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Toxicity and risk of induced second cancer for Hodgkin Lymphoma (HL) treatment using new modalities of radiotherapy for young patients

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ABSTRACT

During the last decade new modalities of radiotherapy were implemented in different radiation oncology department in Algeria. Most of them are based on the concept of inverse modulated radiotherapy (IMRT), volumetric modulated radiotherapy (VMAT) and or helical tomotherapy (HT). The purpose of this study is to explore the trade-offs between cancer care, toxicities of organ's at risk and the risk of induced second cancer in case of hodgkin lymphoma.
A cohort of 20 young patients treatment plans using Field-in-Field radiotherapy (3D-FIF) were assessed using mathematical model to predict the toxicity calculated by the normal tissue complication probability (NTCP) using Lyman-Kutcher-Burman model and the estimated absolute risk (EAR) for the organ's at risk in case of Rt and Lt lung. The associated induced second cancer risk was computed using the organ equivalent dose (OED) defined as a mechanistic model in the A Bomb survivors and hodgkin's patients data relevant to radiotherapy. The results showed that the mean dose received at right and left lung are (7.81±4.6) Gy and (8.74±3.8) Gy respectively. The calculated NTCP for pneumonitis lung end point were 4.2% and 4.5% which correspond to EUD mean = (5.98±3.16) and (6.21±3.49) Gy. The associated estimated absolute risk of induced second cancer was obtained for Right and left lung and are 4.39±3.24 and 5.54±3.41 per 10000 P-Y. Higher risk was observed for three patients of the studied cohort. EAR and toxicity modelling is a better way to evaluate Hodgkin's lymphoma specially when it comes of young patients where the risk of induced second cancer is more important.

1. Introduction

Hodgkin Lymphoma registers 83087 cases in the world in 2020 year. In Algeria, we register 40000 new cases of cancer in 2020. In 2018 we registered 832 cases of Hodgkin lymphoma, it's represent 1.74% of the total cancer cases and is classified in the 18th rank [1].
External beam radiation therapy may ensure a long-term control of Hodgkin Lymphoma. Advanced treatment modalities such as intensity modulated radiation therapy (IMRT) and Tomotherapy are employed for the management of this disease [2].
Initially, Hodgkin Lymphoma was treated using Involoved Field Radiation Therapy "3D-IFRT" which use a large field, but in 1999/2000 the Involved Site Radiation Therapy "ISRT" was introduced in different radiation-oncology department [3]. With this modality, the radiation field is reduced to only the nodes. The results show that 80% of cases lead cancer care.
To describe radiation -induced cancer the concept of an organ equivalent dose was described and developed to describe radiation induced cancer risk from 3D conformal therapy dose distribution. The definition of this concept is based on any dose distribution in an organ is equivalent and corresponds to the same OED if it causes the same radiation induced risk of incidence. It will be noted as OED_{org} to avoid confusion with the equivalent uniform dose known as EUD defined by Niemierko [4, 5].
The main aims of this study were to assess a cohort of treatment plans in terms of toxicity for different organs at risk. This was made using the concept of Equivalent Uniform Dose. Predictive models like normal tissue complication probability [6, 7, 8, 9].
Secondly aim, was to estimate the induced second cancer using the calculation of integral dose [10].and the radiobiological and mathematical modeling of the risk [11]

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. To do this, we used the concept of OED and we estimate the absolute second cancer using an in-house software modelled for mechanistic model in the case of hodgkin lymphoma treatment using 3D field in field (3D-FIF radiotherapy).

2. Materials and Methods

2.1. Material

Treatment planning data of 20 patients were established using conformal radiotherapy with field- in- field modality treatment. For all treatment plans involved 6 and 18 MV x rays produced by Varian Clinac 2100 DHX linear accelerator (Varian Medical Systems, Palo Alto, CA) which is equipped with the Millennium 120-leaves multi-leaf collimator (MLC) with a 0,5cm and 1cm thickness of leaf and photons with 6MV and 18MV.

