Comparison of secondary cancer risks between intensity modulated radiation therapy (IMRT) and intensity modulated proton therapy (IMPT) for rectal cancer

การเปรียบเทียบความเสี่ยงในการเกิดมะเร็งทุติยภูมิจากการฉายรังสีแบบปรับความเข้ม (IMRT) และการฉายอนุภาคโปรตอนแบบปรับความเข้ม (IMPT) สำหรับมะเร็งลำไส้ตรง

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Abstract

Backgrounds: Radiation therapy plays an important role in rectal cancer treatment. However, according to atomic bomb survivor studies, radiation is a risk factor for solid cancer incidence in any tissues. Therefore, radiation therapy is relevant for an increased risk for developing secondary cancer in treated patients.

Objective: To evaluate and compare secondary cancer risks between intensity modulated radiation therapy (IMRT) and intensity modulated proton therapy (IMPT) for rectal cancer in terms of organ equivalent dose (OED) and organ-specific excess absolute risk (EAR^{org}).

Materials and methods: A male adult computational phantom with an average body size of a 68-year-old Thai male was used for IMRT and IMPT treatment planning. For IMRT, 12 fields of 6 MV flattening filter free (FFF) photon beams were used for treatment planning using the Ethos treatment planning system (TPS) (Varian Medical System, Palo Alto, California, USA), while 2-, 3-, and 5-field IMPT plans were calculated using matRad TPS. Dose distributions and OEDs were evaluated for organs at risk (OARs). The calculation of secondary cancer risk was done in terms of EAR^{org} using a mechanistic model for radiation-induced carcinoma and sarcoma.

Results: IMPT delivered lower doses to the OARs than IMRT. The EAR in 10,000 persons per year (PY) for the IMPT plans ranged from 0.60 to 0.71 for the bladder, 0.07 to 0.08 for the bowel and 13.59 to 14.35 for the colon, while the EAR for the IMRT plan was 0.33 for the bladder, 0.96 for the bowel, and 21.90 for the colon. The colon had the highest risk of secondary cancer incidence, although the mean organ dose was much lower than those in other organs. Our result indicated that IMPT decreased secondary cancer risks in most organs compared to IMRT, except for the bladder, where low dose exposure by IMPT led to unfavorably high risk. Moreover, the risk of bone and soft tissue sarcomas after IMRT and IMPT were relatively small.

Conclusion: Based on the mechanistic risk model, the estimated secondary cancer risk after IMPT was generally lower than that after IMRT. The 2-field IMPT plan had the lowest risk among all IMPT plans investigated.

Keywords: Rectal cancer, secondary cancer risk, IMRT, IMPT

บทคัดย่อ

หลักการและเหตุผล: การฉายรังสีมีบทบาทสำคัญในการรักษาผู้ป่วยมะเร็งมะเร็งลำไส้ตรง จากการศึกษาข้อมูลผู้รอดชีวิตจากเหตุการณ์ระเบิดปรมาณูพบว่า รังสีเป็นปัจจัยเสี่ยงในการเกิดมะเร็ง ดังนั้นการฉายรังสีจึงมีความเกี่ยวข้องกับความเสี่ยงที่เพิ่มขึ้นในการเกิดมะเร็งทุติยภูมิในผู้ป่วย

วัตถุประสงค์: เพื่อประเมินและเปรียบเทียบความเสี่ยงในการเกิดมะเร็งทุติยภูมิจากการฉายรังสีปรับความเข้ม (IMRT) และการฉายอนุภาคโปรตอนปรับความเข้ม (IMPT) สำหรับมะเร็งลำไส้ตรง โดยใช้ค่า organ equivalent dose (OED) และ excess absolute risk ของอวัยวะ (EARorg)

วัสดุและวิธีการ: หุ่นจำลองคณิตศาสตร์เทียบเท่าขนาดประชากรเพศชายไทยที่มีอายุเฉลี่ย 68 ปี ถูกนำมาใช้วางแผนการรักษาด้วยเทคนิค IMRT และ IMPT แผน IMRT ใช้โฟตอนพลังงาน 6 เมกะโวลต์ ชนิดไม่มีแผ่นกรองลำรังสี มีการเข้า 12 ทิศทาง คำนวณโดยใช้ระบบวางแผนการรักษา Ethos แผน IMPT มีการเข้าของลำอนุภาค 2, 3 และ 5 ทิศทาง คำนวณโดยใช้ระบบวางแผนการรักษา matRad ผู้วิจัยประเมินค่าการกระจายปริมาณรังสีและ OED สำหรับอวัยวะที่มีความเสี่ยง รวมทั้งคำนวณค่า EARorg โดยใช้แบบจำลอง mechanistic สำหรับการเกิดมะเร็งในกลุ่มคาร์ซิโนมาและซาร์โคมา

