

Can we Reduce the Toxicity of the Mediastinal Irradiation Using New Highly Conformal Techniques?

Victor Pernin, Sofia Zefkili, Dominique Peurien, Alain Fourquet and Youlia M Kirova*

Department of Radiation Oncology, Institute Curie, Paris, France

Abstract

Objectives: Three-Dimensional Conformal Radiotherapy (3DCRT) has been successfully used to treat Hodgkin's Lymphoma (HL) but treatment delivery is often complex and requires large fields that may result in significant exposure of normal tissues to ionizing radiation. The present study was undertaken to compare the dosimetry of Involved Field (IF) 3DCRT to HT in female patients treated for HL.

Materials/Methods: A total of 10 young female patients affected with early stage mediastinal HL and treated with IF radiotherapy after chemotherapy were selected from our database. For each patient, 3DCRT and HT plans were designed to deliver 30 Gy to the target volume and 36 Gy in case of residual masses. HT planning solutions were optimized by inverse planning with specific dose-volume constraints on OAR (breasts, lungs, heart). Dose-Volume Histograms (DVHs) were calculated and then compared, both for target and OAR by a statistical analysis (Wilcoxon's Test).

Results: Mean doses to the PTV were almost identical for all plans. Conformity index was better with HT and homogeneity index didn't differ. Mean dose to the breasts were increased with HT compared to 3DCRT (right breast: 3.28 vs 2.19, $p < 0.05$; left breast: 3.76 vs 2.81, $p < 0.05$) whereas no difference in mean doses appeared for heart, coronary arteries, lungs, thyroid and normal tissue. Maximal doses were reduced with HT for breasts (right breast: 19.9 vs 28.87, $p < 0.05$; left breast: 24.76 vs 30.29, $p < 0.05$) and spinal cord (20.87 vs 33.88, $p < 0.05$). Volume exposed to high doses was smaller with HT whereas volume exposed to low doses was smaller with 3DCRT. Pronounced benefits of HT in terms of heart sparing were observed for patients with lymph nodes anterior to the heart.

Conclusions: Although high dose to organ at risk was reduced with HT, increasing low dose especially to the breasts must be taken into account for IF HT. HT may be considered for large PTV especially when the anterior mediastinum is involved.

Keywords: Radiotherapy; Lymphoma; Toxicity; Second malignancies; Lung and Heart sparing

Introduction

Hodgkin lymphoma belongs to the group of malignancies with a high curability rate, as the 5-year relative survival is close to 84% for all forms of Hodgkin lymphoma combined, as a result of treatment based on chemotherapy and radiotherapy [1]. Progress in the management of Hodgkin lymphoma is related to the development of combination chemotherapy regimens and progress in radiotherapy techniques. However, these treatments are accompanied by late adverse effects such as cardiac toxicity and a risk of second cancers such as lung cancer and breast cancer for women [2-8]. The benefit-risk balance of the various treatment regimens must therefore be carefully assessed in order to achieve optimal disease control without increasing the risk of long-term sequelae.

The toxicity of radiotherapy can be decreased in three ways: reduce the dose, reduce treatment volumes and use innovative radiotherapy techniques such as Intensity-Modulated Radiotherapy (IMRT) [8]. The classical dose of 44 Gy has been reduced to 30-36 Gy. Similarly, treatment volumes have been reduced by replacing subtotal lymphoid irradiation by "involved-field" (IF) radiotherapy, which only includes lymph node territories initially invaded, then "involved-node" radiotherapy, only including invaded lymph nodes, which is currently at the stage of clinical evaluation [9]. In contrast, the respective roles of the various radiotherapy techniques in the treatment of Hodgkin's lymphoma differ from one radiotherapy centre to another and no consensus has been reached on this subject.

Several comparative dosimetric studies have demonstrated

improved coverage of target volumes and better sparing of certain organs at risk when IF radiotherapy is delivered by classical IMRT compared to three-dimensional conformal radiotherapy (3DCRT) for patients with supradiaphragmatic Hodgkin lymphoma, which could result in a reduction of late radiation-induced toxicity [10-12].

Few data are currently available concerning the use of tomotherapy in this indication [13]. The objective of this dosimetric study was to compare 3DCRT treatment plans and tomotherapy treatment plans in women treated by IF radiotherapy at a dose of 30 Gy and at a dose of 30 Gy plus 6 Gy for Hodgkin lymphoma in order to determine the place of tomotherapy in this indication.

Materials and Methods

Patient selection

This dosimetric study was based on 14 female patients with a

*Corresponding author: Youlia M. Kirova, Radiation Oncology, Institute Curie 26, Rue d'Ulm 75005 Paris, France, Tel: 331 44 32 46 37 ; Fax: 331 44 32 46 16; Email: youlia.kirova@curie.fr

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Characteristics	
Age	
- median	23 years [16-45]
Women	14 (100%)
Histology : - sclero-nodular	14 (100%)
Ann Arbor classification- stage II	14 (100%)
Chemotherapy :	
- 3 ABVD	4 (29%)
- 4 ABVD	7 (50%)
- 2 BEACOPP + 2 ABVD	3 (21%)
Irradiation at the dose of 30 Gy :	7 (50%)
- volume of PTV 30 Gy in 3D-CRT (median)	620 cm ³ [272-1536]
- médiastinal invasion alone	2 (14%)
- mediastinal and pericardial invasion	1 (7%)
- mediastinal and cervical invasion	3 (22%)
- mediastinal, cervical and axillary invasion	1 (7%)
Irradiation at the dose of 30 Gy + 6 Gy on the residual tumor :	7 (50%)
- volume of PTV 30 Gy in 3D-CRT (median)	506 [341-898]
- médiastinal invasion alone	3 (22%)
- mediastinal and pericardial invasion	2 (14%)
- mediastinal and cervical invasion	1 (7%)
- mediastinal, cervical and axillary invasion	1 (7%)

Table 1: Patient characteristics (n=14).

Parameters	Objectives
PTV	
- $V_{95\text{Gy}}$	95 %
Lungs	$V_{20\text{Gy}} < 35\%$ $V_{30\text{Gy}} < 20\%$
Heart	$V_{30\text{Gy}} < 40\%$ Mean dose < 20 Gy
Left and right parotid (if high cervical irradiation)	$V_{26\text{Gy}} \leq 50\%$
Canal médullaire	Maximum dose < 30 Gy

Dmax: maximum dose

An order of priority of OAR dose constraints was used for tomotherapy planning: in the case of a lateralised lesion, contralateral lung to the lesion > ipsilateral lung to the lesion > heart > ipsilateral breast > contralateral breast > parotid gland > spinal canal; in the case of a central lesion: left lung > right lung > heart > left breast > right breast > parotid gland > spinal canal.