2.2. Patients and 3D-FIF planning

Nineteen patients with medium age 17.5 years old were planned in this study. All these patients have been referred for external beam therapy. were planned. The prescribed doses vary from 20, 21.6, 30 and 36 Gy and was delivered to patients with 2 Gy per fraction. The characteristic of these patients were summarized in the table1.

Table 1: Characteristic of patients

Age ≤ 20 years	**Years**
Mean, SD	17.5 ± 2.46
Median (min-max)	18 [12 - 20]
Nomber of patients (%)	
M	19
F	5 (26%)
	14 (74%)
Stage (AJCC)	
	I (xxx)
	II(xxx)
RT	
- Post oper	
- Aferclinical ….	
PTV volume (cm^3)	
Mean :	631.21 ± 20.9

All plans were generated using Eclips version 10.6 treatment planning system with AAA. Different geometries were used during planning and most of them used two fields with 0° and 180° with collimator rotation of 90° to avoid a total irradiation of thyroid. The dose constraints for the PTV and organs at risk are listed in table 2. in others plans lateral field with 90° or 270° were choice to reach our target in covering the PTV. All the plans were normalized with 95% of the prescribed dose to cover 95% of the PTV volume.

The different plans were optimized with respect to dose-volume constraints for the PTV and organs at risk that are listed in table 2. All the treatment plans were verified before the beginning of the treatment.

Table 2: Dose volume constraints used in 3D-FIF radiotherapy planning

Structures	**Constraints**
PTV	$D_{95\%} \geq 95\%$
	$D_{98\%} \geq 90\%$
	$D_{50\%} \geq 100\%$
	$D_{2\%} \geq 107\%$
Lt-Lung	$V_{20Gy} < 35\text{-}37\%$
Rt-Lung	$V_{20Gy} < 35\text{-}37\%$
Heart	Dmax < 35 Gy (if total irradiation)
	V_{45Gy} (as low as possible, if irradiated partialy
Thyroid	$V_{50Gy} < 50\%$
Larynx	$D_{mean} < 45$ Gy
Parotide	$D_{mean} < 26$ Gy

2.3. Radiobiological modeling

2.3.1. NTCP evaluation

All plans were analyzed and assessed in terms of quality and toxicity in right and left lung using mathematical models developed by Niemierko and Lyman-Kutcher-Burman. Firstly, the quality of these plans was assessed with cumulative dose-volume histograms (DVHs), where Dmax, Dmin and Dmean were extracted and compared with constraints. The equivalent Uniform dose (equation 1) was calculated for left and right lung and compared to the mean dose due to the architecture of lung (parallel organ).

$$\mathrm{EUD} = \left(\sum_{i=1}^{k} v_i D_i^a\right)^{(1/a)} \equiv \mathrm{gEUD} = \left(\frac{1}{N}\sum_{i=1}^{k} D_i^a\right)^{(1/a)} \quad (1)$$

Integral doses were also calculated to these OARs, this function “ID” is defined as the physical quantity which can create aggression and complication due to radiation therapy. In practice, ID is kept as much as possible at minimum. It was defined as the mean dose times the volume for each structure [12, 13, and 14]. Therefore, the

unit of integral dose is Gykg. The integral doses were calculated directly from the dose volume histogram data.

The toxicity was calculated firstly for (α/β) =3, secondly for different values of (α/β) = 1; 3 ;5. The obtained results for right and left lung were compared to investigate the influence of the fractionation and non-uniformity of dose to the irradiated organs.

