Physica Medica 57 (2019) 100–106

Contents lists available at ScienceDirect

Physica Medica

journal homepage: www.elsevier.com/locate/ejmp

Original paper

Probability of carcinogenesis due to involved field and involved site radiation therapy techniques for supra- and infradiaphragmatic Hodgkin's disease

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ARTICLE INFO

Keywords:
Hodgkin's Lymphoma radiotherapy
Involved site radiotherapy
Involved field radiotherapy
Second cancer risk

ABSTRACT

Purpose: To estimate the second cancer risk associated with Hodgkin Lymphoma (HL) radiotherapy at supradiaphragmatic or infradiaphragmatic region, using the involved field (IFRT) and the involved site radiotherapy (ISRT).

Materials and methods: IFRT and ISRT treatment plans were created for twenty HL patients. Three dimensional plans (3DRT) were employed for all patients. The organ equivalent dose (OED) and lifetime attributable risk (LAR) for organs at risk were estimated with mechanistic, plateau and bell-shaped model. Estimated risk values were compared with nominal risk of unexposed population.

Results: For supradiaphragmatic radiotherapy, the mean OED range was 0.63–8.53 Gy and 0.63–7.26 Gy for IFRT and ISRT, respectively. The corresponding range for infradiaphragmatic radiotherapy was 0.18–7.64 Gy and 0.80–4.95 Gy. The LAR for cancer induction in the partially in field organs at risk after IFRT was 0.5%–8.0% and 0.2%–9.3% at supradiaphragmatic and infradiaphragmatic regions, respectively. The corresponding risk after ISRT method was 0.5%–5.2% and 0.9%–6.0%. Estimated cancer risk for breast, lung, thyroid, colon and rectal with ISRT was found significantly reduced compared to IFRT. The risk of secondary malignancies for lung, mouth, pharynx, rectum and colon was assessed more than 1.2 times higher than nominal risk for IFRT. The respective risk using ISRT was above nominal only for pharyngeal cancer.

Conclusion: ISRT compared with IFRT, results in decreased second cancer risk in most organs considered. Second cancer probability with IFRT was higher than the nominal risk for certain organs, while for ISRT remains higher only for pharyngeal cancer.

1. Introduction

Hodgkin Lymphoma (HL) is a B-cell lymphoid malignancy usually affecting young adults 20–34 years old (yr) [1]. Prognosis of HL patients is usually excellent, with a 5-year relative survival rate reaching 86.6% for patients diagnosed in the period 2008–2014 [2]. Radiation therapy (RT) has a key role in the management of HL patients [3,4]. However, the use of RT has been associated with late effects, including the development of secondary malignancies [5–7]. HL patients present statically significant increased risk of developing second cancer for at least 40 yrs after irradiation [8]. The possibility of secondary malignancies development for HL patients is exceptionally concerning, because of their young age and the high cure rates. Consequently, it is of paramount importance to decrease the exposure to surrounding healthy tissue while maintain high cure rates.

During the last decades, HL radiotherapy approaches have been subjected to substantial changes regarding field size. Initially, extended field radiation therapy (EFRT) had been superseded by the reduced involved field RT (IFRT) [9,10]. Studies have shown that the field reduction doesn't affect the treatment cure rates, whereas second cancer risk was reduced [11–14]. Grinsky et al. [15], recently proposed further target volume reduction with involved node RT (INRT) concept. INRT targets only the initially involved lymph nodes and is contoured based on the prechemotherapy positron emission tomography (PET) in RT treatment position [15]. However, the International Lymphoma Radiation Oncology Group (ILROG) recognized that the prechemotherapy

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https://doi.org/10.1016/j.ejmp.2018.12.036
Received 10 September 2018; Received in revised form 22 December 2018; Accepted 28 December 2018
Available online 03 January 2019

PET in RT treatment position is not always optimally feasible in clinical practice and introduced involved site RT (ISRT) [16]. Definition of ISRT is based on prechemotherapy imaging but not on treatment position. The volume of the target in the ISRT method in most cases is smaller than the one in the IFRT method, resulting in a decrease of the exposure of the organ(s) at risk.

This study aims to assess the induced second cancer risk for organs which were partially included in radiotherapy field during HL radiotherapy, using ISRT or IFRT method.