ผลการศึกษา: IMPT ให้ปริมาณรังสีต่ำกว่า IMRT ในอวัยวะที่มีความเสี่ยง แผน IMPT มีค่า EAR (ต่อ 10,000 คนต่อปี) อยู่ในช่วง 0.60 ถึง 0.71 สำหรับกระเพาะปัสสาวะ 0.07 ถึง 0.08 สำหรับลำไส้เล็ก และ 13.59 ถึง 14.35 สำหรับลำไส้ใหญ่ ในขณะที่ค่า EAR สำหรับแผน IMRT เท่ากับ 0.33, 0.96 และ 21.90 ตามลำดับ ลำไส้ใหญ่เป็นอวัยวะที่มีความเสี่ยงสูงสุดแม้จะได้รับปริมาณรังสีต่ำกว่าอวัยวะอื่น ผลการศึกษาพบว่า IMPT ลดความเสี่ยงในการเกิดมะเร็งทุติยภูมิในอวัยวะส่วนใหญ่เมื่อเทียบกับ IMRT ยกเว้นกระเพาะปัสสาวะ ในกรณีนี้การกระจายปริมาณรังสีระดับต่ำจากเทคนิค IMPT นำไปสู่ความเสี่ยงที่เพิ่มขึ้นในกระเพาะปัสสาวะ นอกจากนี้ความเสี่ยงในการเกิดมะเร็งในกลุ่มซาร์โคมาค่อนข้างต่ำทั้งในแผน IMRT และ IMPT

ข้อสรุป: จากแบบจำลอง mechanistic ความเสี่ยงในการเกิดมะเร็งทุติยภูมิในแผน IMPT ต่ำกว่าแผน IMRT โดยส่วนใหญ่ และแผน IMPT ที่มีการเข้า 2 ทิศทางทำให้เกิดความเสี่ยงต่ำที่สุด

คำสำคัญ: มะเร็งลำไส้ตรง, ความเสี่ยงในการเกิดมะเร็งทุติยภูมิ, การฉายรังสีปรับความเข้ม, การฉายอนุภาคโปรตอนปรับความเข้ม

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Introduction

Rectal cancer incidence was diagnosed as the 8th most common cancer worldwide and the 10th leading cause of cancer deaths accounting for 3.2% of all cancer deaths[1]. In Thailand, the incidence of colorectal cancer was diagnosed as the 3rd most common cancer, which accounted for 11% of all cancer cases. The most common age group that was diagnosed with colorectal cancer was 60–75 years for both sexes. Moreover, 40% of all colorectal cancer cases were diagnosed with rectal cancer[2].

Radiation therapy plays an important role in rectal cancer treatment, such as, prevention of local recurrences, improvement of survival, downstaging the tumor and palliative treatment[3]. The state-of-the-art photon therapy, such as, intensity modulated radiation therapy (IMRT) and volumetric modulated radiation therapy (VMAT), provides better dose conformality to the tumor and reduces dose to normal tissues compared to conventional techniques. However, beam modulation and large beam-on time lead to increase of head leakage, resulting in out-of-field organ dose. Moreover, many gantry angles are typically used, resulting in low dose to normal tissues[4,5]. Proton therapy is another advanced treatment modality for rectal cancer. Proton therapy delivers low dose in the entrance region and a dose peak at a finite range near the end of the beam path, in the so-called Bragg peak region. Proton therapy for rectal cancer is used to improve local control and survival with the ability to reduce dose to normal tissues or organs at risk (OARs) and minimize acute and late toxicities from radiation therapy[6]. The out-of-field dose in proton therapy primarily arises from neutrons from the interactions of primary ions with beam-line components and patients[4].

The effectiveness of radiation therapy should be weighed against short- and long-term adverse effects[3]. Secondary cancer risk after radiation therapy is a long-term effect commonly used to justify treatment techniques[7]. Modeling of radiation-induced cancer risk is usually based on atomic bomb survival data characterized by low dose radiation exposure[7]. Several groups have modeled secondary cancer risk after radiation therapy. For examples, Wheldon et al.[8] and Lindsay et al.[9] used a two-stage radiation carcinogenesis model including cellular repopulation with different assumptions. This model focused on the repopulation effect after single irradiation. They found a bell-shape relationship of the dose-response with the decrease of cancer risk at high dose[8,9]. Similarly, Dasu et al.[10] used a competition model to describe a dose-response relationship by accounting for the probability of DNA mutation and the probability of cell survival in organs in the treatment area. The dose-response relationship from Dasu's model were similar to the two-stage model[10]. Sachs and Brenner[11] developed the risk model to account for the effect of carcinogenesis, cell killing and proliferation of irradiated cells. They found repopulation effect tended to cause resistance to cell killing leading to a nearly constant risk at high dose[11]. The mechanistic

model introduced by Schneider et al.[7,12,13] is one of the most commonly used models. Schneider's model combines low dose data from the atomic bomb survivors and the data of a Hodgkin cohort after radiation therapy to describe the site-specific dose-response relationships of carcinoma and sarcoma induction separately[13]. This mechanistic model accounts for cell killing, fractionation effect, and repopulation of radiation-exposed tissues[13]. Moreover, Schneider et al. proposed the concept of organ equivalent dose (OED) for radiation-induced cancer[14]. The assumption of OED is that for any inhomogeneous dose distributions in an organ, the same OED causes the same radiation-induced cancer incidence rate in that organ[14].