Calculated toxicity is expressed as the probability of complication during the five years after treatment it is calculated according to Lyman-Kutcher-Burman model defined by the equation 1:

$$NTCP = (2\pi)^{-1/2}\int_{-\infty}^{t}\exp(\frac{-x^2}{2})dx \equiv NTCP = \frac{1}{2}\left[1+erf(\frac{t}{\sqrt{2}})\right] \quad (2)$$

with :

$$t = (d_{réf} - TD_{50}(v_{eff}))/(m.TD_{50}(v_{eff}))$$

where :

$$v_{eff}^{(j)} = v_j(\frac{d_j}{d_{réf}})^{1/n} \quad and \quad v = \sum_{j=1}^{k} v_{eff}^{(j)}$$

and:

TD_{50}: is the dose at NTCP =50%, this parameter for each critical structure was obtained from Emami et al. [15] (Table 3).

v_j is the irradiated volume which receiving dose d_j [9].

Table 3 : Radiobiological parameters to calculate toxicity of OARs

Structure	n	m	$TD_{50/5}$	End Point
Lung	0.87	0.18	24.5	Pneumonities
Heart	0.35	0.1	48	Pericarditis
Thyroid	0.22	0.26		Thyroidities
Larynx	0.11	0.075	80	Cartilage necrosis
Larynx	0.08	0.17	70	Laryngeal edema

2.3.2 Evaluation of the risk

Mechanistic model

The model to be considered for the estimation of the risk for secondary induced cancer from irradiation is the mechanistic model. All nineteen patients were assessed in terms of induced second cancer where we estimate the excess absolute risk EAR. To investigate the induced second cancer, we have used mechanistic model based on the organ equivalent dose concept of Uwe schneider. In this part the excess absolute risk was modelled and estimated for left and right lung organ taking account the cell killing and fractionation effects defined as follows [16,17, 18]:

$$EAR = \beta_{EAR} OED \exp\left[\left(\gamma_e(age-30) + \gamma a \ \ln(\frac{age_a}{70})\right)\right] \quad (3)$$

$$OED = \frac{1}{V_t}\sum_i V_{D_i}\frac{e^{-\alpha' D_i}}{\alpha'_i R}\left[1-2R+R^2e^{-\alpha' i} - \left((1-R)^2 e^{-\frac{\alpha' R}{1-R}D_i}\right)\right] \quad (4)$$

$$\alpha' = (\alpha + \frac{\beta D_i}{n})$$

Where α and β are the organ-specific linear quadratic parameter and

n: number of fractions

$V_{i:}$ is the total volume of lung

D_i: Dose received at volume V_i

R: is the cell repopulation factor

All the parameters used in this model (Table 4), were obtained from A-Bomb survivors and Hodgkin's patient data.

Table 4: The model parameters used for estimating the organ

Model parameter	Lung
α	0,061
α/β	3
R	0,81
γ_e	0,002
γ_a	4,23
β_{EAR}(10 P YGy)	7,5 (51-10)

3. Results and Discussion

3.1. Toxicity of OARs

Table 5 shows an overview of the mean and the maximum dose and their corresponding deviation standards at the different organs at risk (spinal cord, larynx, heart and Lt and Rt lung). During this study, we are interested on right and left lung where the results show that the mean doses are: (7.81±4.6) Gy, (8.74±3.8) Gy. These results demonstrate that all recommended constraints are verified. Table 6 summarize all the results obtained on constraints. In case of lung, we have reported that the mean dose on volumes ($D_{mean,\ V20}$ = (15.58 ±12.85) Gy and $D_{mean,\ V30}$ = (9.64 ± 10.17) Gy) are lower than 30 Gy and 20 Gy respectively.

Table 5: Doses Statistic of patients

Organ	D_{min}(Gy)	D_{max} (Gy)	D_{mean} (Gy)
Spinal cord	1.21±2.9	32.71±6.56	17.30±5.80
Larynx	13.07±9.9	31.28±9.54	21.16±9.66
Rt-lung	0.27±0.25	32.54±8.70	7.81±60
Lt-lung	0.20±0.17	33.90±5.46	8.74±3.84
Heart	0.31±0.25	31.19±9.75	7.22±4.71