Table 2: Dose constraints to target volumes and organs at risk.

median age of 23 years (range: 16-45 years) treated at Institute Curie for histologically documented stage II supradiaphragmatic Hodgkin lymphoma treated by a sequential combination of chemotherapy and radiotherapy. All patients were assessed by FDG PET before and after chemotherapy. All patients received ABVD and/or BEACOPP chemotherapy followed by “involved-field” radiotherapy to a total dose of 30 Gy with a 6 Gy boost to the residual tumour for 7 patients. Patient characteristics are shown in (Table 1).

Radiotherapy simulation

Simulation in the treatment position was based on two CT scans with a slice thickness of 3 mm about two weeks before starting radiotherapy: unenhanced CT followed by contrast-enhanced CT. Patients were positioned in the supine position with their arms above the head. A personalized immobilization mask was created for each patient. CT acquisition was performed under free breathing conditions.

Definition of radiotherapy volumes

CT and FDG PET performed before chemotherapy were fused

with CT performed during radiotherapy simulation. Contouring was performed with Eclipse software (Varian Medical Systems, Palo Alto, USA) for all treatment plans. The Clinical Target Volume (CTV) was determined by the same radiation oncologist. Clinical target volumes treated at the total dose of 30 Gy corresponded to initially invaded lymph nodes according to the “involved-field” modality with the following modifications: cervical lymph nodes situated above the larynx were irradiated only when they were initially invaded; right and left supraclavicular lymph nodes were irradiated only when the mediastinum was initially invaded; the lower limit of the mediastinal field did not extend beyond the level of the initially invaded lymph nodes [14]. In the case of residual tumour on contrast-enhanced CT and/or FDG PET, a clinical target volume was determined to continue irradiation to a dose of 6 Gy. For the Planning Target Volume (PTV), a 10 mm margin was added to the CTV. The following organs at risk were delineated: spinal canal, heart, left and right lung, oesophagus, trachea, thyroid, left and right breasts. The origins of the left and right coronary arteries were contoured according to the anatomical atlas. The dose to healthy tissues was also studied by measuring the doses delivered to the external contour (extending 5 cm on either side of the PTV) without the PTV.

Treatment plans

Dosimetries were calculated by Eclipse software (Varian Medical Systems, Palo Alto, CA, USA) and Tomotherapy software (Tomotherapy Incorporated, Madison, WI, USA) for tomotherapy plans. Dose constraints are presented in (Table 2).

3DCRT treatment plan

3DCRT ballistics are based on 6 MV or 20 MV beams using a multi-leaf collimator.

- In the absence of residual tumour after chemotherapy, a total dose of 30 Gy in 15 fractions (2 Gy per fraction) was prescribed to the isocentre of the 30 Gy PTV.
- In the presence of residual tumour after chemotherapy, an initial treatment plan delivering a dose of 30 Gy in 15 fractions (2 Gy per fraction) to the isocentre of the 30 Gy PTV was prescribed followed by a second plan delivering a dose of 6 Gy in 3 fractions (2 Gy per fraction) to the isocentre of the 36 Gy PTV.

To improve dosimetry, a field-in-field technique was used for treatment plans, when necessary. Dosimetries were calculated with Eclipse software using a convolution-superposition dose calculation algorithm in order to take into account the heterogeneities for a Varian Clinac accelerator.

Tomotherapy treatment plan: Tomotherapy treatment plans were elaborated for each patient using the same simulation CT scan as 3DCRT treatment plans. The same PTV and the same organs at risk were therefore used for 3DCRT and tomotherapy treatment plans. Tomotherapy treatment plans presented the following parameters: field width: 2.5 cm, pitch: 0.287 and modulation factor: 3. Dose constraints to target volumes and organs at risk were identical to those used for 3DCRT.

- In the absence of residual tumour after chemotherapy, a total dose of 30 Gy in 15 fractions (2 Gy per fraction) was prescribed to the 30 Gy PTV.
- In the presence of residual tumour after chemotherapy, simultaneous integrated boost (SIB) tomotherapy was

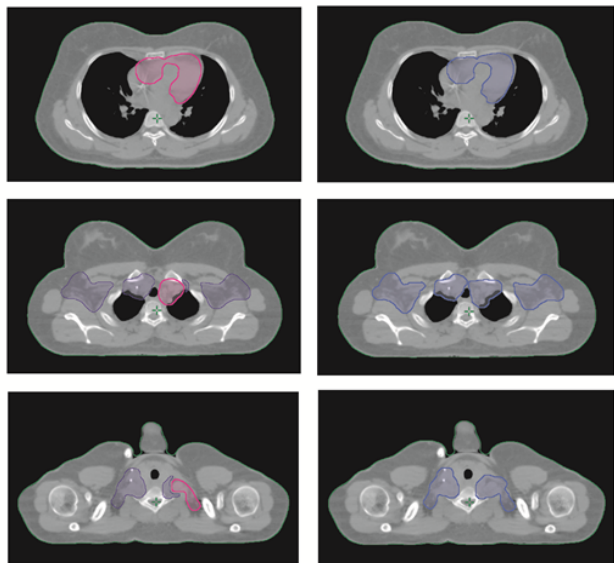


Figure 1: Tomotherapy plan (left) and 3DCRT plan (right): PTV_{tomo} 30 Gy (blue on left) with tomotherapy corresponds to PTV 30 Gy (blue on right) with 3DCRT minus PTV 36 Gy (magenta) with a 5 mm margin between PTV_{tomo} 30 Gy and PTV 36 Gy.

