	1.4	0.04

3DCRT, three-dimensional conformal radiotherapy; NS, non-significant.

and thyroid) and cardiac toxicity in patients treated for mediastinal HL without axillary-node involvement. These risks were compared between 3DCRT and volumetric-modulated arc therapy (VMAT). This study demonstrated a higher risk of lung cancer, but a lower risk of breast cancer with VMAT. No significant difference was observed between the two techniques for the other sites. The risk of cardiac toxicity was lower with VMAT.

The follow-up period of young patients treated by tomotherapy is relatively short and the risk of second cancers in young patients is not known. Following 3DCRT, increased breast cancer surveillance was initiated in the 1990s in view of the increased risk of breast cancer in long-term survivors of haematological malignancies treated by thoracic radiation therapy.^{21–23} Annual mammography is strongly advised or MRI in very young patients as part of the follow-up of lymphomas treated by mediastinal radiation therapy.²¹ In 2013, Ng et al²⁴ conducted a prospective study on the surveillance of HL. This study demonstrated a sensitivity of 68%, 67% and 94% for mammography alone, breast MRI alone and the combination of

the two examinations, respectively, with specificities of 93%, 94% and 90%, respectively. Local and distant surveillance are essential to detect late toxicity after tomotherapy or rapid-arc IMRT as a result of increasing low doses. Other authors discussed the evolution from 3DCRT to IMRT irradiation and the benefit of the volume definition and the use of new adapted techniques.²⁵ Probably the next step is to develop more interesting and safe techniques and propose the treatment by protons to some selected patients.²⁶

CONCLUSION

Improvement of radiation techniques for HL and NHL changed our clinical practice and appears to have improved acute and late clinical safety. Longer follow-up is necessary to evaluate very late toxicity.

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