Table 6: Obtained Results on constraints defined during planning

Structures	Recommended Constraints	Results
Spinal Cord	D_{max} < 45 Gy	D_{max} = (32.71 ± 6.56) Gy
Larynx	D_{max} < 20 Gy	D_{max} = (31.28 ± 9.54) Gy
Heart	D_{max} < 35 Gy	D_{max} = (31.19 ± 9.75) Gy
Rt-Lung	V_{20} < 30%	$D_{mean,\ V20}$ = (15.58 ±12.85) Gy
	V_{30} < 20%	$D_{mean,\ V30}$ = (9.64 ± 10.17) Gy
Lt-Lung	V_{20} < 30%	$D_{mean,\ V20}$= (19,14 ±12.38) Gy
	V_{30} < 20%	$D_{mean,\ V30}$ = (10,32 ± 9,42) Gy

For these above organs at risk right and left-lung, calculated integral dose was quantified and the results are plotted in Fig.1(a) and and Fig.1(b) respectively. Higher integral dose was noticed for patients 12,13,14 and 19.

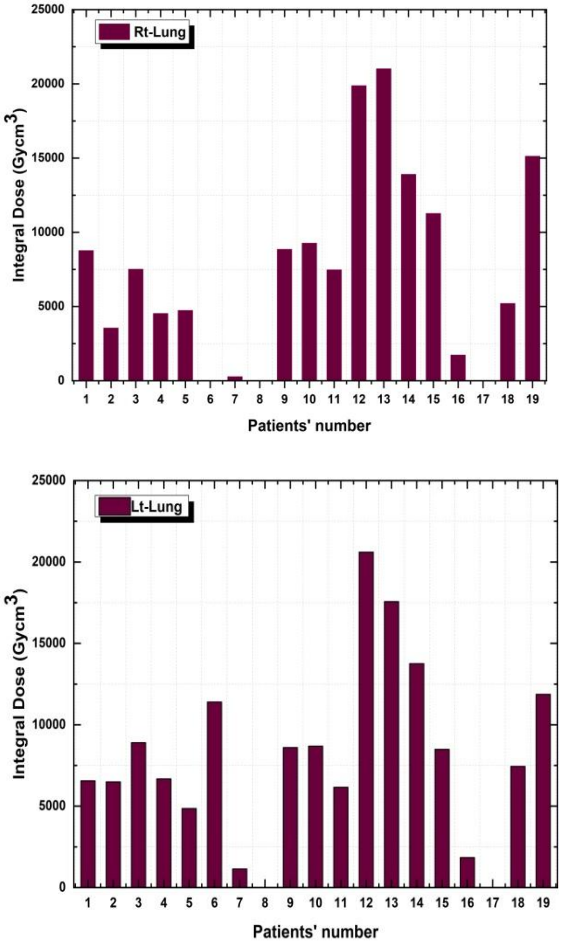

Fig 1. (a) Integral dose for Rt-Lung ; (b) Integral dose for Lt-Lung

The corresponding calculated toxicity « NTCP » for pneumonitis end point were 4.2% in the range [1.4-9.9] and 4.5% in the range [1,4- 8.6] which correspond to EUD_{mean} = (5.98±3.16) and (6.21±3.49) Gy in case of (α/β) = 3.

In the comparison of these calculated toxicity for lung to those given by Vitaliana et Bolzan (0.2 %) [2, 19] our results revealed a greater than those given by Vitaliana but for all the cohort the toxicity still under 5 %. The Rt and Lt lung are well protected during planning, and the the pneumonitis can appear for only some patients (P15; P18 and P19) of the studied cohort.

To optimise the treatment plans, we have studied the variation of toxicity for differents values of (α/β). The obtained results of toxicity function the variation of (α/β) shows that the values of NTCP decrease for (α/β =1) compared to the values of 3and or 5 in case of right and left lung (Fig. 3a ; Fig. 3b).