The aims of this study were to determine the risk of secondary cancer after IMRT and intensity modulated proton therapy (IMPT) for treatment of rectal cancer and to compare secondary cancer risks between the investigated modalities in terms of OED, excess absolute risk (EARorg) and risk ratio (RR)[13].

Materials and methods

Patient Selection

A male adult computational phantom of the National Cancer Institute/University of Florida (NCI/UCF) phantom series[15] was used to represent the average male rectal cancer patient. The NCI/UCF phantoms are whole-body computational phantoms, representing adults and children of different weights and heights[16]. The selected phantom had the weight and height of 70 kg and 170 cm, respectively, similar to the average weight and height, 66.75 kg and 166.57 cm, respectively, of a 68-year-old Thai male, who is in the age group that has the highest incidence of colorectal cancer in Thailand (60 – 75 years)[2]. Concerning anatomical realism, each phantom has more than 100 organs created using non-uniform rational B-spline (NURBS) and polygon mesh (PM) surfaces[15]. The phantoms have been converted to the DICOM-CT format with the DICOM-RT structure set for use in commercial treatment planning systems. The reason for using the computational phantom instead of a patient dataset was that further investigation of dose in organs far from the target could be performed using a Monte Carlo simulation, while patient images for treatment planning are usually confined to the region of therapeutic interest.

Treatment planning

The simultaneous integrated boost (SIB) IMRT plan with 6 MV flattening filter free (FFF) beams was calculated using the Ethos treatment planning system (TPS) (Varian Medical System, Palo Alto, California, USA) with the Ethos Acuros XB (AXB) algorithm for dose calculation. In this study, the Ethos TPS was used to generate a 12-field IMRT plan with the prescribed dose to the PTV of 50 Gy in 25 fractions. The dose constraints were based on QUANTEC[17], RTOG 0418[18], RTOG 1203[19], RTOG 0822[20], and EMBRACE II[21].

Table 1 The treatment planning parameters and dose constraints for the investigated IMPT techniques

Field parameter	2-field IMPT	3-field IMPT	5-field IMPT
Bixel width or lateral spot spacing	5 mm	5 mm	5 mm
Longitudinal spot spacing	2 mm	2 mm	2 mm
Field projections	Right posterior oblique (RPO) and left posterior oblique field (LPO)	Opposed lateral field and posterior-anterior field (PA)	Opposed lateral field, PA, LPO and RPO
Gantry angles	140° and 220°	90°, 180° and 270°	90°, 140°, 180°, 220° and 270°
Number of pencil beams	29,086	43,899	72,985

Target and organ at risk	Dose constraint	Clinical goal
CTV50	$V_{100\%}$	> 95 – 97%
	D_{max}	< 110%
Bladder	V_{40Gy}	< 50%
	V_{30Gy}	< 60%
Femoral heads	V_{45Gy}	< 5%
	V_{40Gy}	< 30%
	V_{30Gy}	< 35%
Small bowel	V_{40Gy}	< 70 cm^3
	V_{35Gy}	< 300 cm^3
	V_{30Gy}	< 350 cm^3
	D_{max}	< 52 Gy

The IMPT planning was performed using matRad, which is a multi-modality open-source 3D treatment planning tool developed for research purposes[22]. MatRad did not have a robust optimization function. Therefore, the treatment planning was done through PTV, by taking into account errors from organ movement and setup uncertainties in a margin extending from the CTV. For the IMPT plans, the prescribed dose was based on the constant relative biological effectiveness (RBE) of 1.1. The prescribed dose to the PTV was 50 Gy equivalent (GyE) in 25 fractions. The dose constraints followed the recommendation of

Parzen et al[23], which was based on RTOG 0822[20]. In addition, all IMPT plans were found to comply with the dose constraints of the 12-field IMRT plan, because the IMPT dose constraints used in this work were stricter than those used for the IMRT technique. The investigated IMPT treatment plans contained 2, 3 and 5 fields with the treatment planning parameters given in **Table 1**.

Secondary cancer risk estimation

The organ-specific excess absolute risk, EAR^{org}, was chosen as the measures of risk from radiation therapy. The EAR represents the difference between the rate of disease incidence occurring in the exposed and unexposed groups[12]. The EAR^{org} in the unit of per 10,000 persons per year (PY) was calculated from the following formula.

$$EAR^{\mathrm{org}} = \frac{1}{V_{\mathrm{T}}} \sum_{i} V(D_i)\, \beta_{\mathrm{JP}}\, RED(D_i) \mu(agex, agea)$$

V_T is the total volume of the organ, $V(D_i)$ is the volume receiving dose of the i_{th} bin of the dose-volume histogram (DVH), $RED(D_i)$ is the risk equivalent dose of the i_{th} DVH bin, β_{JP} is the initial slope of the dose-response relationship at low dose taken from the atomic bomb survivor data as given by Preston et al[24] and μ is the modifying function. The DVHs of organs of interest were obtained from the treatment planning systems.