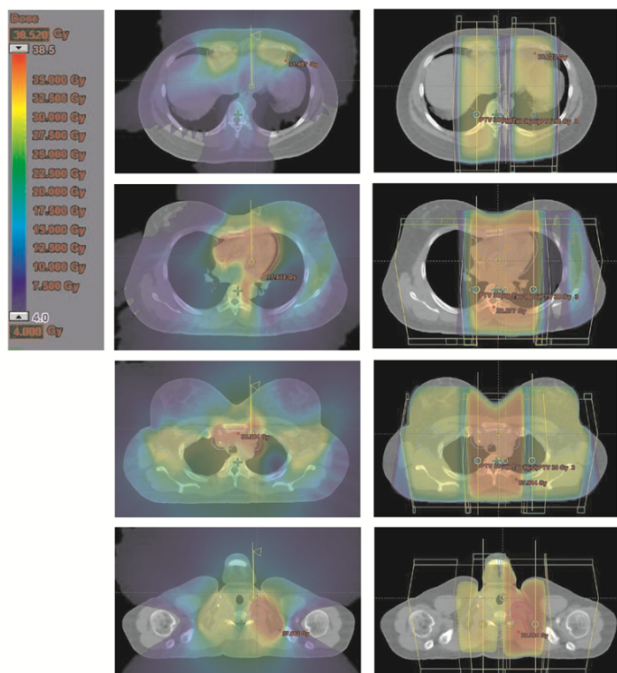


Figure 2: Comparison of isodoses from 4 Gy to 38.5 Gy between tomotherapy (left) and 3DCRT (right) treatment plans for a patient with Hodgkin lymphoma invading anterior mediastinal lymph nodes treated up to a dose of 36 Gy. This qualitative dosimetric comparison demonstrates an increase of the volumes exposed to a dose of 4 Gy with tomotherapy compared to 3DCRT.

performed. PTV_{tomo} 30 Gy and PTV 36 Gy were contoured separately (Figure 1-4). PTV_{tomo} 30 Gy in tomotherapy therefore corresponded to PTV 30 Gy in 3DCRT minus PTV 36 Gy with a 5 mm margin between PTV_{tomo} 30 Gy and PTV 36 Gy. With the SIB technique, treatments of PTV_{tomo} 30 Gy and PTV 36

Gy were combined in a single treatment plan. An alternative schedule to the sequential schedule was therefore defined: by using the linear quadratic model of cell survival, we calculated the total dose and the dose per fraction for PTV_{tomo} 30 Gy and PTV 36 Gy to ensure that they were biologically equivalent to the total dose delivered to PTV 30 Gy and PTV 36 Gy by 2 Gy fractions in the sequential schedule. A α/β ratio of 10 Gy was chosen for tumour response and a α/β ratio of 3 Gy was chosen for late response of normal tissues. A dose of 30.5 Gy in

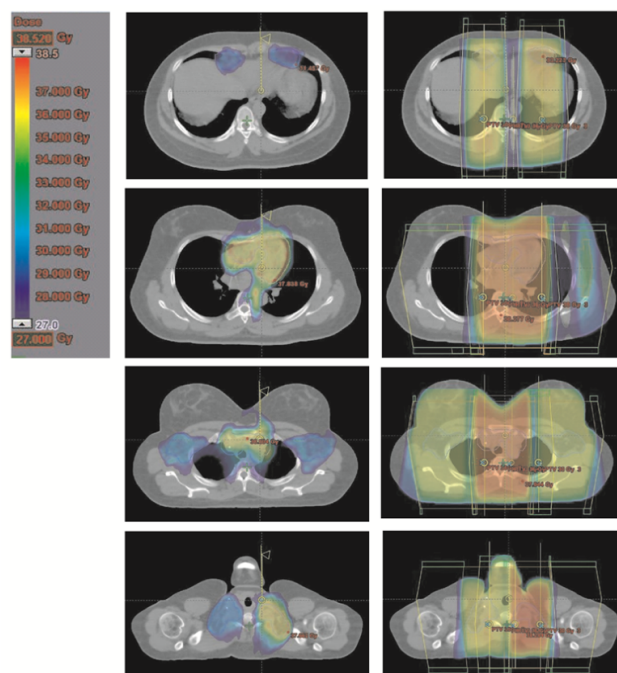


Figure 3: Comparison of isodoses from 27 Gy (90% of the dose to PTV 30 Gy) to 38.5 Gy (107% of the dose to PTV 36 Gy) between tomotherapy (left) and 3DCRT (right) treatment plans for a patient with Hodgkin lymphoma invading anterior mediastinal lymph nodes treated up to a dose of 36 Gy. This qualitative dosimetric comparison demonstrates an improvement of the conformation and homogeneity of the dose with tomotherapy compared to 3DCRT.

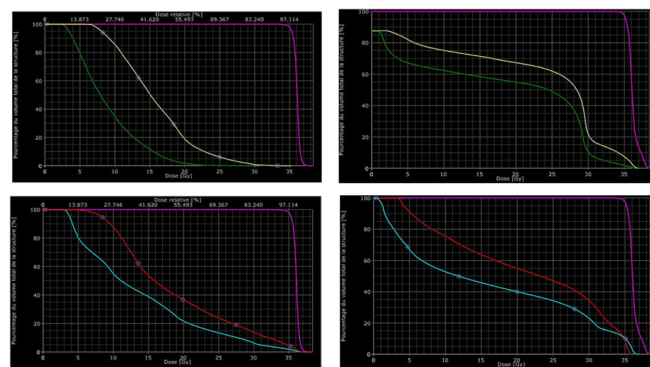


Figure 4: Comparison of dose-volume histograms of the tomotherapy (left) and 3DCRT (right) treatment plans for the same patient with Hodgkin lymphoma invading anterior mediastinal lymph nodes treated up to a dose of 36 Gy. Tomotherapy allowed a reduction of the volumes of heart (red) and lungs (blue), right breast (green) and left breast (yellow) exposed to high doses with a corresponding increase of the volumes exposed to low doses.

Paramètres	3D-CRT	Tomotherapy	P
PTV 30 Gy			
- Mean Dose	30.1 (± 0.4)	30.3 (± 0.9)	NS*
- V ₉₀ (%)	98.1 (± 2.3)	99.9 (± 0.1)	0.03
- V ₉₅ (%)	94.7 (± 4.4)	98.7 (± 0.8)	0.03
- V ₁₀₀ (%)	63 (± 16.5)	52.2 (± 5)	NS
- V ₁₀₇ (%)	1.2 (± 1.7)	0	NS
- Conformity index	2.9 (± 0.8)	1.4 (± 0.2)	0.01
- Homogeneity index	2.9 (± 4.2)	0.5 (± 0.07)	0.03

*NS: non-significant

Table 3: Comparison of doses to the target volume.