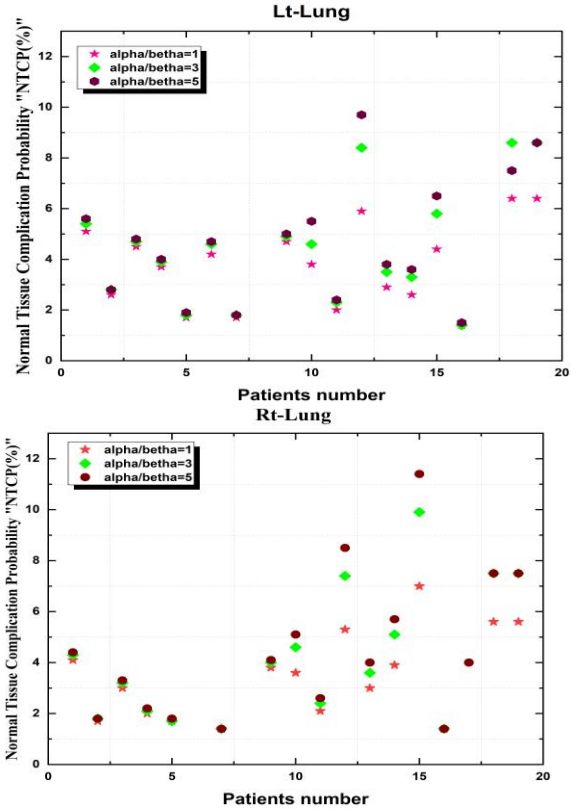

Fig 2. The variation of the toxicity (NTCP) function the values of alpha/betha for Rt (a) and Lt Lung(b)

3.1. Estimated risk

From the DVHs of structures of interest, cancer risk was estimated in terms of OED which proportional to cancer risk and was converted to excess absolute risk using mechanistic model.

The using of OED is justified by taking into account the unavoidable inhomogeneity of clinical dose distributions in organs of interest.

Fig. 2. and 3, shows the right and left lung risk as a

function of organ equivalent dose. The EAR results using our in-house software computed with Matlab showed that the risk is more important for left lung compared to right lung. The EAR was quantified as an estimated absolute risk of induced second cancer for Right and left lung and are 4.39±3.24 and 5.54±3.41 per 10000 P-Y. The maximum level risk is about 11.7 per 10000 P-Y for right lung and 13.28 per 10000 P-Y for left lung for patient 10 and 18 respectively.

These values still less than those given by Uwe Schneider (18.4 /10000 PY) [10], this is due to our limited number of patients.

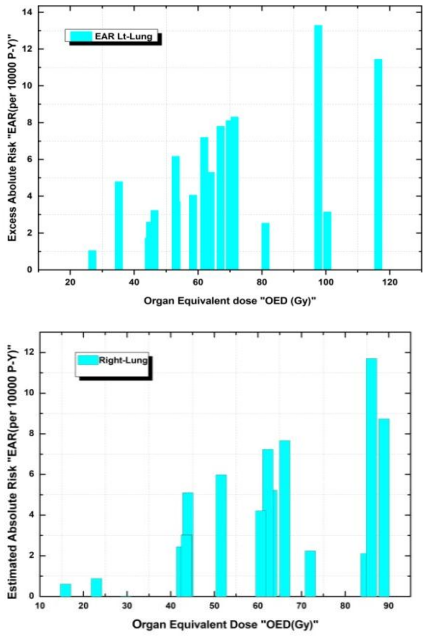

Fig. 3. (a) Estimated Absolute risk for Rt-Lung; (b) Estimated Absolute Risk for Lt-Lung

4. Conclusion

In radiotherapy treatment, we aim to deliver higher and uniform dose to the target and to reduce dose to organ at risk. in this study, we have assessed the treatment quality of 3D-FIF and quantify the toxicity and induced second cancer for Hodgkin Lymphoma using physical tools and radiobiological modeling for calculating the toxicities and induced second cancer for right and left lung. Higher integral dose higher risk was noticed for some patients which need a clinical follow-up for them. NTCP and EAR modeling have been deveolpped to rank the plans in terms of the optimized plan before treaing the patients.

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Conflict of Interest

The authors declare that they have no conflict of interest

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