2. Materials and methods

2.1. Patients

Twenty consecutive patients with supradiaphragmatic or infradiaphragmatic HL, who had been treated with radiotherapy in our department, were involved in the present study. All patients underwent a treatment planning Computed Tomography (CT) in supine position with a 16 slice unit (Somaton Sensation 16, Siemens Medical Solution, Forchein, Germany) by using a 5-mm slice thickness. Contouring and 3D radiotherapy planning were performed with the XiO system (CMS, Inc., St. Louis, MO, USA). Planning tumor volume (PTV) and organs at risk were defined by an experienced radiation oncologist. In supradiaphragmatic cases the following organs-at-risk (OAR) were contoured: thyroid, esophagus, lung, mouth, pharynx and breast for female patients. For infradiaphragmatic cases, the bladder, rectum and colon were delineated. The aforementioned OARs were partially included in the treatment fields during RT radiotherapy. However, for two patients, the mouth and pharynx were excluded from the treatment fields. Moreover, the thyroid gland was excluded from the treatment volume of one patient. Both lungs were considered as one OAR. Similarly, breasts were regarded as one structure. For each patient two PTVs were defined, based on the IFRT and ISRT techniques, in accordance with international guidelines and previously published works [16,17]. Lymph nodes groups for each PTV are presented in Table 1.

Table 1
Lymph nodes group included in PTV for each studied patient.*

Supradiaphragmatic		Infradiaphragmatic	
Patient n_o	PTV Lymph Nodes	Patient n_o	PTV Lymph Nodes
1	Mediastinal Clavicular	11	Iliac Inguinal
2	Mediastinal Clavicular Cervix Axilla	12	Iliac Inguinal
3	Mediastinal	13	Iliac Inguinal
4	Mediastinal Clavicular	14	Iliac
5	Mediastinal Cervix	15	Iliac
6	Mediastinal	16	Iliac Inguinal
7	Mediastinal	17	Iliac Inguinal
8	Mediastinal Axilla	18	Iliac Inguinal
9	Clavicular	19	Iliac
10	Mediastinal Clavicular Cervix Axilla	20	Iliac Paraortic

* PTV, Planning Tumor Volume.

2.2. 3D conformal radiotherapy

All treatments were performed isocentrically with 6 MV X-rays, in a linear accelerator of our department (Primus, Siemens, Germany) which is equipped with a multileaf collimation system (MLC). For IFRT and ISRT methods, 3D plans were performed with 2 parallel opposed fields (Anterior-Posterior [AP], Posterior-Anterior [PA]) with gantry angles equal to 0° and 180°. Equal-weighted beams were used for all treatments. The prescribed dose to isocenter was 30 Gy delivered in 15 daily fractions of 2 Gy. All treatment plans were optimized to ensure that 95% of the prescribed dose covers at least 95% of PTV volume.

2.3. Organ equivalent dose

When the dose in an organ is high and exceeds 2.5 Gy and is inhomogeneously distributed, the average organ dose is not considered as the appropriate value for cancer incidence rate evaluation [18,19]. In this study, organs of interest were partly included within the irradiation field and part of them received doses equal to those delivered to target volume. In such inhomogeneous organ dose distribution, previous studies [20–24] suggested the use of the organ equivalent dose (OED) [19] instead of average dose, for second cancer risk assessment. The OED concept takes into account cell killing, fractionation and repopulation effects into account [19]. For OED estimations, differential dose volume histograms (DVH) with 0.01 Gy bin width were obtained by the treatment planning system, for each organ of interest. OED was given as follows:

$$OED = \frac{1}{V_T}\sum_i V_{Di} RED_{Di} \tag{1}$$

where V_T is the total organ volume, V_{Di} is the volume of the organ in bin i which receives dose D_i, and RED_{Di} is the risk equivalent dose for dose D_i. RED_{Di} was calculated using Schneider's mechanistic model [18], according the following equation:

$$RED_{Di} = \frac{e^{-a_i D_i}}{a_i' R}\left[1 - 2R + R^2 e^{a_i'} - (1-R)^2 e^{-\frac{a_i' R}{1-R}D}\right] \tag{2}$$

where R is organ repopulation-repair parameter after irradiation. The a_i' factor pertained to cell killing and is equal to:

$$a' = a + \beta \mathrm{d} = \alpha + \beta \frac{D_i}{D_T}\mathrm{d_T} \tag{3}$$

where $\mathrm{d_T} = 2$ Gy is the dose fraction, and D_T the total target dose equal to 30 Gy. The fraction α/β was considered equal to 3 for all studied organs [18].

