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Secondary Cancer Risk after Radiotherapy of Seminoma Stage One

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ABSTRACT

Introduction: In radiation treatment of stage one seminoma (SOS) induced secondary cancer in organs at risk (OARs), is late toxicity of major concern. This study aimed to compare the secondary cancer risk in radiotherapy of SOS in two-dimensional conventional (2D) radiation therapy and three-dimensional conformal radiation therapy (3DCRT).

Material and Methods: CT scan images of 10 patients with SOS were used to design 2D conventional and 3D conformal treatment plans using 25 Gy in 20 sessions. The life attributable risk (LAR) of the liver, stomach, and colon were calculated using the organ equivalent dose (OED) model for organs in the radiation field and the Biologic Effects of Ionizing Radiation VII (BEIR VII) model for organs out of the field.

Results: LAR of OARs in radiation fields such as the liver and stomach were obtained 40% higher in the 2D treatment than in the 3D treatment, while as for the colon, it was 17% lower in the 2D treatment than in the 3D treatment. The LAR values of kidneys located outside the radiation field in the 2D treatment were calculated at 0.04%.

Conclusion: Increasing the prescribed dose (25 vs. 20) as well as the number of treatment sessions (20 vs. 10) resulted in increase in the LAR of the liver, stomach, and colon. Therefore, estimating the cancer risk of critical organs exposed to radiation through examining the effects of dose fractionation and prescribed doses can be used in optimizing of the treatment plan for seminoma, selecting a better treatment method by oncologists, and patient follow-up.

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Introduction

One of the most common malignancy among young men is testicular cancer, accounting for 1% of all male tumors. Seminoma accounts for 60% of this malignancy. Near 85% of seminoma patients are diagnosed with stage one for which primary treatment is either an Orchiectomy or adjuvant treatments such as radiation therapy [1]. Different therapeutic techniques of radiation therapy, such as intensity-modulated radiation therapy (IMRT), two-dimensional conventional (2D radiation therapy), and three-dimensional conformal radiation therapy (3DCRT) have been used for the treatment of this cancer [2].

Due to high success rates of adjuvant radiation treatment of stage one seminoma (SOS), induced secondary cancer in organs at risk (OARs), located in or out of the radiation fields, is late toxicity of major concern. The secondary cancer risk (SCR) in SOS has been estimated for organs in and out of the field for different radiotherapy techniques, such as 2D, dog leg, 3DCRT and IMRT, radiation field placement, and prescribed tumor dose, fractionation scheme, and risk model used [3,4].

Testicular cancer survivors come across a twofold increased risk of secondary cancers after chemotherapy and radiotherapy. The late effects of radiotherapy in most patients with SOS can be limited by following up these patients [5]. The risk of secondary cancer after radiotherapy of seminoma was calculated by Mazonaki et al. for organs located within the radiation field, such as kidney, liver, stomach, colon, and pancreas. The results showed the highest and lowest level of excess absolute risk (EAR) for the colon and the kidney, respectively. The prescribed dose in this study was 20 Gy in 10 fractions [6]. The secondary cancer risk depends on the organ type, the received dose, and the dose fractionation scheme [7,8]. Therefore, we aimed to compare the risk of the incidence of secondary cancer in radiotherapy of SOS for a dose of 25 Gy in 20 fractions in 2D and 3DCRT.

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Materials and Methods

Patients

Computed tomography (CT) images of 10 patients with seminoma stage one were used for treatment planning. The patient's ages ranged from 32 to 49 years. All patients had undergone CT scans using a Somatom Emotion scanner (16 slice ,Siemens Healthcare, USA). Patient's information were considered confidential and entered into the TPS without registration. Also, these information were only used for this study and were not shared with anyone other than researchers. No additional costs will be imposed on the patient in addition to routine treatment.

Treatment Planning

An ISOgray version 4.1.3.23L treatment planning system which had been commissioned for the 6MV photon beam of an Elekta Synergy platform linear accelerator (both manufactured by Elekta, Stockholm, Sweeden) was used for treatment planning. Using each patient's CT images, a 2D conventional and a 3D conformal treatment plan were designed by means of two parallel opposed fields. In 2D conventional plans, the treatment field covered the abdominal lymph nodes adjacent to the aorta and inferior vena cava (IVC) from T9 T10 vertebrae to the lumbosacral joint, depending on the involvement of the right or left testicles, the anterior posterior fields were designed using a width of 7 cm and 9-10 cm respectively. In the 3D conformal plans, the gross tumor volume (GTV), clinical target volume (CTV), and organs-at-risk (OARs) were contoured by our radiation oncologist (ICRU 50,60). GTV consisted of the abdominal nodes surrounding the abdominal aorta and inferior vena cava. CTV was delineated by adding a 10-mm margin to the GTV. In order to account for setup uncertainties, the planning target volume (PTV) was delineated by adding a 15-mm margin to the CTV. OARs were also delineated for risk analysis. For the optimum 2D and 3D plans, the dose-volume histograms (DVHs) were calculated using 25 Gy in 20 fractions for organs located inside the treatment field, including the stomach, liver, kidneys, colon, and pancreas.