Parameters	3D-CRT				P
	Mean	Median	Mean	Median	
<i>Right breast</i>					
- Mean dose (Gy)	2.3	1.6	3.6	3.6	NS*
- Maximum dose (Gy)	26.4	29.5	18.4	20.4	0.03
- V _{4Gy} (%)	8.1	6.9	35.4	30.6	0.01
- V _{10Gy} (%)	7.3	5.3	10.5	6.1	NS
- V _{15Gy} (%)	5	3.9	2.1	0.6	0.03
- V _{20Gy} (%)	3.9	2.6	0.1	0.1	0.03
- V _{30Gy} (%)	0.5	1.3	0	0	NS
<i>Left breast</i>					
- Mean dose (Gy)	5	1.9	5.6	4.5	NS
- Maximum dose (Gy)	27.6	30.9	25	28.4	NS
- V _{4Gy} (%)	22.3	8.2	41.2	35	0.01
- V _{10Gy} (%)	18	5.7	22.8	15.8	NS
- V _{15Gy} (%)	14.9	3.2	10.9	6.4	NS
- V _{20Gy} (%)	13.1	2.6	5.5	1.6	NS
- V _{30Gy} (%)	1.1	0.5	0.3	0	NS

*NS: non-significant

Table 4: Comparison of mean and median dosimetric parameters for the breasts.

17 fractions (1.8 Gy per fraction) was therefore prescribed to PTV_{to} 30 Gy and a dose of 35.7 Gy in 17 fractions (2.1 Gy per fraction) was prescribed to PTV 36 Gy.

Dosimetries were calculated by inverse planning with Tomotherapy software. For each patient, tomotherapy treatment plans were optimized in order to be able to deliver irradiation under real conditions.

Evaluation

Three dosimetric studies were performed:

- Comparison of 3DCRT and tomotherapy treatment plans for 7 patients with no residual tumour treated at the dose of 30 Gy
- Comparison of 3DCRT and tomotherapy treatment plans for 7 patients with residual tumour treated at the dose of 30 Gy with a 6 Gy boost to the residual tumour.
- Comparison of 3DCRT and tomotherapy treatment plans for all patients (N=14)

Summation of 3DCRT treatment plans comprising PTV 30 Gy and PTV 36 Gy was performed to allow dosimetric comparison with SIB tomotherapy plans.

3DCRT and tomotherapy plans were compared quantitatively by analysis of physical doses on dose-volume histograms and qualitatively

by visualization of isodose curves. The parameters analysed for PTV included mean dose, V_{90%}, V_{95%}, V_{100%}, V_{107%} of the prescribed dose, Conformity Index (CI) and Homogeneity Index (HI).

The RTOG (Radiation Therapy Oncology Group) conformity index (CI) was defined by the following formula [15]:

$$Conformity\ index_{RTOG} = \frac{V_{RI}}{TV}$$

(TV: Target volume; V_{RI}: prescription isodose volume)

The RTOG homogeneity index (HI) was defined by the following formula:

$$Homogeneity\ index_{RTOG} = \frac{Imax}{RI}$$

(Imax: Maximum isodose in the target volume; RI: Reference Isodose)

Parameters analysed for organs at risk included: mean dose, maximum dose, V_{4Gy}, V_{10Gy}, V_{20Gy}, V_{30Gy}, and V_{36Gy} for the right breast, left breast, lungs, heart, origin of the right coronary artery, origin of the left coronary artery, oesophagus and healthy tissues. The following parameters were analysed for the thyroid: mean dose, median dose, V_{18Gy}, V_{26Gy} and the parameters analysed for the spinal canal and trachea were maximum dose and mean dose, respectively.

Statistical analysis

Median values for each dosimetric parameter derived from dose-volume histograms of 3DCRT and tomotherapy treatment plans were compared by a nonparametric test for paired series (Wilcoxon test) using GraphPad Prism 5 software (Graph Pad Software, San Diego, CA, USA). Differences were considered to be significant for p<0.05.

Results

Evaluation of tomotherapy and 3DCRT treatment plans at the dose of 30 Gy

Doses to target volumes: The mean doses delivered to the PTV 30 Gy were equivalent with 3DCRT and tomotherapy with significantly improved V₉₀ and V₉₅. The Conformity Index (CI) 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 3).

Doses to organs at risk

- Right and left breasts

No significant difference in terms of the mean dose to the right breast and the left breast was observed between 3DCRT and tomotherapy, but, as expected, the V₄ was higher with tomotherapy than with 3DCRT. 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) (Table 4).

- Lungs

Tomotherapy did not allow any reduction of the mean dose to the lungs. Volumes exposed to low doses were increased with tomotherapy and volumes exposed to doses greater than or equal to 20 Gy were increased with 3DCRT. The median V_{20Gy} with tomotherapy and 3DCRT was therefore 16.2% and 23.9%, respectively (p=0.01) (Table 5).

- Heart and origins of the coronary arteries

A reduction of the mean doses to the heart and V_{15Gy} and V_{20Gy} was

Parameters	3D-CRT		Tomotherapy		P
	Mean	Median	Mean	Median	
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
- V _{4 Gy} (%)	42.4	35.55	62	63.8	0,03
- V _{10 Gy} (%)	31.7	28.9	38.2	46.3	0,04
- V _{15 Gy} (%)	28.2	26.1	24.8	27.7	NS
- V _{20 Gy} (%)	25.6	23.9	16.2	16.1	0,01
- V _{30 Gy} (%)	9.8	6.8	2.3	1.4	0,04

* non significant

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

Parameters	3D-CRT		Tomotherapy		P
	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*
- V _{4 Gy} (%)	45	35.2	51.2	43.7	NS
- V _{10 Gy} (%)	39.6	29.9	33.7	26.2	NS
- V _{15 Gy} (%)	36.4	26.5	24.7	13.1	0.03
- V _{20 Gy} (%)	34.1	23.1	18.6	6.6	0.01
- V _{30 Gy} (%)	16.6	0.3	3.4	0.2	NS
Origin of right coronary artery					
- Mean dose (Gy)	24.4	29.6	21.4	25.8	NS
- Maximum dose (Gy)	25.4	29.8	22.9	27	NS
- V _{4 Gy} (%)	85.7	100	85.7	100	NS
- V _{10 Gy} (%)	85.7	100	77.9	100	NS
- V _{15 Gy} (%)	84.2	100	71.4	100	NS
- V _{20 Gy} (%)	81.2	100	71.4	100	NS
- V _{30 Gy} (%)	37.6	31.8	25	0	NS
Origin of left coronary artery					
- Mean dose (Gy)	24.6	26.7	22.9	24.1	NS
- Maximum dose (Gy)	26.4	30	25.6	27.4	NS
- V _{4 Gy} (%)	85.7	100	96.8	100	NS
- V _{10 Gy} (%)	84.2	100	85.5	100	NS
- V _{15 Gy} (%)	82.1	100	84.2	100	NS
- V _{20 Gy} (%)	79.7	100	77	100	NS
- V _{30 Gy} (%)	34.1	19.9	30	0	NS

* non-significant

Table 6: Comparison of mean and median dosimetric parameters for the heart and the origins of the coronary arteries.

observed with tomotherapy compared to 3DCRT (p=0.03, p=0.03 and p=0.01, respectively). No significant difference was observed between tomotherapy and 3DCRT in terms of dosimetric parameters of the origins of the coronary arteries (Table 6).