Two limited cases were referred in Schneider's analysis [18], related to the repopulation/repair parameter. At the first assumption where R = 0 (bell shape model) the tissue ability of repopulation/repair was avoided. The equation for $\mathrm{RED_{di}}$ calculation with the bell shape model was the following:

$$RED_{\mathrm{di}} = \mathrm{d}_i e^{-a_i' \mathrm{di}} \tag{4}$$

Plateau model is the second case, where full repopulation/repair occurred R = 1. For the plateau model the $\mathrm{RED_{di}}$ was computed using the following equation:

$$RED_{\mathrm{di}} = \frac{1 - e^{-a_i' \mathrm{di}}}{a_i'} \tag{5}$$

The parameters for RED calculations were taken from previous studies [18,20,21] and are presented in Table 2. Schneider et al. [18] do not provide α and R values for the thyroid; consequently OED thyroid calculations are impossible with the mechanistic model. Additionally, thyroid α value is not defined for plateau model. In the case of the esophagus, the α and R stomach values were used following previous

Table 2
The parameters used for organ equivalent dose (OED) estimations for each calculated model.

Organ	Mechanistic Model		Plateau Model	Bell-Shaped Model
	α (Gy^{-1})	R	α (Gy^{-1})	α (Gy^{-1})
Thyroid	–	–	–	0.0318
Esophagus	0.460	0.46	–	0.111
Lung	0.042	0.83	0.056	0.022
Mouth/Pharynx	0.043	0.97	0.045	0.017
Female Breast	0.044	0.15	0.115	0.041
Bladder	0.219	0.06	0.633	0.213
Rectum	0.033	0.56	0.065	0.031
Colon	0.001	0.99	0.001	0.001

studies [21,25]. Moreover, the parameter α for stomach was not defined for plateau model by Schneider et al. [18].

2.4. Risk estimation

The excess absolute risk (EAR) for cancer induction at organ at risk after HL radiotherapy was estimated with the following formula:

$$EAR = \beta^{'} \mathrm{OED} e^{\gamma_e(\mathrm{age_e}-30)+\gamma_\alpha \ln\frac{\mathrm{age_a}}{70}} \quad (6)$$

where $\beta^{'}$ is the initial slope of the dose response curve at low dose region for the Western population, γ_e and $\gamma_a$are the age modifying parameters, $\mathrm{age_e}$ and $\mathrm{age_a}$ represent the patient's age at the time of exposure and when it was attained, respectively. All the required parameters for each organ were taken from Schneider's study [18] and were presented in Table 3. All calculations were performed with age_a equal to 70 yr and age_e equal to 26 yr which agree with the mean age of patients diagnosed with HL [1]. For each studied organ, the mean OED derived from all the examined patients was employed for all EAR calculations.

Lifetime Attributable Risk (LAR) calculations for second cancer risk for partially in field OARs are based on EAR values given by Eq. (6), using the following equation:

$$LAR = \int_{age_e+L}^{age_{a,max}} EAR(\mathrm{D}_t, age_e, age_a)\frac{S(age_a)}{S(age_e)}\mathrm{d}(\mathrm{age_a}) \quad (7)$$

where L is the latent period of 5 yr for cancer development after irradiation [26], $S(\mathrm{age_a})/S(\mathrm{age_e})$ represents the probability for male and female patients to survive from the age of radiotherapy ($\mathrm{age_e}$) to the attend age ($\mathrm{age_a}$). The above probability was taken by the most recently published life tables of the Unite States population [27].

The calculated LAR for each studied organ was compared with the corresponding baseline risk for unexposed population, as published in the SEER Cancer Statistic Review (2). Each estimated LAR, which was initially determined as the probability of carcinogenesis per 10,000 persons, was presented as a % value in order to facilitate the direct comparison with the baseline risk.

Table 3
Parameters applied for excess absolute risk calculations for cancer induction after supradiaphragmatic or infradiaphragmatic HL radiotherapy.

