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ORIGINAL ARTICLE

Volumetric modulated arc therapy versus intensity-modulated proton therapy in the irradiation of infra diaphragmatic Hodgkin Lymphoma in female patients

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ABSTRACT

Purpose: To investigate the role of infra diaphragmatic intensity-modulated proton therapy (IMPT) compared to volumetric modulated arc therapy (VMAT) for female Hodgkin Lymphoma (HL) patients and to estimate the risk of secondary cancer and ovarian failure.

Methods: A comparative treatment planning study was performed on 14 patients, and the results were compared according to conventional dose-volume metrics. In addition, estimates of the excess absolute risk (EAR) of secondary cancer induction were determined for the bowel, the bladder and the rectum. For the ovaries, the risk of ovarian failure was estimated.

Results: The dosimetric findings demonstrate the equivalence between VMAT and IMPT in terms of target coverage. A statistically significant reduction of the mean and near-to-maximum doses was proven for the organs at risk. The EAR ratio estimated for IMPT to VMAT was 0.51 ± 0.32, 0.32 ± 0.35 and 0.05 ± 0.11 for the bowel, bladder and rectum, respectively. Concerning the risk of ovarian failure for the chronologic age ranging from 18 to 46 years, the expected net loss in fertility years ranged from 4.8 to 3.0 years for protons and 12.0 to 5.7 years for photons.

Conclusion: This in-silico study confirmed the beneficial role of IMPT from a dosimetric point of view. Mathematical models suggested that the use of protons might be further advantageous due to the expected reduction of the risk of secondary cancer induction and its milder impact on the reduction of fertility.

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Intensity-modulated proton therapy; VMAT; RapidArc; lymphoma; secondary cancer risk estimate; ovarian failure

Introduction

As a result of significantly improved systemic therapy, Hodgkin lymphoma (HL) is nowadays a disease that can be cured to a high degree. Five-year survival rates are above 90% for all stages [1–4]. However, intensive therapy can lead to relevant long-term side effects. Due to the often young age of onset and the favourable good prognosis, second tumour induction [5–12] and cardiac toxicity [13,14] can relevantly reduce overall survival. Fatigue [15] and hypogonadism [16,17] can lead to a relevant reduction of quality of life. Therefore, de-escalation of therapy to avoid long-term toxicity is frequently adopted as a toxicity mitigation strategy [1–3].

In radiotherapy (RT) for Hodgkin lymphoma, de-escalation of therapy has a long history. From total nodal irradiation (TNI) or extended-field radiotherapy (EFRT) to involved-field radiotherapy (IFRT) for early stages [18]/RT of PET-positive residues for advanced stages [19], the radiation field has been successively reduced.

Currently, in the early favourable and unfavourable stages, IFRT has been replaced by involved-site radiotherapy (ISRT) or involved-node radiotherapy (INRT) [2,4,20,21], so that only initially affected lymph nodes are irradiated and not the affected lymph node stations. Furthermore, RT is omitted in the case of a negative Positron emission tomography (PET) in the intermediate and advanced stages [2,19]. Since INRT/ISRT is a relatively new radiation concept, there are no definitive clinical data for the second tumour rate. Both the publication of the H10 study of the EORTC and the publication of the HD17 study of the GHSG [2,4] reported few cases of second tumours (e.g., 42 cases in the H10 trial over about 2000 patients enrolled); due to the low number, it is challenging to draw solid conclusions. From in-silico studies, compared with IFRT, ISRT significantly reduces the risk of secondary malignancy [22–24]. Nevertheless, ISRT applied with photons still results in a relevant dose exposure. Compared to photon-based intensity-modulated radiotherapy (IMRT)/volumetric modulated arc therapy (VMAT), intensity-

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modulated proton therapy (IMPT) allows further dose reduction for organs at risk (OARs).

First clinical studies show that irradiation with protons is safe and feasible in patients with Hodgkin lymphoma [25–30]. Planning studies demonstrate that mediastinal IMPT spares the organs at risk better than IMRT [31,32], resulting in a lower risk of secondary malignancy [33]. A planning comparison showed an advantage in OARs dose exposure for infra diaphragmatic passively scattered proton therapy over photon irradiation [28].