- Oesophagus

No significant difference in terms of dosimetric parameters of the oesophagus was observed between tomotherapy and 3DCRT (Table 7).

- Spinal canal, trachea and thyroid

The maximum dose to the spinal canal was lower with tomotherapy than with 3DCRT (21.3 Gy vs 31.2 Gy; p=0.01). No significant difference in terms of the mean dose to the trachea was demonstrated, while the mean dose to the thyroid was lower with tomotherapy (26.1 Gy vs 28 Gy; p=0.03) (Table 8).

Healthy tissues

A significant increase in the volumes exposed to a dose of 4 Gy was observed with tomotherapy compared to 3DCRT (62.4% vs 35.1%; p=0.03). On the other hand, larger volumes were exposed to doses greater than or equal to 15 Gy with 3DCRT compared to tomotherapy (p=0.01) (Table 9).

Evaluation of tomotherapy and 3DCRT treatment plans at the dose of 30 Gy with a 6 Gy boost to the residual tumour

Doses to target volumes

Dosimetric parameters of the PTV 30 Gy were equivalent with 3DCRT and tomotherapy. For PTV 36 Gy, the conformity index (CI) was better with tomotherapy than with 3DCRT (1.2 vs 5; p=0.01), with no difference in terms of the homogeneity index (Table 10).

Doses to organs at risk

- Right and left breasts

No significant difference in terms of mean dose to the right breast and the left breast was observed between 3DCRT and tomotherapy. Maximum doses were significantly lower with tomotherapy (p=0.01). V_{4Gy} and V_{10Gy} were significantly increased with tomotherapy compared to 3DCRT (p=0.01), while V_{20Gy} and V_{30Gy} were significantly decreased (Table 11).

- Lungs

Tomotherapy did not decrease the mean dose delivered to the

ParametersAR	3D-CRT		Tomotherapy		P
	Mean	Median	Mean	Median	
Esophagus					
- Mean dose (Gy)	22.8	24	21.1	22	NS*
- Maximum dose (Gy)	31.4	31.5	31.9	31.8	NS
- V _{4 Gy} (%)	80.3	84.1	81.3	85.4	NS
- V _{10 Gy} (%)	76.9	80.8	73.2	74.5	NS
- V _{15 Gy} (%)	75.7	79.3	70	71.9	NS
- V _{20 Gy} (%)	73.4	77.9	65.8	67.6	NS
- V _{30 Gy} (%)	37.1	20.6	32.7	31.6	NS

* Non-significant

Table 7: Comparison of mean and median dosimetric parameters for the esophagus.

Parameters	3D-CRT		Tomotherapy		P
	Mean	Median	Mean	Median	
Spinal canal					
- Maximum dose (Gy)	31.6	31.2	22.6	21.3	0.01
Trachea					
- Mean dose (Gy)	31.4	28.7	31.5	28	NS*
Thyroid					
- Mean dose (Gy)	26	28	24	26.1	0.03
- V _{18 Gy} (%)	85.9	97.6	76	84.9	NS
- V _{25 Gy} (%)	75	80.3	66.7	68.5	NS

* Non-significant

Table 8: Comparison of mean and median dosimetric parameters for the spinal canal, trachea and thyroid.

Parameters	3D-CRT		Tomotherapy		P
	Mean	Median	Mean	Median	
Healthy tissue					
- Mean dose (Gy)	8.2	7	7.9	8.1	NS*
- Maximum dose (Gy)	32.5	32.1	33.4	33.4	NS
- V _{4 Gy} (%)	35.8	35.1	54.2	62.4	0,03
- V _{10 Gy} (%)	28	23.8	29.8	29.1	NS
- V _{15 Gy} (%)	24.6	21	18.7	16.5	0,01
- V _{20 Gy} (%)	21.7	18.4	11.7	9.6	0,01
- V _{30 Gy} (%)	7	4.7	1.1	1	0,01

* Non-significant

Table 9: Comparison of mean and median dosimetric parameters for healthy tissues.

Parameters	3D-CRT	Tomotherapy	P
PTV 30 Gy			
- V ₉₀ (%)	99.9 (± 0.3)	99.8 (± 0.3)	NS*
- V ₉₅ (%)	98.8 (± 1.5)	99 (± 0.9)	NS
- V ₁₀₀ (%)	86.7 (± 13.2)	79.9 (± 8.1)	NS
PTV 36 Gy			
- Mean dose	36.5 (± 0.2)	36 (± 0.1)	0.01
- V ₉₀ (%)	99.6 (± 0.5)	100	NS
- V ₉₅ (%)	98.6 (± 2.1)	99 (± 1.5)	NS
- V ₁₀₀ (%)	80 (± 12.6)	54.9 (± 3.9)	0.03
- V ₁₀₇ (%)	0	0	NS
- Conformity index	5 (± 1.2)	1.2 (± 0.2)	0.01
- Homogeneity index	0.7 (± 0.2)	0.5 (± 0.1)	NS

* Non-significant

Table 10: Comparison of doses to target volumes.