Mesurrement of recived dose for organs out of field

The dose delivered to the out-of-field organs was measured using a MapCHECK2 2D-Arrays dosimeter (Sun Nuclear FL, USA, number of diode detectors: 1527, largest field of measurement: 32 x 26 cm field, diode spacing: 4mm, sensitivity: 32 nc/Gy). In order to simulate the midline depth of each out-of-field organ, including the testies and the kidneys, sutible thickness of polystyrene plates were added on top of the dosimeter (Figure 1). The detector was irradiated using the 2D and 3D designed treatment field configurations. The XY coordinates of the midplane contour of each organ with respect to the central beam axis were used to designate the organ proxy diodes . The mean organ dose was determined by averaging the signal of these diodes.

Figure 1. Polystyrene plates were added on top of the dosimeter in order to measure the out of field organ.

Estimation of secondary cancer risk

Different models have been used to calculate the risk of secondary cancers in radiotherapy, relying on the type of the organ and the level of the dose received by the organ, and the dose fractionation scheme.

Organs located inside the field

Using the relationship between dose -response and the OED concept, excess absolute risk (EAR) can be calculated for healthy organs from which cancer incidence data are available and are unintentionally irradiated during radiotherapy. EAR is defined as the rate of cancer in an exposed population minus that in an unexposed population (equation 1) [8].

$$\mathrm{EAR}^{\mathrm{org}} = \frac{1}{\mathrm{V_t}} \sum_{\mathrm{i}} \mathrm{V_{(Di)}}\, \beta\, \mathrm{RED_{(Di)}} \mu(\mathrm{age}_x, \mathrm{age}_a) \qquad (1)$$

Where *V*t is the total organ volume, $\mathrm{V_{(Di)}}$, is the organ volume of the dose bin *i* absorbing a radiation dose equal to *D*i, β is the initial slope of the dose-response curve at low dose and μ contains the population dependent variables, $\mathrm{age}_x$is the patient's age at the time of radiation therapy, and $\mathrm{age}_a$is the attained age. For a nonhomogeneous dose distribution, OED is defined as organ specific dose-response (RED) relationship for radio-induced cancer and is calculated by using DVHs derived by TPS database (equation 2):

$$\mathrm{OED} = \frac{1}{\mathrm{V_t}} \sum_{\mathrm{i}} \mathrm{V_{Di}} * \mathrm{RED_{Di}} \qquad (2)$$

RED can be calculated in severe models. First model of RED is mechanistic Dose-response model which accounts for both cell killing and fractionation effects was considered for carcinoma induction (equation 3):

$$\mathrm{RED\ (D)} = \frac{e^{-a_i' Di}}{a_i' R}\left[1 - 2R - R^2 e^{a_i' Di} - (1 - R^2) e^{\left(-\frac{a_i' R}{1-R} Di\right)}\right] \qquad (3)$$

Where *R* is the organ-specific repopulation factor denoting the tissue ability for repair after radiotherapy. The cell-kill parameter αi′ is related with the decrease of the initial cells. For cases in which repopulation and

repair effects can be ignored due to fractionation, a bell-shaped dose-response model is derived by assuming R=0; otherwise, the plateau dose-response model is derived for full repopulation and repair effect by assuming R=1. After calculating EAR, the lifetime attributable risk (LAR) for organs in the field in 100,000 persons can be calculated by using the equation 4:

$$LAR = \int_{age_{x+L}}^{age_a} EAR(D, age_x, age_a)\, {S(age_a)}/{S(age_x)}\, d(age_a) \quad (4)$$

Where age x is the mean age of patients with seminoma who undergo radiotherapy at age a. In this study, according to studies, age x was estimated to be 39 years and age a was 70 years [9].

${S(age_a)}/{S(age_x)}$ is used to refer **to** the probability of surviving patients from age $_x$ to age $_a$ that were taken from the life tables of US people. L is the latent period and, according to Schneider's paper, takes equal 5 years for solid cancer [10].