However, studies on IMPT in infra diaphragmatic involvement are lacking to date. The primary aim of this in-silico planning study was to appraise the dosimetric differences between IMPT and VMAT for infra diaphragmatic lymphoma in female patients. An additional aim was to estimate the excess absolute risk (EAR) of secondary cancer for the bowel, the bladder and the rectum. Finally, severe ovarian toxicity might induce organ failure and anticipated menopausal age; a model was applied to predict the different expected patterns for protons and photon treatments.

Material and methods

Patients selection, contouring and dose prescription

In the German Hodgkin Study Group (GHSG) HD17 trial, 1100 patients aged 18–60 years with unfavourable early-stage HL were enrolled. Following two cycles of etoposide, cyclophosphamide, doxorubicin, bleomycin, vincristine, procarbazine, prednisone (escalated BEACOPP) and two cycles of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD), they were randomised to receive either 30 Gy IFRT independent of PET or, in the experimental arm, 30 Gy INRT only if post-chemotherapy PET was positive [2]. For our in-silico planning study, we selected all the female GHSG HD17 patients with infra diaphragmatic HL who supplied us with both a CT scan before and post-chemotherapy. Table 1 summarises the disease involvement for the patients included in the study. We contoured the gross tumour volume (GTV) and the clinical target volume (CTV) according to the International Lymphoma Radiation Oncology Group (ILROG) guideline for ISRT [21]. For the clinical treatments and the photon planning, a margin of 7 mm was defined for the planning target volume (PTV). We used the ISRT definition instead of the INRT definition because ISRT has become the standard in daily practice. As OARs, we contoured bladder, bowel, femoral heads, kidneys, ovaries, rectum, spinal canal, and uterus.

Table 1. Summary of disease involvement for all the patients included in the study.

Involvement	*N*	%
Iliacal right	5	35.7
Inguinal right	5	35.7
Iliacal left	11	78.6
Inguinal left	10	71.4
Paraaortic	10	71.4
Celiac	2	14.3
Mesenteric	4	28.6
Hepatic hilum	1	7.1

OARs were contoured according to the clinical standards. The bowel was defined as the entire peritoneal cavity.

The dose prescription was 30 Gy in 15 daily fractions as in the clinical routine. All the plans were normalised to 100% as the mean dose to the CTV; the dose-volume objectives for the target volumes and organs at risk are summarised in Table 2.

Photon planning

The photon plans were optimised according to the volumetric modulated arc therapy technique (RapidArc, RA). The 6 MV flattening filter-free beam from a TrueBeam linear accelerator (Varian Medical Systems, Palo Alto, USA) was selected for the study. Inverse planning was performed employing the Photon Optimiser algorithm of the Eclipse treatment planning (version 16.0) system. The final dose calculation was done with the Acuros-XB algorithm with the calculation grid set to 2.5 mm. For all plans, the beam arrangement was defined according to a class solution consisting of two complete arcs with a collimator angle set to

Table 2. Summary of the quantitative analysis of the dose volume histograms for the main structures over the entire cohort of 14 patients for the VMAT (RapidArc) based photon plans and for the intensity modulated proton plans.