Parameters	3D-CRT		Tomotherapy		P
	Mean	Median	Mean	Median	
Right breast					
- Mean dose (Gy)	52.1	1.9	4.3	3	NS*
- Maximum dose (Gy)	32.29	32.4	21.8	21.8	0.01
- V _{4 Gy} (%)	19.5	8	39.8	24.1	0.01
- V _{10 Gy} (%)	15.8	6	11.6	4.7	NS
- V _{15 Gy} (%)	13.8	3.9	4.3	1.9	NS
- V _{20 Gy} (%)	12.5	3.2	1.2	0	0.01
- V _{30 Gy} (%)	3.2	0.9	0	0	0.03
- V _{36 Gy} (%)	0	0	0	0	-
Left breast					
- Mean dose (Gy)	6,5	2	5.9	2.6	NS
- Maximum dose (Gy)	34.3	34.8	26.6	16,2	0.01
- V _{4 Gy} (%)	23.8	8.3	41.5	25.7	0.01
- V _{10 Gy} (%)	19.3	6.2	22.5	0.4	NS
- V _{15 Gy} (%)	17.4	5.1	13.6	0	NS
- V _{20 Gy} (%)	16	4.1	6.2	0	0.04
- V _{30 Gy} (%)	6.7	4.5	0.4	0	0.03
- V _{36 Gy} (%)	1.6	0	0.1	0	NS

* Non-significant

Table 11: Comparison of mean and median dosimetric parameters for the breasts.

lungs. Volumes exposed to low doses were significantly increased with tomotherapy (V_{4Gy} and V_{10Gy}) and volumes exposed to doses greater than or equal to 20 Gy were significantly increased with 3DCRT (Table 12).

- Heart and origins of the coronary arteries

A reduction of V_{20Gy} for the heart was only observed with tomotherapy compared to 3DCRT (23.6% vs 35.9%; p=0.01). No significant difference in terms of dosimetric parameters of the origins of the coronary arteries was observed between tomotherapy and 3DCRT (Table 13).

- Oesophagus

Tomotherapy allowed a slight reduction of the mean dose delivered to the oesophagus compared to 3DCRT (21.7 Gy vs 26 Gy; p=0.01). No significant difference was observed between tomotherapy and 3DCRT for the other dosimetric parameters of the oesophagus (Table 14).

- Spinal canal, trachea and thyroid

A significant reduction of the maximum dose to the spinal canal

was observed with tomotherapy compared to 3DCRT (24.2 Gy vs 36.9 Gy; p=0.01) and a reduction of the mean dose to the trachea was observed with tomotherapy compared to 3DCRT (27.1 Gy vs 31.5 Gy; p=0.01). The mean dose to the thyroid was significantly increased with tomotherapy (23.6 Gy vs 15.4 Gy; p=0.03) (Table 15).

- Healthy tissues

A significant increase of volumes exposed to a dose of 4 Gy was observed with tomotherapy compared to 3DCRT (58.9% vs 31.2%; p=0.01), while significantly larger volumes were exposed to doses greater than or equal to 15 Gy with 3DCRT compared to tomotherapy (Table 16).

Evaluation of tomotherapy and 3DCRT treatment plans for the 14 patients

Right and left breasts: No significant difference in terms of the mean dose to the right breast and left breast was observed between

Parameters	3D-CRT		Tomotherapy		P
	Mean	Median	Mean	Median	
Lungs					
- Mean dose (Gy)	9.7	8.6	10.3	10.3	NS*
- Dmax (Gy)	36.8	37.4	37.3	37.5	NS
- V _{4 Gy} (%)	40.9	36.6	66.3	60.9	0.01
- V _{10 Gy} (%)	31.6	29.6	44.4	42.8	0.01
- V _{15 Gy} (%)	28.1	27.2	24.5	27.7	NS
- V _{20 Gy} (%)	25.2	25.6	16	16.6	0.01
- V _{30 Gy} (%)	13.4	12.4	3.6	3.3	0.01
- V _{36 Gy} (%)	1.4	1.1	0.2	0.1	0.03

* Non-significant

Table 12: Comparison of mean and median dosimetric parameters for the lungs.

Parameters	3D-CRT		Tomotherapy		P
	Mean	Median	Mean	Median	
Heart					
- Mean dose (Gy)	11.4	12.2	10.5	10.7	NS*
- Maximum dose (Gy)	34.2	35.3	34.4	34.2	NS
- V _{4 Gy} (%)	45.5	45	54.2	44.7	NS
- V _{10 Gy} (%)	39.4	40.6	41.6	37.6	NS
- V _{15 Gy} (%)	34.8	38.4	30.9	31.1	NS
- V _{20 Gy} (%)	31.8	35.9	23.2	23.6	0,01
- V _{30 Gy} (%)	14.7	10.1	8.3	7.2	NS
- V _{36 Gy} (%)	1.3	0	0.4	0	NS
Origin of right coronary artery					
- Mean dose (Gy)	28.8	32.2	29.3 (± 10.7)	32,3	NS
- Maximum dose (Gy)	29,5 (± 11.9)	34	30.9 (± 9.8)	34	NS
- V _{4 Gy} (%)	85.7 (± 37.8)	100	97.7 (± 6.1)	100	NS
- V _{10 Gy} (%)	85.7 (± 37.8)	100	85.7 (± 37.8)	100	-
- V _{15 Gy} (%)	85.7 (± 37.8)	100	85.7 (± 37.8)	100	-
- V _{20 Gy} (%)	85.7 (± 37.8)	100	85.7 (± 37.8)	100	-
- V _{30 Gy} (%)	71.4 (± 38.8)	100	74.8 (± 43.5)	100	NS
- V _{36 Gy} (%)	16.8 (± 37.2)	0	18.8 (± 23.7)	0	NS
Origin of left coronary artery					
- Mean dose (Gy)	26.8	29.5	26.9	28.3	NS
- Maximum dose (Gy)	29.9	30	28.2	29.7	NS
- V _{4 Gy} (%)	98.5	100	100	100	NS
- V _{10 Gy} (%)	93.2	100	100	100	NS
- V _{15 Gy} (%)	86.1	100	100	100	NS
- V _{20 Gy} (%)	77.1	100	86	100	NS
- V _{30 Gy} (%)	42.9	0.8	40.5	0	NS
- V _{36 Gy} (%)	0	0	10.2	0	NS

* Non-significant

Table 13: Comparison of mean and median dosimetric parameters for the heart and the origins of the coronary arteries.

Parameters	3D-CRT		Tomotherapy		P
	Mean	Median	Mean	Median	
Esophagus					
- Mean dose (Gy)	25.5	26	22,1	21.7	0.01
- Maximum dose (Gy)	36.6	36.7	36	36.9	NS*
- V _{4 Gy} (%)	84	90	85,2	85.5	NS
- V _{10 Gy} (%)	79,4	80.3	77,1	74.3	NS
- V _{15 Gy} (%)	76.9	78.6	70,7	66.8	NS
- V _{20 Gy} (%)	74.5	76.6	64,5	63.8	NS
- V _{30 Gy} (%)	54.9	52.6	36,7	35.1	NS
- V _{36 Gy} (%)	12.7	9,8	3.7	3.4	NS

* Non-significant

Table 14: Comparison of mean and median dosimetric parameters for the esophagus.