Organs located out of field

We used BEIR VII model for the estimaion of secondary cancer risk for out of field organs. EAR and ERR for organs out of field were obtained according to equation 5 [7]:

$$EAR(D, e, s, a) \text{ or } ERR(D, s, e, a) = B_S D \exp(\gamma e^*)(\tfrac{a}{60})^{\eta} \quad (5)$$

Where, D, e, and a are average organ dose, age at exposure and attained age of disease, respectively. Other parameters were prersented in BEIR VII report. LAR for organs out of field in 100000 persons was found by using the equation 6 in BEIR-VII report[7] :

$$LAR_{(D,e)} = (\sum_a^{90} EAR(D, e, a) \times \lambda_C \times {S(a)}/{S(e)}\, da)^{0.7} \times (\sum_a^{90} EAR(D, e, a) \times {S(a)}/{S(e)}\, da)^{0.3} \quad (6)$$

Where λ_C is the baseline cancer risk and S(a)/S(e) is the probability of a person of surviving to age a following exposure at age e. Baseline cancer risk was taken from the life tables of US people[10].

Statistical analysis

Statistical analysis was carried out with SPSS (version 22) for Windows. We used the Kolmogorov–Smirnov examination to test the normality distribution for all variables. The discrepancies between the SRP doses and the mean doses in the PTVs and organs at risk were analyzed using a paired t-test.

Results

Due to the more accurate contouring- the abdominal aortic artery, inferior vena cava, and renal artery and vein are contoured-, the width of the radiation field increases, especially in the area of the renal artery and vein. As a result, the kidneys receive a higher dose in 3DCRT than they receive in the 2D treatment. For all patients, the mean-field width was 9.4. cm in the 2D plan and 11.7 cm in the 3D plan. In addition, the mean length of treatment volume was 24.2 cm in the two methods. The organs located inside the treatment field included kidneys, liver, pancreas, stomach, and colon, and organs such as testicles were placed outside radiation field. For patients whose right testicle was involved , the field width was considered 7 cm in 2D, and for these patients, both kidneys were placed out of the treatment field.

For both treatment plans, the DVH showed acceptable clinical target coverage and met-dose limits for all OARs. Table 1 shows the specifications of doses received by the kidneys, liver, pancreas, stomach, and colon obtained from DVH in both treatment methods. Our study showed that the target volume had better coverage in the 3D treatment than in the 2D treatment, but due to the greater width of the radiation field in the 3D treatment, kidneys received a higher dose in this treatment than in the 2D treatment. Dose received by kidneys , liver , stomach, pancreas, and colon in 2D was 22%, 20%, 39%, 82% , 24% , and in 3D 28%, 12%, 26%, 77% , 30% of the prescribed dose, respectively .

Table 1. Specifications of received dose by the planning target volume (PTV), kidneys, liver, pancreas, stomach and colon obtained from dose volume histograms (DVHs) in 2-Dimensional (2D) and 3-Dimensional (3D) treatment plans

		3D	2D	p-value
PTV	D mean(Gy)	24.4	23.9	0.04
	V25 (%)	25.2	24.7	0.05<
Kidneys	D mean(Gy)	7.1	5.6	0.04
	V25 (%)	1.8	0.5	0.003
	V18 (%)	34.6	19.4	0.05<
Liver	D mean (Gy)	3.2	5.2	0.01
	V25 (%)	0.1	0.1	0.05<
Pancreas	D mean(Gy)	19.3	20.7	0.02
	V25 (%)	17.5	20.2	0.02
Stomach	D mean(Gy)	6.4	9.7	0.05<
	V25 (%)	1.0	3.6	0.05<
Colon	D mean(Gy)	7.6	6.6	0.05<
	V25 (%)	12.6	13.7	0.05<

In four of the patients with involvement of the right testis, both kidneys were completely excluded from radiation field in the 2D plan, also testicles had been placed out of radiation field in both treatments. The mean dose of kidneys in these patients was 1.51Gy. Moreover, mean testicular measured doses for the 2D and 3D plans were 7.7, and 6cGy, respectively. The EAR for the in-field OARs was calculated at the age of 70 years for patients who underwent radiotherapy at 39 years (Figure 2).

In both treatments, the most and the least amounts of EAR were related to the colon and the kidneys, respectively. The type of treatment plan did not create a significant impact on EAR. As already mentioned, the same equation is used for the calculation of OED for the colon, stomach, and the liver. Among these organs, the EAR of the colon was remarkably more than those of the other two organs (Figure 2). LARs of secondary Cancer Incidence in stomach, liver, and colon are shown in Figure 3.