Structure	Objective	IMPT	VMAT	*p*
CTV				
D_{mean} [Gy]	= 30	30.0 ± 0.0	30.0 ± 0.0	–
$D_{98\%}$ [Gy]	≥29.4 (98.0 %)	29.4 ± 0.1	29.6 ± 0.1	n.s.
$D_{1\%}$ [Gy]	Minimise	30.8 ± 0.4	30.8 ± 0.2	n.s.
HI [%]	<5	2.7 ± 0.5	2.7 ± 0.5	n.s
PTV				
D_{mean} [Gy]	= 30	30.0 ± 0.1	29.9 ± 0.1	n.s
$D_{95\%}$ [Gy]	≥28.8 (95.0%)	29.2 ± 0.2	28.8 ± 0.2	n.s
CI	1	0.81 ± 0.03	0.86 ± 0.02	0.01
Healthy tissue (Body – target volume)				
D_{mean} [Gy]	Minimise	0.9 ± 0.3	2.4 ± 0.7	<0.001
V_{10Gy} [%]	Minimise	3.4 ± 1.1	6.9 ± 2.3	<0.001
Uterus				
D_{mean} [Gy]	Minimise	1.2 ± 1.9	5.8 ± 2.9	<0.001
Right Ovary				
D_{mean} [Gy]	≤2.0	0.7 ± 1.6	3.5 ± 3.4	<0.001
Left Ovary				
D_{mean} [Gy]	≤2.0	2.0 ± 3.4	4.7 ± 2.3	<0.001
Bladder				
D_{mean} [Gy]	Minimise	1.9 ± 1.7	6.4 ± 2.6	<0.001
D_{1cm3} [Gy]	Minimise	16.3 ± 11.5	19.4 ± 9.5	0.01
Rectum				
D_{mean} [Gy]	Minimise	0.40.9	4.5 ± 2.2	<0.001
D_{1cm3} [Gy]	Minimise	5.6 ± 11.1	10.9 ± 7.8	0.01
Right femoral head				
D_{1cm3} [Gy]	Minimise	2.3 ± 3.7	4.1 ± 3.2	0.03
Left Femoral head				
D_{1cm3} [Gy]	Minimise	5.6 ± 3.6	10.0 ± 4.3	0.001
Bowel				
D_{1cm3} [Gy]	Minimise	30.3 ± 0.5	30.5 ± 0.4	0.09
V_{15Gy} [%]	Minimise	9.8 ± 4.5	13.9 ± 5.3	<0.001
V_{20Gy} [%^{3}]	Minimise	6.3 ± 3.2	6.9 ± 2.9	0.01
Spinal canal				
$D_{0.1\ cm3}$ [Gy]	Minimise	1.1 ± 0.9	7.9 ± 1.5	<0.001
Right Kidney				
D_{mean} [Gy]	Minimise	0.1 ± 0.3	2.1 ± 2.8	0.01
Left Kidney				
Dmean [Gy]	Minimise	0.3 ± 0.5	2.4 ± 3.2	0.02

VMAT: Volumetric modulated arc therapy; IMPT: intensity modulated proton therapy; D_x: dose received by *x*% or *x*cm^3 of the volume; $D_{mean:}$ mean dose; *Vx*: volume receiving less then *x*Gy; HI: homogeneity index (D_5−D_{95}/D_{mean}). The *p*-value is relative to the Wilcoxon signed-rank paired test.

10–350°. Depending on the length of the target, for some of the patients, it was necessary to double the number of arcs using two isocentres; dose feathering was enabled to manage the overlapping region between arcs belonging to different isocenter groups.

Proton planning

The IMPT plans were designed and optimised for the ProBeam proton system (Varian Medical Systems, Palo Alto, USA) using the beam spot scanning technique. The beam data are derived from the commissioning of the Scripps Proton Centre (San Diego, California, USA), constitute the reference beam data in Eclipse and were used with permission. The dose distribution optimisation was performed using the Nonlinear Universal Proton Optimiser (v16.0). The Proton Convolution Superposition algorithm (v16.0) was used in the final dose calculation with a grid size of 2.5 mm and a constant relative biological effectiveness RBE of 1.1. A range shifter of 5 cm was applied to all fields to compensate for the shallower depth of the targets.

All patients were planned with three anterior fields with different gantry angles tuned according to the target position to minimise the irradiation of the healthy tissue. This beam geometry was chosen due to the target location. Similarly to the photon plans, two isocentres were used for some patients due to the length of the target; no automatic auto-feathering tool is available in the optimisation engine for IMPT, but all the beams from all isocentres have been simultaneously optimised to generate the desired dose distribution.

Robust optimisation was performed for all plans to account for setup and range uncertainties considering ±4mm shifts in the isocentre along with the *x-y-z* coordinates and ±3% in beam range. In this case, proton plans were optimised with respect to the CTV only, while the dosimetric data for the PTV were recorded for reporting and comparison with the photon plans.

Quantitative assessment of dose-volume metrics

Several V_x and D_x parameters, derived from the dose-volume histograms (DVH), were used to perform the dosimetric analysis. In these metrics, V_x represents the volume receiving at least an x level of dose (in % or Gy), and D_x is the minimum dose that covers an x fraction of volume (in % or cm^3). The healthy tissue was defined as the Body (in the CT scan) minus the target volume.