Organ	β_0 (per 10^4 PY Gy)	γ_e ($years^{-1}$)	γ_α ($years^{-1}$)
Thyroid	0.40	−0.046	0.60
Esophagus	3.20	−0.002	1.90
Lung	8.00	0.002	4.23
Mouth/Pharynx	0.73	−0.024	2.38
Female Breast	8.20	−0.037	1.70
Bladder	3.80	−0.024	2.38
Rectum	0.73	−0.024	2.38
Colon	7.40	−0.056	6.90

3. Results

3.1. Organ equivalent dose calculations

The mean OEDs for organs partially included in treatment field during HL radiotherapy, was calculated to be the mean of the OED values of the patients included in the study and they are presented in Table 4, for both supradiaphragmatic and infradiaphragmatic irradiations, for each calculated model. For a total radiotherapy dose of 30 Gy, mean OED range was 0.63–8.53 Gy for IFRT and 0.63–7.26 Gy for ISRT, depending on the organ of interest and the calculation model. Lung showed the most elevated OED reduction with the ISRT method when compared to IFRT. The OED for lung was 3.87–3.93 Gy for ISRT. The corresponding range for IFRT technique was found 6.00–6.08 Gy. The OED for esophagus varied from 0.63–0.64 Gy to 0.63–0.66 Gy for IFRT and ISRT, respectively. Thus esophagus was the organ which did not show any OED reduction.

The OED range after infradiaphragmatic radiotherapy varied within the range of 0.18–7.64 Gy and 0.80–4.95 Gy for IFRT and ISRT, respectively. The OED values of the colon and rectum were 7.47–7.64 Gy and 6.06–7.16 Gy, correspondingly with IFRT technique. The corresponding ranges with ISRT method were lower than those with IFRT and equal to 4.84–4.95 Gy and 4.03–4.56 Gy for colon and rectum, respectively. Conversely, the OED range for bladder was increased for ISRT technique (0.80–1.20 Gy) when compared with IFRT (0.18–1.24 Gy).

3.2. Second cancer risk estimates after HL radiotherapy

3.2.1. Supradiaphragmatic irradiation

For a typical patient of 26 yr with supradiaphragmatic HL, the LAR values (derived from mean OED) of cancer induction to thyroid, esophagus, lung, mouth, pharynx and breast, after IFRT or ISRT radiotherapy are presented in Fig. 1. The difference between the probability of developing radiation induced malignancies with the mechanistic model, when compared with those assessed with plateau and bell shaped model varied from 0.2% to 8.0%. The LAR range for cancer development with IFRT method was found 0.50%–8.02%, depending on the organ at risk and the calculation model. The corresponding range attributable to ISRT technique was 0.50%–5.19%. The IFRT compared to ISRT, resulted in LAR reduction between 15% and 36%, excluding the case of the esophagus, where the LAR with IFRT and ISRT remained constant.

The LARs for developing second cancer for lung, mouth and pharynx were found 1.2–1.3 times higher than the baseline risk. The LARs for the development of thyroid and breast cancer were 1.2–2.6 times lower when compared to baseline risk. Using the ISRT technique the LARs for the lung, mouth, breast and thyroid cancer induction were 1.2–3.9 times lower, while those for pharyngeal cancer were found 1.1 times higher, than the baseline risk. Esophageal cancer risk after HL radiotherapy was assessed comparable to baseline risk of unexposed population, for IFRT and ISRT method.

3.2.2. Infradiaphragmatic irradiation

The LAR values of cancer appearance for a typical 26-yr old patient in bladder, rectum and colon due to infradiaphragmatic HL irradiation, are shown in Fig. 2. The cancer risk range with IFRT method was found to be 0.20%–9.28%, depending on the OAR and the calculation model, whereas the corresponding range with ISRT was 0.86%–6.01%. The cancer risk probability for colon and rectal cancer, as estimated with mechanistic model, differs from those calculated with bell-shaped and plateau model, between 0.5% and 43%. The risks of developing bladder cancer as estimated with plateau model were found 3.8 and 1.3 times higher than the corresponding risks with mechanistic model, for IFRT and ISRT, respectively. The LARs for colon and rectal cancer induction with IFRT or ISRT were found 1.7–2.0 and 1.1–1.4 times higher than

Table 4
Mean OED (Gy) for supradiaphragmatic and infradiaphragmatic radiotherapy using IFRT and ISRT method, for each calculated model.