Since β_{JP} was defined for the population with the age at exposure of 30 years and the attained age of 70 years, the modifying function μ was used to adjust the EAR for the different age at exposure and attained age, as follows.

$$\mu(agex, agea) = \exp\left(\gamma_e(agex - 30) + \gamma_a \ln\left(\frac{agea}{70}\right)\right)$$

γ_e and γ_a are the age modifying factors, agex is the age at exposure and agea is the attained age. In this study, the EAR was calculated for the age at exposure of 60 years and the attained age of 75 years according to the incidence of colorectal cancer in Thailand[2].

The RED corresponds to the dose-response relationship, which is proportional to the probability of radiation-induced cancer[13]. In this study, the REDs for carcinoma and sarcoma induction were calculated separately using the model of Schneider et al.[13], as follows.

$$RED(D) = \frac{e^{-\alpha' D}}{\alpha' R}\left(1 - 2R + R^2 e^{\alpha' D} - (1-R)^2 e^{-\frac{\alpha' R}{1-R} D}\right) \quad \text{For carcinoma}$$

$$RED(D) = \frac{e^{-\alpha' D}}{\alpha' R}\left(1 - 2R + R^2 e^{\alpha' D} - (1-R)^2 e^{-\frac{\alpha' R}{1-R} D} - \alpha' RD\right) \quad \text{For sarcoma}$$

R is the repopulation/repair parameter, and α' is the cell killing factor, which corresponds to the reduction of cells as described by the linear-quadratic model. α' is calculated from the following formula.

$$\alpha' = \alpha + \beta d$$

α and β are the cell killing parameters of the linear-quadratic model for the organ of interest and d is dose per fraction. **Table 2** lists all parameters used for the calculation of the EAR^{org} and the RED.

The OED was also calculated for organs of interest that received inhomogeneous dose distributions during radiotherapy. The OED is equivalent to the volume-averaged RED[13], given as the following formula.

$$OED = \frac{1}{V_T}\sum_i V(D_i)RED(D_i)$$

It is to note that the parameters for calculating the REDs for some organs, such as, the prostate, the kidney and the spinal cord were not available. Therefore, the REDs, and thus the EARs and the OEDs, of these organs were not estimated in this work.

Finally, the comparison between the different treatment modalities for the same group of population, age at exposure and attained age was performed using the risk ratio[13], given by the following formula.

$$Risk\ ratio = \frac{EAR_A^{org}}{EAR_B^{org}} = \frac{OED_A}{OED_B}$$

As seen in risk ratio formula, the risk ratio between treatment modalities for the same group of population can be calculated by either the ratio of EAR^{org} or the ratio of OED.

Table 2 The parameters used for the calculation of excess absolute risks (EARsorg).

Organ	α	R	β	γ_e	γ_a
Bladder	0.219	0.06	3.20	-0.024	2.38
Bowel	0.591	0.09	8.00	-0.056	6.90
Colon	0.001	0.99	8.00	-0.056	6.90
Bone	0.067	0.50	0.20	-0.013	-0.56
Soft tissue	0.060	0.50	0.60	-0.013	-0.56

Results

The dose distributions from the different treatment plans are shown in **Figure 1**. **Table 3** summarizes the mean doses to the organs of interest. For these organs, the mean organ doses from IMRT were larger than those from IMPT. Of all investigated IMPT plans, using two oblique fields (RPO and LPO) gave the lowest mean doses to most organs, and the mean organ doses from the 5-field IMPT plan were lower than those from the 3-field IMPT plan, except for the sacrum.