For the CTV, the homogeneity index (HI) measured the dose variance and was defined as $HI=(D_{5\%}-D_{95\%})/D_{mean}$. The conformality of the plans was scored (relatively to the PTV) according to the conformality index

$$CI = \frac{V^2_{PTV,prescr\ \ dose}}{V_{PTV} V_{prescr,dose}}$$

where $V_{prescr\ dose}$ is the volume receiving the prescription dose and $V_{PTV,\ prescr\ dose}$ is the volume of the PTV receiving the prescription dose.

Some metrics were also computed for the PTV for reporting purposes only.

The average DVHs were computed, for each structure, with a dose binning resolution of 0.02 Gy. Proton doses are reported in Cobalt equivalent Gy (corrected for the 1.1 RBE factor).

The statistical significance of the differences between the various datasets was computed employing the Wilcoxon matched-paired signed-rank test with a threshold to significance set to 0.05 with the SPSS package (version 22, IBM Corporation, Armonk, USA).

Modelling the risk of ovarian failure

Using Wallace's model [34], the non-growing follicles (NGF) surviving percentage g can be functionally linked to the delivered dose (z) in Gy according to $\log_{10}(g(z))=2–0.15z$. Therefore, for each patient and technique, it is possible to compute g from the differential DVH of the combined ovaries (analysed with an interval width of 0.02 Grey) as:

$$g = \sum_{i=1}^{d_{max}} \left(10^{2-0.15*(1/2*(d_i+d_{i+1}))} * \frac{v_i}{v_{both\ ovaries}} \right)$$

Assuming a theoretical chronologic age at the beginning of therapy of 18–46 years in two-year intervals, it is possible to compute the expected time to menopause for each age and each resulting percentage of NGF. For this the Hansen's model [35] provided the absolute number n of follicles at a given age:

$$\log_{10}(n) = (-0.00019) * (age\ in\ years)^{2.452} + 5.717$$

N should be then scaled according to the corresponding survival fraction g, and the equation of Hansen's model solved to obtain the 'actual' fertility age after irradiation. From the latter, it is possible to compute the remaining fertility years assuming the standardised, average menopausal age of 50.4 years from Hansen's data and, consequently, the expected net fertility years loss expressed as the difference between the theoretical remaining fertility years (without irradiation) and the actual remaining fertility years (after irradiation).

Modelling the risk of secondary cancer induction

The EAR for the induction of any type of secondary solid cancer, for any specific organ (*org*) having received a given radiation dose, is defined as:

$$EAR^{org} = \mu\ \frac{1}{V_T} \sum_i V(D_i)\ \ RED(D_i)$$

where V_T is the total organ volume. The sum is over all the bins of the differential DVH, $V(D_i)$ is the absolute volume receiving a dose D_i. μ is the slope of cancer induction based on the atomic bomb survivors' data corrected for the age distribution. *RED(D)* is the dose-response, modelled to fit the Hodgkin patient's data group. The organ equivalent dose (OED): $OED = \frac{1}{V_T}\sum_i V(D_i)\ \ RED(D_i)$ was introduced as the dose in Grey, which, when uniformly distributed, causes the same radiation-

induced cancer incidence. The so-called full model [36] was applied in the present study and includes all the biological aspects of cell killing, repopulation/repair, and fractionation:

$$OED = \frac{1}{V_T}\sum_i V(D_i)\ \frac{e^{-\alpha' D_i}}{\alpha' R}\ \left(1 - 2R + R^2 e^{\alpha' D_i} - (1-R)^2\ e^{-\frac{\alpha' R}{1-R} D_i}\right)$$

where R is the parameter accounting for repopulation and/or repair and models the ability of the tissue to recover between two fractions (ranging from 0 for no recovery to 1 for complete recovery).

In the present study, R was set to 0.09, 0.06 and 0.99 for the bowel, bladder and rectum respectively; α' was set to 0.591, 0.219, 0.01 Gy^{-1} respectively [36]. The values of μ were set to: 5.0, 1.91 and 0.367. Since Schneider's model does not cover the rectum, we used the values for the colon assuming similar radiation sensitivity.