Organ	OED (Gy)					
	IFRT			ISRT		
	Mechanistic Model	Plateau Model	Bell-Shaped Model	Mechanistic Model	Plateau Model	Bell-Shaped Model
	Supradiaphragmatic Radiotherapy					
Thyroid	–	–	5.79	–	–	4.71
Esophagus	0.63	–	0.64	0.63	–	0.66
Lung	6.08	6.00	6.07	3.90	3.87	3.93
Mouth	7.58	7.61	8.19	6.45	6.51	6.95
Pharynx	7.92	7.94	8.53	6.72	6.76	7.26
Breast	1.97	2.00	1.97	1.32	1.34	1.32
	Infradiaphragmatic Radiotherapy					
Bladder	0.33	1.24	0.18	0.92	1.20	0.80
Rectum	7.16	6.99	6.06	4.56	4.48	4.03
Colon	7.59	7.64	7.47	4.91	4.95	4.84

Abbreviations: OED, organ equivalent dose; IFRT, involved field radiation therapy; ISRT, involved site radiation therapy.

the baseline risk, respectively. The baseline risk for bladder cancer induction was 6.0–12.1 and 2.4–3.8 times higher than the estimated LARs for IFRT and ISRT method, correspondingly.

4. Discussion

HL radiotherapy inevitably exposes the surrounding healthy tissues. As a result, the risk of secondary cancer may be increased at the above organs. The decrease of the target volume with ISRT method, reduces the volume of irradiated healthy tissues, with potential reduction of second cancer risk and late radiation toxicities [15,16]. In the current study, we provide data regarding second cancer risk, after HL supradiaphragmatic and infradiaphragmatic irradiation, with ISRT and standard IFRT method.

The probability of radiotherapy induced cancer risk was estimated for thyroid, lung, breast, pharynx, esophagus and mouth, which were partially included in treatment field during supradiaphragmatic HL radiotherapy. The colon, rectum and bladder cancer risk was studied for HL patients irradiated at infradiaphragmatic region.

The decrease of target volume resulted in second cancer risk reduction higher than 15%, in case of supradiaphragmatic radiotherapy. Infradiaphragmatic HL irradiation with ISRT method led to rectal and colon cancer risk reduction higher than 34%. Increased LAR up to 79% was computed for bladder cancer induction with ISRT when compared with IFRT.

In the present study, the probability of lung and breast cancer after supradiaphragmatic irradiation using the ISRT method, exhibited the greatest reduction, in comparison to IFRT method. To our knowledge, limited dosimetric data have been published comparing the cancer risk probability of IFRT to ISRT after supradiaphragmatic radiotherapy. Moreover, there are no epidemiological data relating the second cancer risk for HL patients treated with ISRT, given that this technique has been recently introduced in practice. Mazonakis et al. [25] reported that the use of ISRT method for HL mediastinal radiotherapy, results in significantly reduced breast and lung cancer risk when compared with IFRT. Additionally, they found that the risk of esophageal cancer remains constant for IFRT and ISRT technique. Murray et al. [21] compared the second malignancy risk after mediastinal HL radiotherapy, with different target volume definition techniques (IFRT, ISRT, INRT, residual volume radiotherapy). They reported that for a 25-year old patient, ISRT leads to substantial cancer risk reduction for lung, thyroid and breast, compared to IFRT. Furthermore, they found that esophageal second cancer risk remains comparable for all techniques. The above results are in agreement with our findings regarding HL patient irradiated in supradiaphragmatic region.