Parameters	3D-CRT		Tomotherapy		P
	Mean	Median	Mean	Median	
Spinal canal					
- Maximum dose (Gy)	36.1	36.9	23.6	24.2	0.01
Trachea					
- Mean dose (Gy)	30.4	31.5	27	27.1	0.01
Thyroid					
- Mean dose (Gy)	20.4	15.4	20.1	23.6	0,03
- V _{18 Gy} (%)	59.5	45.8	58.4	59.5	NS*
- V _{25 Gy} (%)	58.1	43.1	47.8	37.3	NS

* Non-significant

Table 15: Comparison of mean and median dosimetric parameters for the spinal canal, trachea and thyroid.

Parameters	3D-CRT		Tomotherapy		P
	Mean	Median	Mean	Median	
Healthy tissue					
- Mean dose (Gy)	8.5	8.3	8.5	8.3	NS*
- Maximum dose (Gy)	38	37.9	37.4	38.1	NS
- V _{4 Gy} (%)	32.4	31.2	58.4	58.9	0.01
- V _{10 Gy} (%)	27.2	27.3	33.7	33.6	NS
- V _{15 Gy} (%)	24.2	24.6	18.7	16.4	0.01
- V _{20 Gy} (%)	21.7	22.7	14.6	12.3	0.04
- V _{30 Gy} (%)	11.2	12.2	2.7	1.3	0.02
- V _{36 Gy} (%)	1.5	0.6	0.2	0.1	0.01

* Non-significant

Table 16: Comparison of mean and median dosimetric parameters for healthy tissues.

tomotherapy and 3DCRT, but a significant increase of V_{4Gy} (p=0.0001) and a significant reduction of V_{20Gy} and V_{30Gy} were observed with tomotherapy compared to 3DCRT (Table 17).

Lungs: Tomotherapy did not allow any reduction of the mean dose to the lungs. Volumes exposed to low doses (V_{4Gy} and V_{10Gy}) were significantly increased with tomotherapy and volumes exposed to doses greater than or equal to 20 Gy were significantly increased with 3DCRT (Table 18).

Heart

Tomotherapy allowed a reduction of the mean dose to the heart compared to 3DCRT (7.4 Gy vs 9.6 Gy; p=0.02). V_{4Gy} was significantly increased with tomotherapy and volumes exposed to doses greater than or equal to 20 Gy were significantly increased with 3DCRT (Table 19).

Oesophagus

Tomotherapy allowed a slight reduction of the mean dose delivered to the oesophagus compared to 3DCRT (21.9 Gy vs 24.7 Gy; p=0.005) together with a reduction of V_{20Gy} (65.6% vs 76.5%; p=0.02) (Table 20).

Spinal canal, trachea and thyroid

A significant reduction of the maximum dose to the spinal canal was observed with tomotherapy compared to 3DCRT (23.7 Gy vs 33.4 Gy; p=0.0001). A significant reduction of the mean dose to the trachea was observed with tomotherapy compared to 3DCRT (28.1 Gy vs 30.1 Gy; p=0.02). The thyroid volume receiving a dose of 25 Gy (V_{25Gy}) was significantly decreased with tomotherapy (53.9% vs 80.3%; p=0.005) (Table 21).

Healthy tissues

No significant difference in mean doses to healthy tissues was observed between tomotherapy and 3DCRT treatment plans. A significant increase of V_{4Gy} and V_{10Gy} was observed with tomotherapy compared to 3DCRT. Significantly larger volumes were exposed to doses greater than or equal to 15 Gy with 3DCRT compared to tomotherapy (Table 22).

Discussion

Compared to 3DCRT, tomotherapy delivered low doses of 4 Gy to

Parameters	3D-CRT		Tomotherapy		P
	Mean	Median	Mean	Median	
Right breast					
- Mean dose (Gy)	3.7	1.9	4	3.3	NS*
- Maximum dose (Gy)	29.7	30.8	20.1	20.8	0.0002
- V _{4 Gy} (%)	15.2	8.6	37.2	24.9	0.0001
- V _{10 Gy} (%)	11.6	6.3	11.1	5.4	NS
- V _{15 Gy} (%)	9.4	4.2	3.2	1.3	0.004
- V _{20 Gy} (%)	8.2	3.4	0.7	0	0.0002
- V _{30 Gy} (%)	1.9	0	0	0	0.01
Left breast					
- Mean dose (Gy)	5.7	2.5	5.7	4.6	NS
- Maximum dose (Gy)	31	31.5	25.8	27	0.0009
- V _{4 Gy} (%)	23	10.8	41.9	33.5	0.0001
- V _{10 Gy} (%)	18.7	7.8	22.7	13.8	NS
- V _{15 Gy} (%)	16.2	5	12.2	4.7	NS
- V _{20 Gy} (%)	14.5	4	5.8	1.5	0.0024
- V _{30 Gy} (%)	3.9	1	0.4	0	0.01

* Non-significant

Table 17: Comparison of mean and median dosimetric parameters for the breasts.

Parameters	3D-CRT		Tomotherapy		P
	Mean	Median	Mean	Median	
Lungs					
- Mean dose (Gy)	9.6	9.5	9.9	10.5	NS*
- Maximum dose (Gy)	34.2	32.8	34.9	35.6	NS
- V _{4 Gy} (%)	41.6	38.3	64.1	62.3	0.0002
- V _{10 Gy} (%)	31.7	32	41.3	42.9	0.0004
- V _{15 Gy} (%)	28.1	28.9	26.7	27.7	NS
- V _{20 Gy} (%)	25.4	26.3	16.1	16.3	0.0001
- V _{30 Gy} (%)	11.6	12.1	2.9	2.8	0.0006

* Non-significant

Table 18: Mean comparison and dosimetric parameter medians for the lungs.