Our study carried out the risk of secondary cancers in radiotherapy of seminoma at the prescribed dose of 25 Gy in 20 treatment sessions; it was found that the LAR of the stomach and liver was slightly lower in the 3D treatment than in the 2D treatment. By considering the mechanical model as a criterion in our study, the risk of secondary cancer for the liver and stomach was obtained 40% higher in the 2D treatment plan than in the 3D treatment plan, while for the colon, it was 17% lower in the 2D treatment than in the 3D treatment.

The mean volume of kidneys, which had received doses greater than 18 Gy, was 34.6% in the 3D treatment and 19.4% in the 2D treatment. Only in four patients, more than 30% of the two kidneys' volume received a dose of 18 Gy, which belonged to the 3D treatment. This suggested that the kidneys are more susceptible to radiation damage in the treatment of SOS with 3DCRT compared to the 2D. Using values obtained from dosimeter, EAR, ERR in 10,000 persons, and LAR in 100,000 persons were obtained by BEIR VII model for the kidneys for several age groups of 50, 60, 70, 80 years, considering that the age of the patients during treatment was 39. The result shows that the LAR data had a heavy dependence on age at exposure, and LAR decreased as a function of age. The LAR of the ages of 50, 60, 70, 80 were 0.09%, 0.06%,0.04%, and 0.01%, respectively.

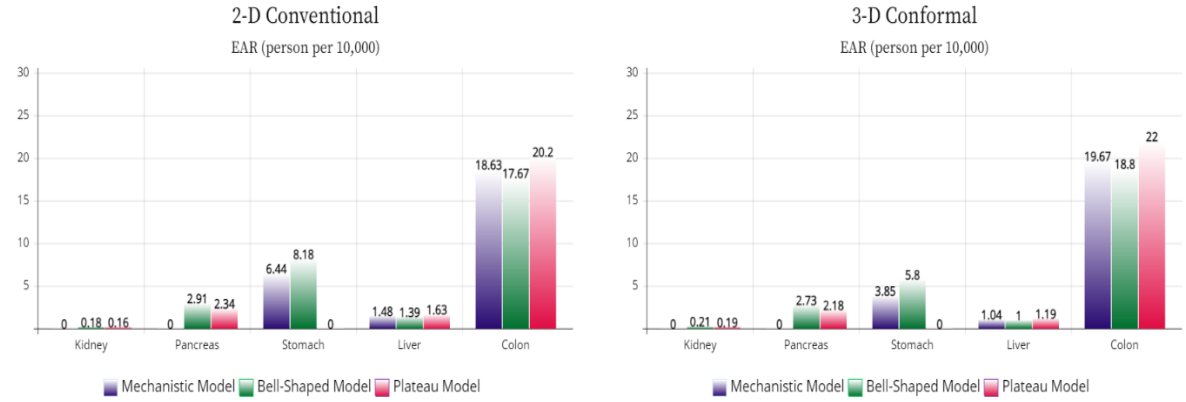

Figure 2. Excess absolute risk (EAR) values in 10000 persons-year in 2-Dimensional (2D) and 3- Dimensional (3D) plans for in- field organs of kidney, pancreas, colon, stomach, and liver.

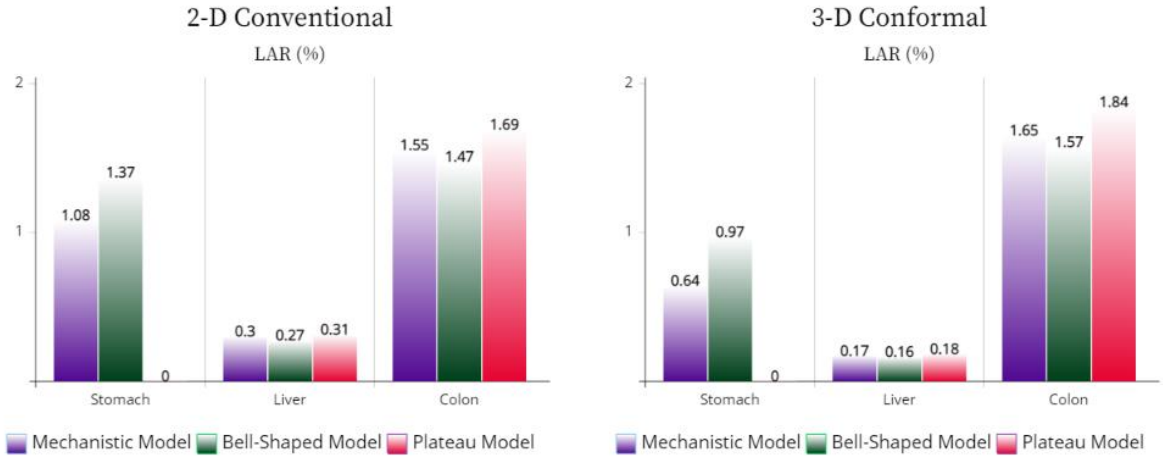

Figure 3. Life attributable risk (LAR) of secondary Cancer Incidence (%) Left and right charts are related to 2-Dimensional (2D) and 3-Dimensional (3D) plans, respectively.