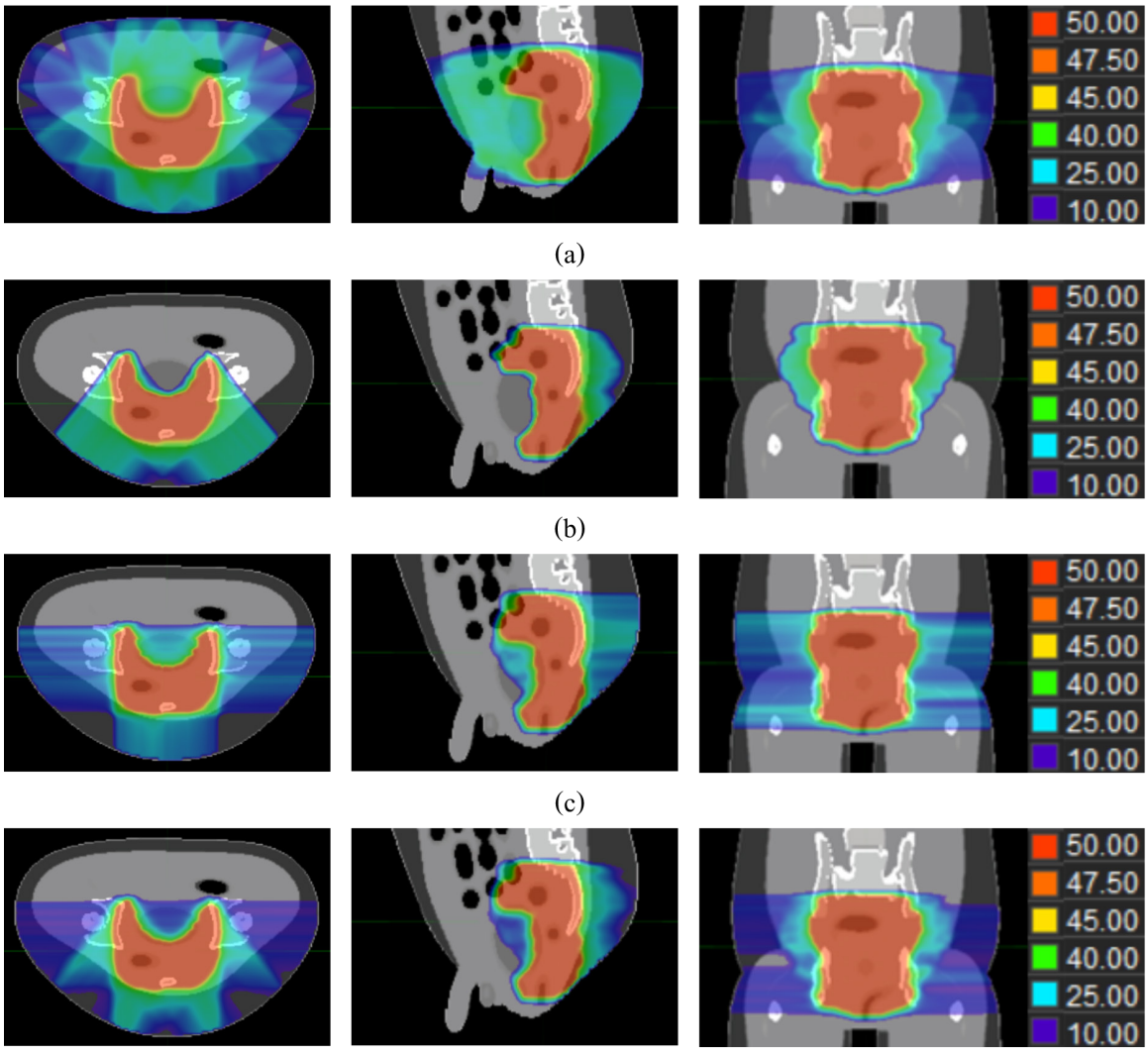

Figure 1 The dose distributions of (a) 12-field IMRT, (b) 2-field IMPT, (c) 3-field IMPT and (d) 5-field IMPT.

The REDs as the functions of organ dose are plotted in **Figure 2**. As the organ dose increased, the RED for carcinoma induction increased at low doses and decreased at high dose, while the RED for sarcoma induction was negligible at low dose and increased at high dose. **Figure 3** and **Figure 4** show the examples of differential dose volume histograms, risk equivalent dose, and risk equivalent dose weighted with the dose volume for carcinoma induction in the bladder and sarcoma induction in the pelvic bone, respectively.

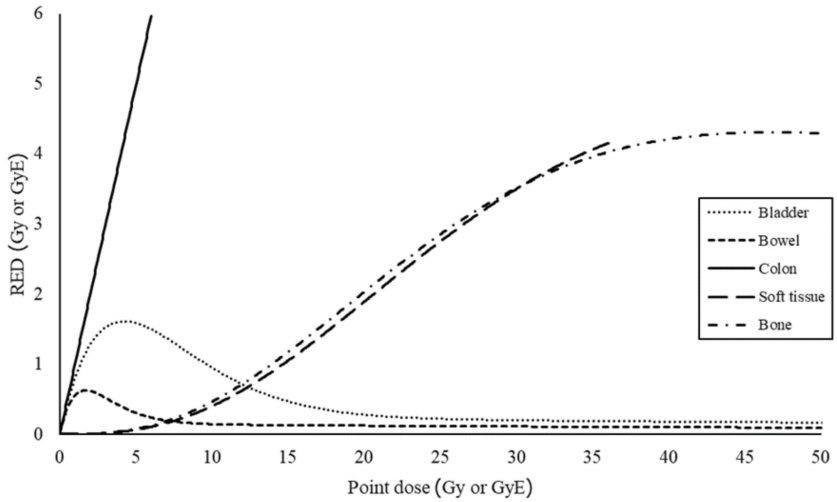

Figure 2 The risk equivalent doses (REDs) for carcinoma induction in the bladder (dotted line), the bowel (short dashed line) and the colon (solid line), and the RED for sarcoma induction in soft tissues (long dashed line) and bones (dash-dotted line).