In the absence of reliable estimates of these values, besides the absolute EAR estimates, the EAR ratio for protons versus photons was also reported to more reliably quantify the potential benefit of IMPT.

Results

Patients

For general plan comparison and calculation of second tumour risk, we included 14 female GHSG HD-17 patients. For modelling the risk of ovarian failure, we excluded one patient with oophorectomy so that 13 patients were included for this purpose.

Dosimetric comparison

Figure 1 presents the average dose-volume histograms for the RA and IMPT plans for all the target volumes and the organs at risk considered in the study. The graphs confirm the equivalent degree of coverage and homogeneity achieved for the target volumes. For the OARs, the IMPT plans presented an average and substantial better-sparing effect over the dose range 0 to ~15–20Gy and in general for the mean doses. The near-to-maximum doses for the OARs more proximal to the target (or partially included) were comparable between the techniques as, for example, the ovaries, the bladder, the rectum and the bowels.

Table 2 summarises the quantitative analysis of the DVHs for the CTV, the PTV, and the OARs. Only the relevant metrics are reported.

Regarding target volumes, the two techniques resulted equivalent in terms of coverage and met the planning objectives on average. $V_{98\%}$ exceeded 98% for the CTV, while $V_{95\%}$ was greater than 95% for the PTV. The dose homogeneity resulted better than 3% for both groups.