To the best of our knowledge, there are no dosimetric data in the literature concerning the risk of secondary malignancies after radiotherapy in the infradiaphragmatic region, with ISRT technique. Eggermont et al. [28] studied 3121 patients who underwent infradiaphragmatic HL radiotherapy with extended field technique; they observed increased risk for colorectal cancer induction in comparison with unexposed population. Mulvihil et al. [29] compared INRT method to IFRT for 17 pediatric patients with HL above or below the diaphragm. The OAR they studied at the region below the diaphragm were lungs and kidneys, which makes the comparison with our results impossible because in our study they were not partially included in the treatment field(s). In the current study, the risk of rectal and colon cancer was found to be significantly reduced, using the ISRT method instead of IFRT, for patients with infradiaphragmatic HL. In addition, our study revealed that the LAR for bladder cancer induction with ISRT is higher than with IFRT. The above inconsistent results indicate that a larger volume of bladder was exposed to doses up to 3 Gy when the IFRT method was used. However, when the ISRT method was used, lower volume of bladder was exposed to high doses. Regarding non-linear models, exposures to doses up to 3 Gy could cause risk reduction, because of the theoretical shift in the balance between cell kill and induction of DNA mutation [30,31].

Three different non-linear models were used in the present study for second cancer risk estimations, as previously proposed by Schneider et al. [18]. The LAR of breast, lung, esopharigial, pharyngial, mouth and colon cancer obtained by the mechanistic model differ less than 8% for those estimated with the bell shaped and plateau models. The difference between mechanistic and bell shaped model for rectal cancer risk was higher than 12%, which is in agreement with Murray et al. [32]. The LAR for bladder cancer with mechanistic model shows significant difference with plateau model and is in agreement with previous studies [18,22,32].

The LAR values for cancer induction for lung and mouth were 1.2–1.3 times lower than the corresponding baseline risk, with IFRT method. The corresponding risk with ISRT method was 1.2–1.3 times lower than the baseline probability. The risk of breast, thyroid and bladder cancer incidents were found 1.2–12 times lower compared with baseline risk, for IFRT or ISRT methods. LAR values lower than the baseline risks imply that the use of radiotherapy may result in a relatively small increase of the cancer risk corresponding to that of the unexposed population. The LARs for pharyngeal, rectal and colon cancer development were 1.1–2.1 times higher than the baseline probability, for both techniques. The probability of esophageal cancer in exposed patients was estimated to be comparable to baseline risk.

Several risk models exist in the literature assessing secondary cancer [33,34]. In the present study the concept of organ equivalent dose (OED) was applied [18]. The adopted OED model was based on DVH