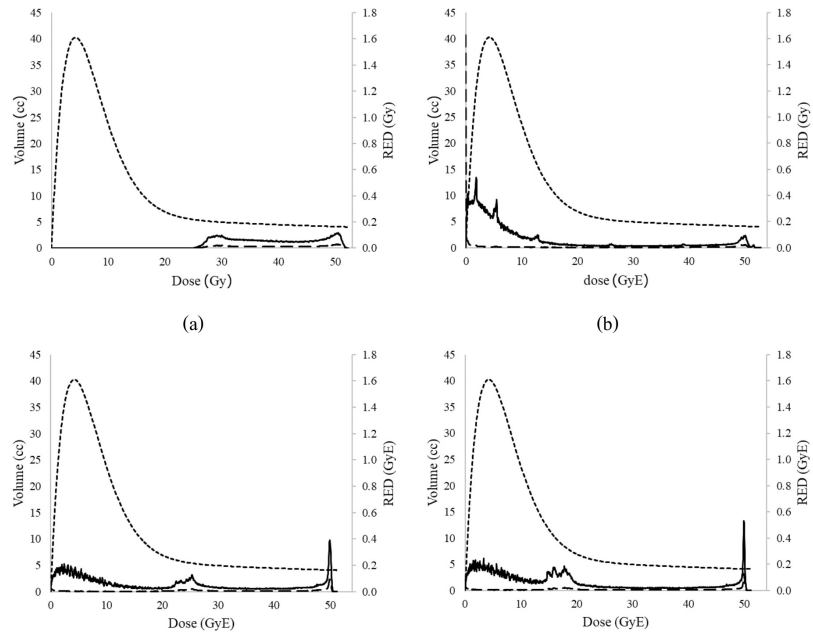

Figure 3 Differential dose volume histograms (long dashed line), risk equivalent dose (short dashed line), and risk equivalent dose weighted with the dose volume (solid line) for carcinoma induction in the bladder: (a) 12-field IMRT, (b) 2-field IMPT, (c) 3-field IMPT and (d) 5-field IMPT.

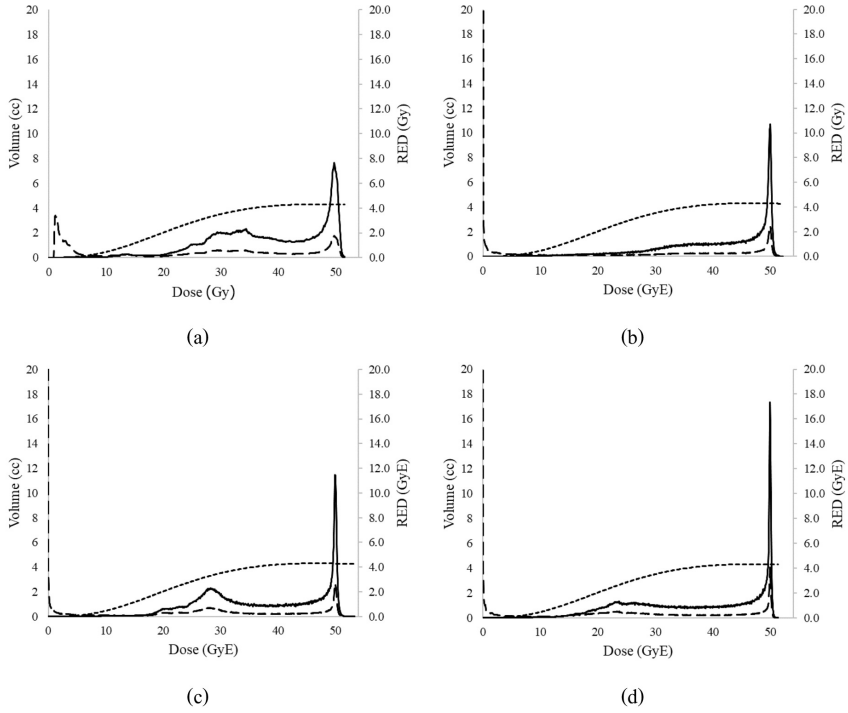

Figure 4 Differential dose volume histograms (long dashed line), risk equivalent dose (short dashed line), and risk equivalent dose weighted with dose volume (solid line) for sarcoma induction in the pelvic bone: (a) 12-field IMRT, (b) 2-field IMPT, (c) 3-field IMPT and (d) 5-field IMPT.

The OEDs and EARs of the organs of interest are reported in **Table 4** and **Table 5**, respectively. The colon had the highest risk of secondary cancer in both IMRT and IMPT plans, although the mean colon dose was much lower than those in the bladder, the pelvic bone, and the sacrum. Both OEDs and EARsorg indicated that the radiation-induced cancer risk after radiation therapy for rectal cancer was lower for IMPT compared with IMRT, except for the bladder. Moreover, the EARs for sarcoma induction, including bone and soft tissue sarcomas, were found to be small despite the relatively high doses received. **Figure 5** shows the risk ratios between the IMPT plans and the IMRT plan, and between the different IMPT plans investigated. The 2-field IMPT plan was found to have the lowest risks in most organs except for the bladder. The estimated secondary cancer risks for the 3- and 5-field IMPT techniques were relatively similar.