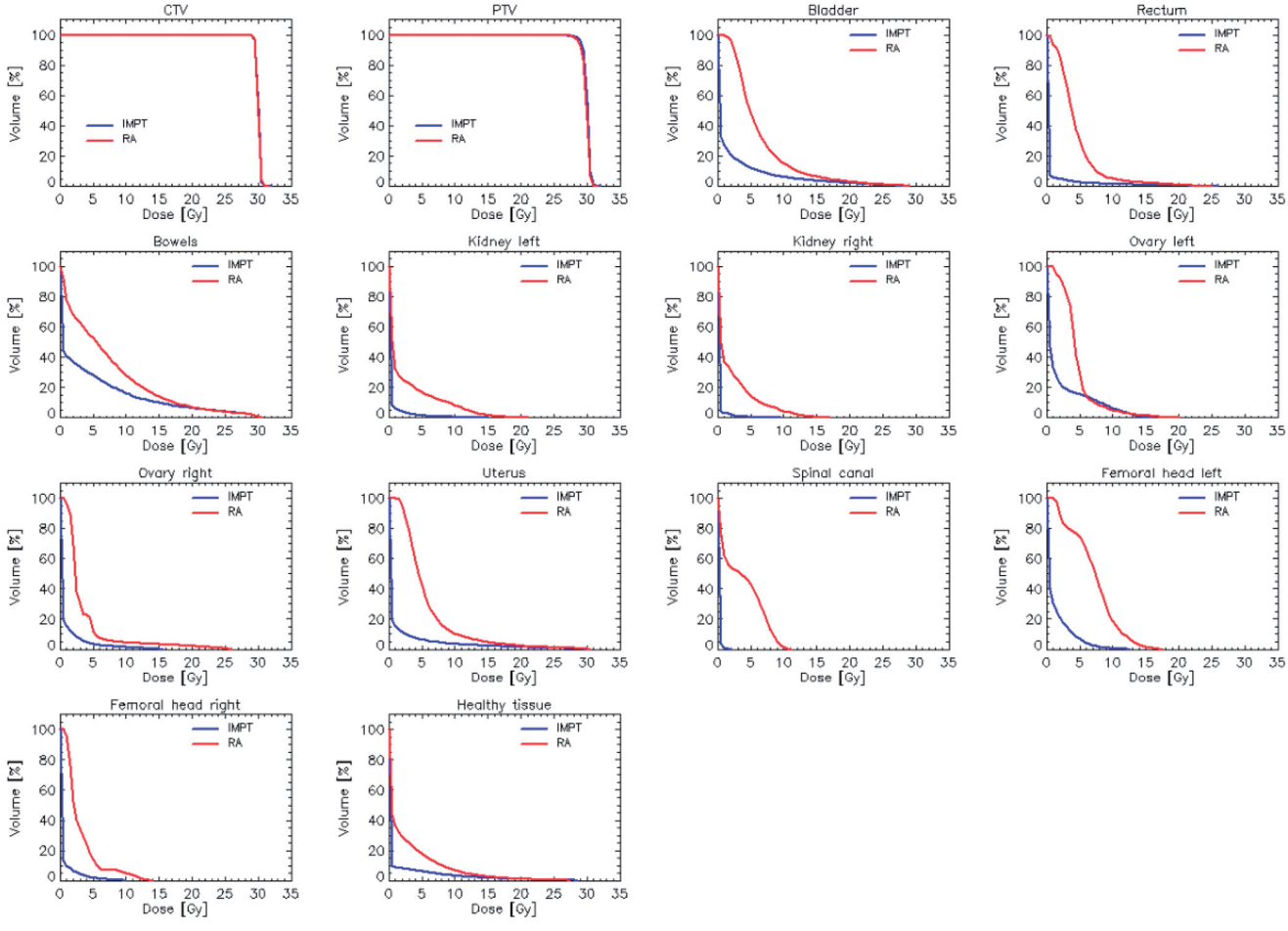

Figure 1. Average dose-volume histograms for the target volumes and the main organs at risk investigated.

For all the OARs, the IMPT technique allowed a statistically significant additional sparing compared to VMAT for both the mean and near-to-maximum dose metrics. Only for the bowel, the latter resulted equivalent for the two techniques. Concerning the ovaries, the photon RA plans failed on average to respect the constraint of 2 Gy to the mean dose. At the same time, this was more easily respected for the IMPT plans (although not for all patients, depending on the proximity of the ovaries with respect to the target).

As expected, Proton plans resulted superior to RA in the case of the remaining healthy tissue not identified as any specific OAR with a reduction of the mean dose or V_{10Gy} of more than a factor 2.

Secondary cancer risk estimates

The analysis of the EAR (expressed in cases per 10,000 patient-years) was summarised in Table 3. Relatively to photons, bladder resulted in the worst absolute estimated EAR while for protons, bowel and bladder resulted in similar absolute estimates, higher than the prediction for the rectum. The EAR ratio between IMPT and RA demonstrated that the risk of secondary cancer induction could be significantly mitigated with IMPT by a factor of about 2 to about 10, depending on the OAR considered.

Risk of ovarian failure

Figure 2a presents the expected menopausal age as a function of the chronologic age at irradiation from 18 to 46 years. Figure 2b illustrates the corresponding expected fertility years loss with respect to the nominal average menopausal age fixed at 50.4 years. The data are shown as average over the cohort of patients, and the uncertainty is represented at one standard deviation. For the chronologic age ranging from 18 to 46 years, the expected net fertility years loss ranged from 4.8 (at 18 years) to 3.0 years (at 46 years) for protons and from 12.0 to 5.7 years for photons.

Table 3. Estimates of the Excess absolute risk (EAR) (per 10,000 patient-years) of secondary cancer induction estimated with the full model over the entire cohort of 14 patients.

	VMAT	IMPT	IMPT/VMAT	*p*
Bowel	1.48 ± 0.34	0.68 ± 0.30	0.51 ± 0.32	<0.001
Bladder	2.50 ± 0.40	0.69 ± 0.62	0.32 ± 0.35	<0.001
Rectum	1.57 ± 0.73	0.15 ± 0.31	0.05 ± 0.11	<0.001

EAR: excess absolute risk; VMAT: Volumetric Modulated Arc Therapy; IMPT: intensity modulated proton therapy.
Results are shown as averages (with uncertainty expressed as one standard deviation). The p-value is relative to the Wilcoxon signed-rank paired test.

Discussion

Due to advances in systemic therapy, Hodgkin lymphoma has become a highly curable disease. Regardless of stage, the OS after five years is clearly above 90% [1–4]. Due to the high cure rate and the often young age of disease onset, the reduction of long-term toxicity by a de-escalation of therapy has come to the centre of attention. In radiotherapy, gradual reduction of irradiation volumes up to the current ISRT has contributed to reducing toxicity or secondary malignancies [22–24,37]. One more possibility to minimise the sequelae of irradiation is proton radiotherapy [29–33].