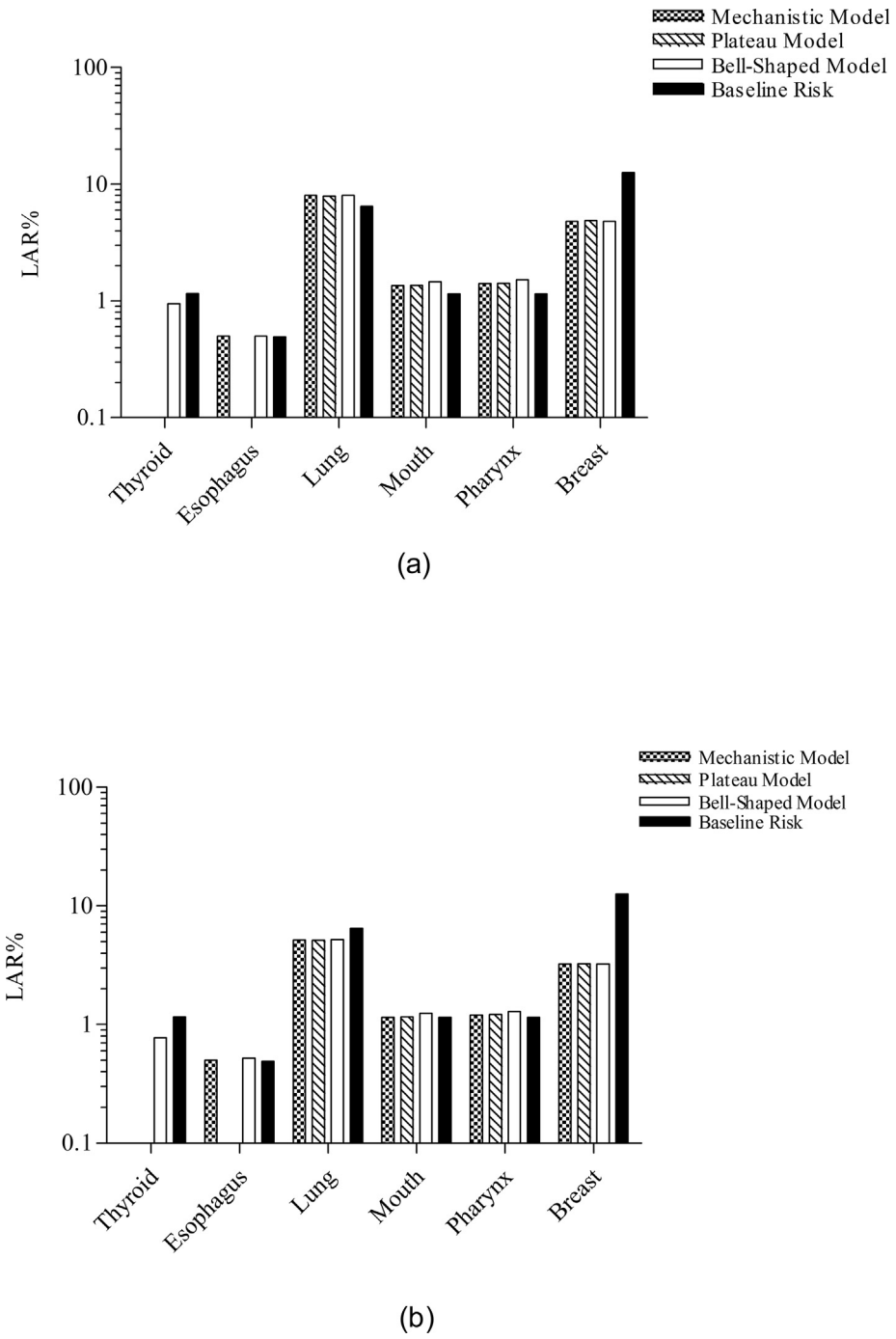

Fig. 1. Lifetime attributable risk (LAR %) for thyroid, esophagus, lung, mouth, pharynx and breast cancer induction after supradiaphragmatic HL radiotherapy with (a) IFRT and (b) ISRT method. The corresponding baseline risks are presented. Abbreviations: HL, Hodgkin's Lymphoma; IFRT, involved field radiation therapy ISRT, involved site radiation therapy.

calculations, a fact that makes the current method practical. Despite the fact that Schneider's model is practical, it requires the knowledge of relative tissues sensitivities [33]. In addition, in terms of the radiobiological aspect of the work, the literature reports several radiobiological factors that can affect second cancer risk, such as: age of exposure, tissue type, volume of irradiation, technique of radiotherapy, previous exposures [35,36]. Risk models tend to include some of the above parameters and indeed, Schneider's model (adapted in the present work) takes into account age and tissue type factors. Additionally, there are other alternative methods for out-of-field organ calculations which could be used as epidemiological study's input (mathematical and phantom measurements); however, these methods are time consuming [37]. The presented second cancer risk after HL radiotherapy is limited by the uncertainties of the applied models. The parameters used in these models obtained by atomic bomb survivors and HL patients data [18]. Inaccuracies of LAR estimations as obtained by three models may be associated with the errors in the definition of β'parameter, related to the slope of the dose response curve at the low dose region. Moreover, uncertainties of risk estimations are related with errors in the determination of the repopulation factor R and parameters α and β. Additionally, in the present study all plans were performed with 3D conformal radiotherapy technique. However, the use of intensity modulated radiotherapy technique (IMRT) or volumetric arc therapy (VMAT) for HL patients is under examination, as it appears to