Table 3 The mean organ doses from various treatment planning techniques.

Organ	Mean dose (GyE)			
	12-field IMRT	2-field IMPT	3-field IMPT	5-field IMPT
Bladder	39.42 ± 7.76	17.81 ± 19.18	30.40 ± 15.5	27.63 ± 16.48
Bowel	8.34 ± 13.36	1.49 ± 6.80	1.71 ± 7.64	1.65 ± 7.37
Colon	9.51 ± 16.74	5.95 ± 15.94	6.28 ± 16.11	6.23 ± 16.09
Femoral Left	5.13 ± 8.06	0.19 ± 1.65	4.92 ± 8.75	3.52 ± 6.31
Femoral Right	5.05 ± 7.99	0.21 ± 1.79	4.93 ± 8.62	3.50 ± 6.22
Pelvic bone	25.78 ± 17.61	15.70 ± 19.73	19.41 ± 18.74	18.67 ± 18.66
Sacrum	20.64 ± 19.34	14.56 ± 20.69	14.56 ± 20.26	14.70 ± 20.62
Male reproductive	17.90 ± 10.84	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Prostate	47.57 ± 3.53	39.98 ± 10.56	42.14 ± 8.66	41.82 ± 8.95
Kidney Left	0.40 ± 0.19	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Kidney Right	0.42 ± 0.20	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Spinal cord	0.31 ± 0.52	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00

Table 4 The organ equivalent doses (OEDs) from various treatment planning techniques.

Organ	OED (GyE)			
	12-field IMRT	2-field IMPT	3-field IMPT	5-field IMPT
Bladder	0.18	0.39	0.33	0.38
Bowel	0.40	0.03	0.03	0.03
Colon	9.12	5.66	5.98	5.94
Femoral Left	0.43	0.01	0.49	0.26
Femoral Right	0.42	0.01	0.48	0.25
Pelvic bone	2.51	1.50	1.95	1.83
Sacrum	1.76	1.30	1.32	1.32
Male reproductive	1.74	0.00	0.00	0.00

Table 5 The organ-specific excess absolute risks (EARsorg) from various treatment planning techniques.

Organ	EAR^{org} (10,000 PY)$^{-1}$			
	12-field IMRT	2-field IMPT	3-field IMPT	5-field IMPT
Bladder	0.33	0.71	0.60	0.69
Bowel	0.96	0.07	0.07	0.08
Colon	21.90	13.59	14.35	14.25
Femoral Left	0.06	0.00	0.06	0.03
Femoral Right	0.05	0.00	0.06	0.03
Pelvic bone	0.33	0.20	0.25	0.24
Sacrum	0.23	0.17	0.17	0.17
Male reproductive organs (penis and scrotum)	0.68	0.00	0.00	0.00

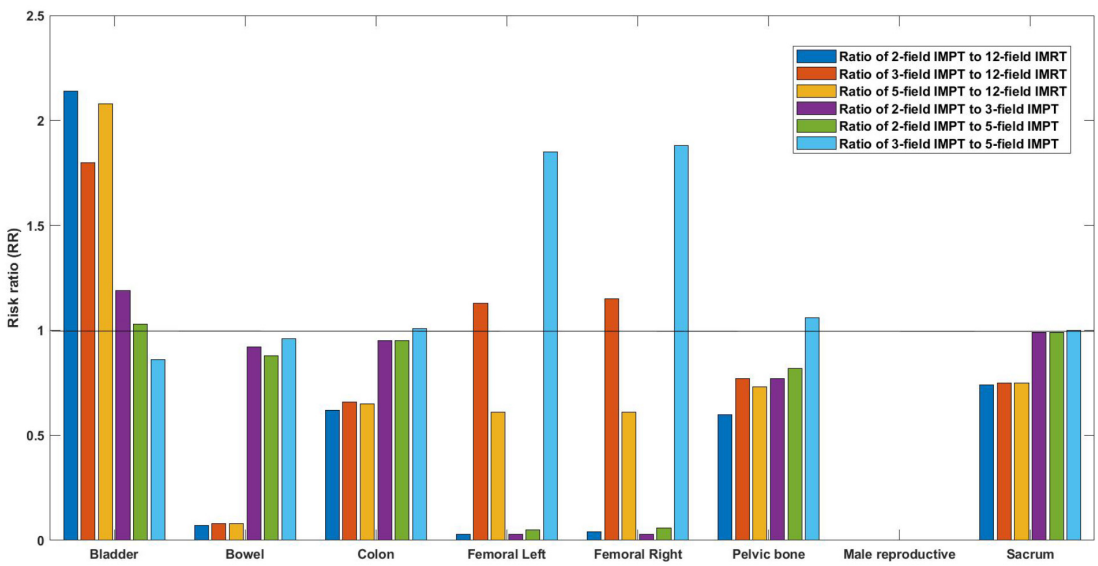

Figure 5 Risk ratio (RR) of excess absolute risks for different modalities.