Parameters	3D-CRT		Tomotherapy		P
	Mean	Median	Mean	Median	
Heart					
- Mean dose (Gy)	11.5	9.6	9.7	7.4	0.02
- Maximum dose (Gy)	32.3	31.6	32.2	31.9	NS*
- V _{4 Gy} (%)	45.2	42.4	54.7	44.2	0.002
- V _{10 Gy} (%)	39	33.6	37.6	27.9	NS
- V _{15 Gy} (%)	35.6	31.1	27.8	21.1	0.02
- V _{20 Gy} (%)	33	28.5	20.9	16	0.0001
- V _{30 Gy} (%)	15.6	5.2	5.8	2.7	0.04

* Non-significant

Table 19: Comparison of mean and median dosimetric parameters for the heart.

Parameters	3D-CRT		Tomotherapy		P
	Mean	Median	Mean	Median	
Esophagus					
- Mean dose (Gy)	24.1	24.7	21.6	21.9	0.005
- Maximum dose (Gy)	34	33.9	34	33.4	NS*
- V _{4 Gy} (%)	82.1	84.2	83.2	85.5	NS
- V _{10 Gy} (%)	78.1	79.8	75.2	74.4	NS
- V _{15 Gy} (%)	76.3	78.2	70.3	69.5	NS
- V _{20 Gy} (%)	74	76.5	65.1	65.6	0.02
- V _{30 Gy} (%)	46	50.8	34.7	33.5	NS

* Non-significant

Table 20: Comparison of mean and median dosimetric parameters for the esophagus.

Parameters	3D-CRT		Tomotherapy		P
	Mean	Median	Mean	Median	
Spinal canal					
- Maximum dose (Gy)	33.9	33.4	23.1	23.7	0.0001
Trachea					
- Mean dose (Gy)	29.6	30.1	27.5	28.1	0.02
Thyroid					
- Mean dose (Gy)	23.2	28	22.4	24.1	NS*
- V _{18 Gy} (%)	72.7	97	67.2	75	NS
- V _{25 Gy} (%)	66.6	80.3	57.3	53.9	0.005

* Non-significant

Table 21: Comparison of mean and median dosimetric parameters for the spinal canal, trachea and thyroid.

Parameters	3D-CRT		Tomotherapy		P
	Mean	Median	Mean	Median	
Healthy tissue					
- Mean dose (Gy)	8.3	7.8	8.1	8.2	NS*
- Maximum dose (Gy)	35.2	35.8	35.4	34.5	NS
- V _{4 Gy} (%)	34.1	31.7	56.3	60.3	0.0002
- V _{10 Gy} (%)	27.6	26.1	31.8	29.7	0.02
- V _{15 Gy} (%)	24.4	23.5	19.7	16.4	0.005
- V _{20 Gy} (%)	21.7	21.3	13.1	9.8	0.0004
- V _{30 Gy} (%)	9.1	9.4	1.9	1.3	0.001

* Non-significant

Table 22: Comparison of mean and median dosimetric parameters for healthy tissues.

larger volumes of the breast, lungs and healthy tissues, while decreasing the volumes exposed to intermediate-to-high doses. No correlation was observed between breast volumes and the dose received by the breasts in this study.

The heart was also more effectively spared by tomotherapy, as the mean dose to the heart was comparable to that delivered by 3DCRT, but with a 27% reduction of V_{20Gy} (23.2% vs 31.8%; p=0.01). Although tomotherapy allowed better protection of the heart and therefore a lower risk of cardiac complications, it failed to lower the risk of coronary artery disease.

The relative reduction of the maximum dose received by the spinal canal was 32% (23.1 Gy vs 33.9 Gy; p=0.0001); this dose reduction was related to dose constraints determined before inverse planning. Reduction of the dose delivered to the spinal cord can be useful when subsequent irradiation is necessary.

Quantitative comparisons with dosimetric studies performed according to the “involved-field” concept comparing IMRT and 3DCRT techniques are difficult due to the small number of patients included, the variable total radiation doses and the use of different dosimetric parameters in these studies

Better heart sparing, especially in the presence of anterior mediastinal invasion, has been reported by other dosimetric studies evaluating IMRT. In the study by Goodman et al., IMRT allowed a reduction of the mean dose to the heart and lungs [10]. According to Girinsky et al., the mean V_{30Gy} to the heart was 14% with IMRT and 19.7% with 3DCRT, which corresponds to a 29% relative reduction [11]. Nieder et al. reported that IMRT failed to improve coverage of target volumes compared to 3DCRT, but allowed a reduction of the median dose to the heart, a reduction of the breast volumes exposed to high doses and an increase of breast volumes exposed to low doses [16]. De Sanctis et al. also reported an increase of the breast volumes exposed to low-dose irradiation (V_{5Gy} and V_{10Gy}) [12].

This reduction of the doses delivered to the heart with tomotherapy was achieved at the cost of an increased volume of organs at risk exposed to low doses, especially the breasts and lungs. Although a reduction of the volumes exposed to intermediate-to-high doses with 3DCRT may be associated with a decreased risk of second cancer, the effect of an increased volume of healthy tissues exposed to low doses of radiotherapy remains unknown at the present time [17-19]. Consequently, in the absence of data concerning the risk of second cancer, the benefit-risk balance of “involved-field” tomotherapy appears to be favourable when the heart is included in irradiation fields in order to decrease long-term cardiac toxicities, but with no associated reduction of the risk of coronary artery disease and myocardial infarction [20,21]. More generally, age at the time of diagnosis, the presence of cardiac or pulmonary comorbidity, the patient’s anatomy and staging of Hodgkin lymphoma must be taken into account in the choice of radiotherapy technique in order to achieve an optimal benefit-risk balance.

In order to lower the risk of subsequent breast cancer, it may be recommended to contour the mammary gland and store the dose-volume histogram in the patient’s file, especially in the case of young women under the age of 30 due to the increased radio sensitivity of the breast at this age.

The choice of radiotherapy technique to treat supradiaphragmatic Hodgkin lymphoma must be based on individual criteria such as anatomy, age at the time of diagnosis and the presence of cardiac or pulmonary comorbidity. Approaches comprising the use of IMRT techniques and reduction of irradiation volumes by “involved-node” radiotherapy are currently under evaluation in order to further reduce late toxicities of irradiation for patients with Hodgkin lymphoma [22].

Conclusion

This is the first study to evaluate the impact of “involved-field” tomotherapy on coverage of target volumes and sparing of organs at risk. This study demonstrated improvement of the conformity index and homogeneity index for PTV 30 Gy and improvement of the conformity index for PTV 36 Gy. 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.

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