In a collective of GHSG HD17 patients with infra diaphragmatic HL planned for ISRT, we demonstrated that IMPT significantly reduced the dose in all OARs compared to VMAT. In particular, the risk of secondary cancer induction for bladder, rectum, and bowel is considerably lower after IMPT. Because only three patients included in the study had involvement in the upper abdomen, an analysis of pancreas, liver, colon or stomach would not have statistical validity and, for this reason, was not included. The risk of secondary cancer induction to those organs should not be neglected in the case of more direct involvement. However, in our clinical experience, in infra-diaphragmatic early-stage HL, the most common localisation is in the pelvis or lower abdomen. Furthermore, IMPT resulted in a significantly longer calculated time to premature menopause compared to VMAT.

Various planning studies have demonstrated the advantage of sparing the OARs and reducing the second tumour risk of proton radiotherapy over photon radiotherapy in supradiaphragmatic HL [29–33]. These data are almost entirely lacking for infra diaphragmatic HL, although infra diaphragmatic irradiation also significantly increases the risk of second cancer [38,39]. Only Sachsman [28] investigated infra diaphragmatic proton radiotherapy. For this purpose,

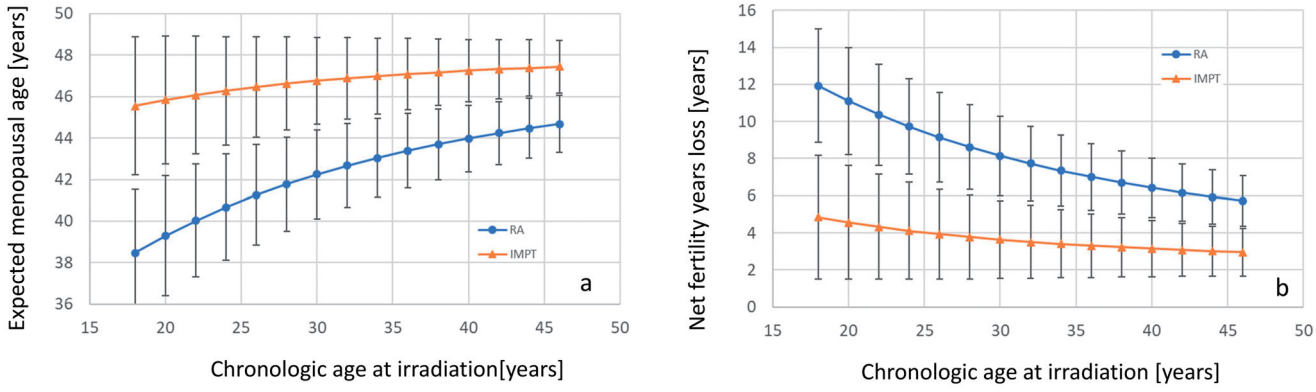

Figure 2. (a) The expected menopausal age; (b) the expected fertility years loss with respect to the nominal average menopausal age fixed at 50.4 years. Both graphs are expressed as a function of the chronologic age at irradiation from 18 to 46.

they performed a plan comparison between 3 D-RT, IMRT, and passively scattered proton therapy in 13 patients [28,40]. Due to the small number of patients in our study and the publication of Sachsman, a direct comparison of the data is difficult. This is especially true since Sachsman primarily studied patients in the upper abdomen, whereas we mainly included patients in the pelvis/paraaortic region. Both studies showed a clear advantage for proton radiotherapy. Based on a comparison of the DVHs, it can be assumed that in our comparison, the use of IMPT compared with VMAT leads to a greater advantage than the use of passively scattered proton therapy compared with IMRT in Sachsman's study. However, this can only be assumed due to the small number of patients in both studies and the different disease patterns.

To our knowledge, we were the first to demonstrate an advantage for infra diaphragmatic proton therapy compared to photon therapy with respect to secondary cancer risk. This is a relevant issue, especially in the young population of HL patients, since more patients die of a solid secondary tumour than Hodgkin lymphoma during an extended follow-up [39]. Since the 1960s, the mortality of Hodgkin lymphoma has improved significantly due to modern therapy regimens [39]. In contrast, mortality due to secondary tumours remains unchanged [39]. The combination of modern target volume concepts such as ISRT and the use of modern radiation techniques such as IMPT could significantly reduce mortality from second tumours.