Discussion

In terms of dose distributions, IMPT was found to be superior to IMRT. Similarly, the organ-specific EARs of IMRT plans were higher than those of IMPT for most organs, except for the bladder. In general, the OARs near the target volume, which received dose higher than 2 Gy, such as, bowel, tended to have lower secondary cancer risks. In contrast, some OARs, such as, the bladder, which could be exposed by both low and high doses in the IMPT plans (see **Figure 3**), had a higher secondary cancer risk than IMRT. The contradictory result for the bladder could be explained by the obtained differential DVH (**Figure 3**) and the characteristic of the mechanistic model for carcinoma induction (**Figure 2**). Using the mechanistic model for carcinoma, exposure to low dose was associated with high RED, while exposure to high dose resulted in low RED due to the cell killing effect[13]. Since IMPT tended to give lower dose exposure to the bladder than IMRT, the RED weighted with the dose volume. Therefore, the OEDs and EARs, became higher after IMPT than those after IMRT. To reduce low dose exposure to the bladder in the IMPT technique, the beam-specific PTV definition could be useful.

In this study, we found that 2-field IMPT yielded the lowest EARs for the OARs, compared with the other IMPT plans. Similar results were observed by the dosimetric analysis of Parzen et al.[23], who concluded that 2-field IMPT was superior to 3- and 5-field IMPT.

The incidence of secondary cancer after radiation therapy is expected to occur mostly in organs adjacent to target volume[25]. Our result was consistent with this expectation. Namely, the EARs for the colon and the bladder, which were located in field and near field in both IMRT and IMPT techniques, were found to be higher than the EARs for other organs The similar result was observed in the study of Zwahlen et al. for rectal cancer radiation therapy using 3D conformal radiation therapy (3D-CRT) and volumetric modulated arc therapy (VMAT), where the higher excess lifetime attributable risk (LAR) for organs close to the target volume, such as, the colon, the sigmoid and the bladder, were higher than those for other organs[26].

The variation of age at exposure was another major factor associated with the variation of the risk of radiation-induced cancer, but the relationship between the adult exposure age and the risk of radiation-induced cancer was not yet clear[27]. However, the weight of epidemiological data suggested that increasing age at exposure for adults typically did not decrease the radiation-induced cancer risk[28,29]. From the study of the Japanese atomic bomb survivors data, the excess relative risks as a function of age at exposure for cancer incidence was higher in children and decreased after around 30-40 years of age[27]. However, the excess relative risk rose again at ages of more than 40 years old[27]. Similarly, the follow-up data of radiation workers who were older than 45 years old reported by Richardson et al.[30] showed a

strong association of an increased cancer mortality rate at an older age[30]. Rectal cancer is a disease associated with old patients. In our study, the age of exposure was defined as 60 years old, where the secondary cancer risk is expected to increase with the age at exposure.

In general for radiation therapy, primary radiation is the risk factors for secondary cancer incidence[31]. However, secondary neutrons generated during proton therapy was also important and should be taken into account to completely explain the risk of radiation-induced cancer[32]. In this study, secondary radiations, e.g., neutrons and scattered radiations, generated during the treatment were not yet considered. Several methods can be performed to assess the magnitude of secondary radiations or out-of-field doses, such as, Monte Carlo simulations and measurements using anthropomorphic phantoms[33].

It is to note that the mechanistic risk model itself has intrinsic uncertainties associated with the combination of epidemiological data from atomic bomb survivors and the Hodgkin cohort treated with radiotherapy data[13]. Since the mechanistic model was derived from Japanese atomic bomb survivor data and Caucasian Hodgkin patients, the genetic susceptibility of these populations may be different from the population of interest in this study. For radiotherapy patients it is therefore more common to use the risk model to compare between treatment modalities rather than using the model to compute absolute risks.[13]. Another uncertainty of the calculation was due to the absence of rectal distension in the computational phantom.

In future work, Monte Carlo simulation should be used to incorporate neutron dose in secondary cancer risk estimation for proton therapy and computational phantoms or patient CT datasets with different conditions of rectal distension should be used to identify the spectrum of risks associated with rectal cancer radiation therapy.

Conclusion

This study evaluated secondary cancer risks in terms of organ equivalent doses (OEDs) and organ-specific excess absolute risks (EAR^{org}) after IMRT and IMPT for rectal cancer using a male adult computational phantom to represent Thai rectal cancer patients and the mechanistic risk models of Schneider et al[13] for carcinoma and sarcoma induction. Compared to IMRT, IMPT delivered lower dose to the OARs and lower the estimated secondary cancer risks in most organs, except for the bladder. The colon was found to have the highest risk of developing secondary cancer, while the risks of developing secondary bone and soft tissue sarcomas were negligibly small. For the bladder, the low dose exposure by IMPT was not favorable due to the associated high risk obtained from the mechanistic model. Of all IMPT plans investigated, 2-field IMPT had the lowest risks, while 3- and 5-field IMPT plans yielded the similar risks.

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