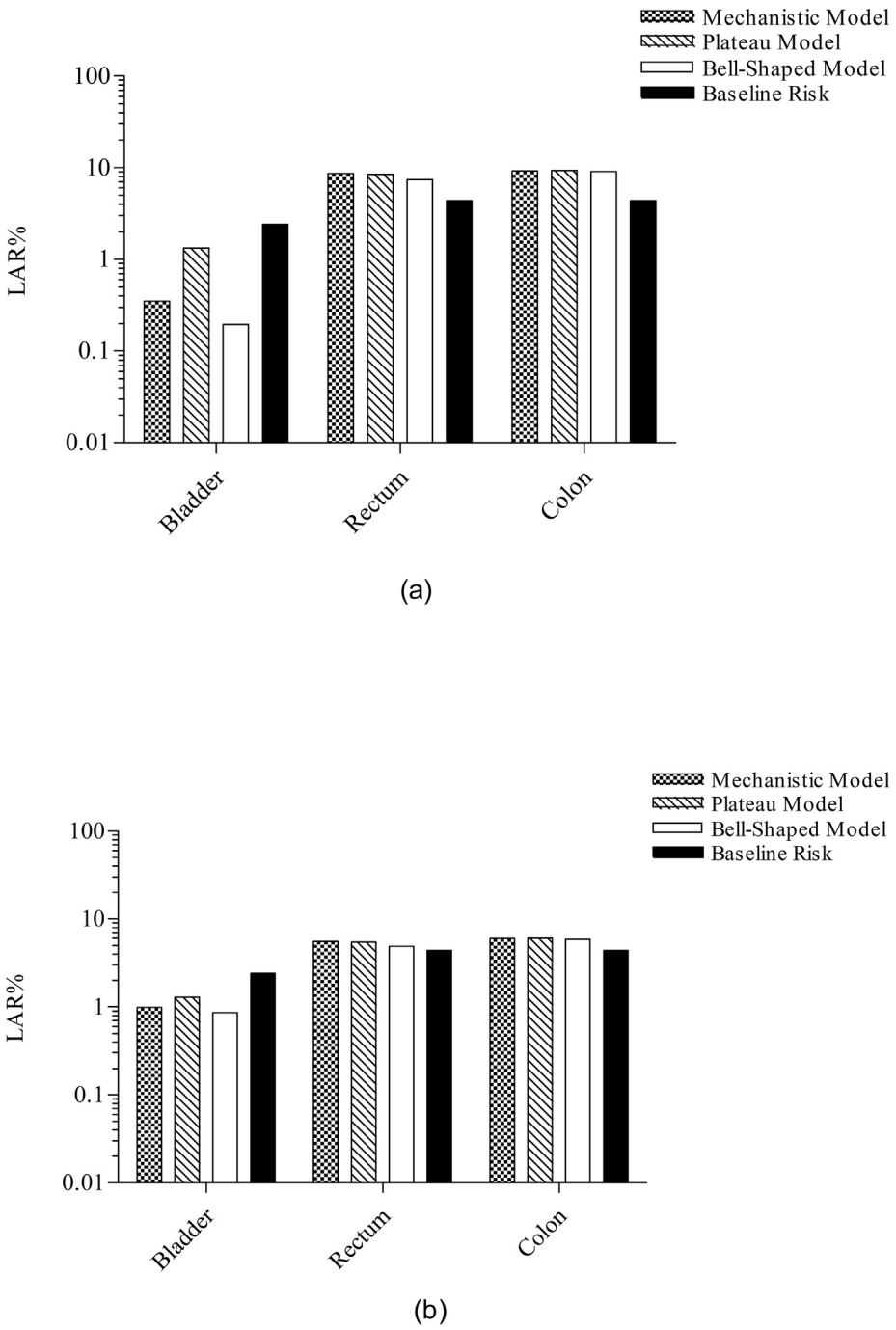

Fig. 2. Lifetime attributable risk (LAR %) for bladder, rectum and colon cancer induction after infradiaphragmatic HL radiotherapy with (a) IFRT and (b) ISRT method. The corresponding baseline risks are presented. Abbreviations: HL, Hodgkin's Lymphoma; IFRT, involved field radiation therapy ISRT, involved site radiation therapy.

increase the risk of secondary cancer induction at OAR [20,30,38].

5. Conclusion

The current study provides data about second cancer risk to partially in field organs after HL radiotherapy in supradiaphragmatic or infradiaphragmatic region, with IFRT and ISRT techniques. Supradiaphragmatic radiotherapy with ISRT method revealed that the risk of breast, lung and thyroid cancer, reduced considerably when compared with IFRT. The use of ISRT for infradiaphragmatic radiotherapy reduces the rectal and colon cancer risk. However, the ISRT technique instead of IFRT leads to increased second cancer risk for bladder, but the risk remains lower than the baseline risk of unexposed population. The current second cancer risk assessments can provide useful insight to the radiation oncologists to decide whether the ISRT method is appropriate for HL patients. Moreover, the calculated second cancer risk can be of value during the follow up period of HL survivors.

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