Besides secondary cancer risk and cardiac toxicity [13,14], premature menopause is one of HL therapy's most serious long-term toxicities [17,41]. In addition to the loss of fertility and unwanted childlessness, there are further serious consequences such as osteoporosis [42], increased cardiovascular risk [43], and depressions [44]. Overall, premature menopause results in increased mortality [45]. Various studies show that chemotherapies, especially those based on alkylating agents, lead to a high degree of ovarian failure [16,17,41,46]. Nevertheless, infra diaphragmatic radiotherapy is considered a major risk factor for ovarian failure [47] due to the high radiation sensitivity of the ovaries [46]. Numerous studies have demonstrated the ovarian toxicity of infra diaphragmatic RT in HL [41,47,48]. However, these relate to EFRT. Therefore, a reduction of ovarian toxicity can be expected with modern target volume concepts such as ISRT. We showed that infra diaphragmatic ISRT leads to early menopause but that a relevant sparing of the ovaries is possible. Furthermore, we were able to show that by using IMPT compared to VMAT, better ovarian protection is possible and thus, the calculated time to early menopause after IMPT is significantly longer. Especially in younger women, there are clear differences between IMPT and VMAT with regard to the time until menopause. A limitation of our study is that no oophoropexy was performed in our patients. Ovarian transposition often allows ovarian sparing even with conventional radiation techniques [49–51]. However, the advantage of oophoropexy in Hodgkin lymphoma could not always be confirmed [51–54]. Furthermore, for Hodgkin lymphoma with paraaortic involvement, medial ovarian transposition is recommended [51]. In this case, the protection of ovaries with modern VMAT may be even worse than with the described conventional techniques due to the low dose exposure of VMAT irradiation. In contrast, we were able to show that sufficient ovarian sparing can be achieved with IMPT even without oophoropexy. With the use of ovarian transposition, we expect even more protection of the ovaries.

Several limitations of the study shall be mentioned. The primary limit is in the in-silico nature of the study. All the results and the conclusions were derived from numerical computation and the application of bio-mathematical models. This is standard practice in assessing one radiotherapy treatment's potential absolute or relative benefits but cannot substitute the evidence gathered from adequately designed clinical trials. The strength of a dosimetric in-silico comparison is the possibility to focus on physics or technique related aspects factorising out all the clinical factors impacting in-vivo study. Inter-patient anatomical variability is accounted for depending on the sample of the cohort investigated. In this respect, the number of patients included in the planning comparison is relatively small, although consistent with most similar investigations where the cohorts range typically from 10 to 30 cases. This would be insufficient in an adequately powered clinical trial, but it is considered decently adequate for an in-silico proof of principle. Among the limitations of the study, we also want to mention that the dose calculation accuracy of the algorithms in terms of out-of-field dose and neutron contamination was not assessed in detail. Concerning the secondary cancer risk models, these are based on atomic bomb survivor data, subsequently corrected with organ's specific data. It is clear that, in the absence of validated models, the results shall be considered with care, and, rather than looking at the absolute values, the relative difference between IMPT and VMAT provides a more reliable metric. In general, internal organ's motion, respiratory motion and presence of erratic air in the bowel was not taken into detailed account. Robust optimisation was applied for IMPT with uncertainty parameters derived from clinical experience, but further mitigation strategies should be needed in view of clinical implementation. This was out of the scope of the in-silico investigation but, to list some, abdominal compression, rescanning, gating should be considered. The beam orientation for IMPT should also be tuned on an individual basis for the same reasons.

Conclusion

Overall, we could show that infra diaphragmatic IMPT has a dosimetric gain in comparison to VMAT, and this might turn into a reduction of long-term toxicities. While numerous studies have shown the benefits of supradiaphragmatic proton therapy of HL in terms of long-term toxicity compared to photon therapy, we are – to our knowledge – the first to demonstrate this for infra diaphragmatic IMPT of HL. Especially in younger patients with a long follow-up, it can be assumed that this reduction of long-term toxicities will also be reflected in an overall survival gain.

Disclosure statement

No potential conflict of interest was reported by the authors..

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