Discussion

Our study aimed to compare the secondary cancer risk in radiotherapy of seminoma in 2D and 3DCRT at the prescribed dose of 25 Gy in 20 treatment sessions. We found that the LAR of the stomach and liver was slightly lower in the 3D treatment than in the 2D treatment. By considering the mechanical model as a criterion in our study, the risk of secondary cancer for the liver and stomach was obtained 40% higher in the 2D treatment than in the 3D treatment, while for the colon, it was 17% lower in the 2D treatment than in the 3D treatment. The lower LAR of the colon in the 2D plan relative to the 3DCRT plan can be due to the smaller width of the radiation field in the 2D treatment plan (7cm vs. 9-10cm compared to 3DCRT). Compare to the study conducted by Mazonakis et al, in our study, the LAR in 3DCRT treatment plan for the stomach, the colon, and the liver were 38%, 76%, and 45% higher, respectively. The difference between LAR in our study and Mazonakis et al's study can be due to difference in the prescribed doses and fractionation scheme [6].

Several factors can be effective in reducing the risk of secondary cancers in radiotherapy of stage I seminoma. In one study, reducing the target volume using a para-aortic field reduced the risk by one-half to one-third relative to that in the dog-leg fields. In addition, using a dose of 20 Gy instead of 30 Gy in the para-aortic field reduces the risk of secondary cancers by almost half [11]. When treating dogs for abdominopelvic tumors, reducing of the PTV margin to 3-4 mm significantly reduced the normal tissue complications probability of OARs [12].

In breast cancer radiotherapy, the risk of secondary cancers for OARs has been estimated using the OED model for different treatment methods and prescribed doses. The results showed that increasing the prescribed dose (63 vs. 50 Gy) and treatment sessions (28 vs. 25 fractions) can affect the EAR of the lungs and contralateral breast [13-16]. However, the prescribed dose and fractionation are not the only factors that affect the secondary cancer risk. Treatment planning results from choosing different treatment modalities such as 3DCRT, IMRT, and VMAT also has a considerable effect on the dose of PTV and OAR [17]. As recommended by Dobler et al., the received dose of OARs can be adjusted by using FFF [14].

In our study, doses received by testes without testicular shields were 7.67 cGy in 3DCRT and 6.37 cGy in 2D. The doses that cause permanent sterility of the testicles fall within 3-5 Gy [18]. Also, a dose of 0.1 Gy can significantly reduce the number of sperms. Therefore, for these patients, it is recommended not to have children for at least 3 years after treatment for spermatozoa with abnormalities and genetic mutations to be eliminated [19]. Considering the level of the dose received by testes in our study, the use of testicular shields are essential for SOS patients treated using 2D and 3DCRT techniques.

The in-field organs with the highest and lowest LAR were the colon and liver, respectively. These results were similar to Horwich et al. study [20]. They examined the risk of secondary cancers in patients having undergone radiotherapy of stage I seminoma. They showed that radiotherapy does not significantly increase secondary cancer risk for organs outside the radiation field. Follow-up with patients who underwent radiotherapy for testicular cancer involving the abdominal field showed that the incidence of stomach cancer after 30 years post-radiotherapy increased by 1.45% [21]. In our study, the risk of stomach cancer, three decades after radiation therapy, increased up to 1.37 %.

Among the limitations of the OED model, we can refer to the insufficient organ-based data. For example, in this model, there are limited data for the pancreas and kidneys for calculating the risk of secondary cancer following radiotherapy. Therefore, the accuracy of this model for estimating LAR values for the pancreas and kidneys is questionable [22]. Limitations of this study include the small number of patients studied and lack of access to an advanced therapeutic technique such as IMRT, and failure to use the following methods: flattening filter-free (FFF) and deep inspiration breath-hold (DIBH). Also, due to the lack of baseline cancer risk and life table based on the population of Iran, the data related to the US population was used [10].

Conclusion

The current study presented risks for secondary malignant diseases in organs, part of which had fallen within the treatment field and/or completely outside the treatment field. The results showed that by increasing the prescribed dose (25 vs. 20) as well as the number of treatment sessions (20 vs. 10), the estimated LAR of at-risk organs increased by 76%. Therefore, to optimize the treatment planning for seminoma and selection of a better treatment method, examining the effects of dose fractionation and prescribed doses can be effective to estimate the secondary cancer risk.

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