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Radiobiological evaluation of the 3D-conformal radiotherapy of the pancreas cancer: results of a comparative study between filed-in-filed technique and the use of conventional wedges

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Abstract

Introduction: This study is conducted to compare the radiobiological parameters of two 3D conformal radiotherapy (3DCRT) techniques including the wedge-based three fields (W3F) and field-in-field (FIF) used for treatment planning of the pancreas cancer.

Methods: Twenty-five patients with the pancreatic cancer were selected for this study. Treatment planning of the all cases was done using the Isogray treatment planning system (TPS). The mean dose and equivalent uniform dose (EUD) to the PTV and critical structures such as the liver, kidneys, and spinal cord were obtained from the dose–volume histograms (DVHs) and compared between the W3F and FIF techniques.

Results: Evaluation of the V_{30Gy} and V_{28Gy} parameters respectively for the liver and kidneys revealed the larger irradiated volumes in the W3F technique compared with the FIF technique. The EUD and mean dose values of the PTV in the FIF were slightly ($P > 0.05$) lower than the W3F plan. Furthermore, it was observed that the FIF method significantly ($P < 0.05$) produces lower levels of the EUD and mean dose for the organs at risk (OARs) in comparison with the W3F. In particular, the EUDs of the bilateral kidneys and spinal cord in the FIF plans were significantly ($P < 0.05$) reduced by 38% and 8.02%, respectively, as compared to the W3F technique.

Conclusion: The FIF method has the advantage in terms of reducing the dose received by the critical OARs. This outcome consequently leads to decreasing the radiobiological complications. To conclude, the FIF can be considered as a potential substitute for the W3F technique in the clinical situations of the pancreatic malignancies.

Keywords: Pancreas cancer, Conformal radiotherapy, Treatment planning, Wedge-based three fields, Field-in-field technique, Equivalent uniform dose

Introduction

The purpose of radiation therapy is to maximize the dose delivered to the target while minimizing the dose to the organs at risk (OARs) (1,2). However, dose distribution depends on several factors such as treatment planning technique (3).

Furthermore, radiotherapy poses challenges *in terms of the accurate dose* generation when irregular tissues encounter along the photon beam path (3,4). For instance, in case of the upper abdominal radiation therapy (e.g., malignancies of the gastro-esophageal junction, stomach, gall bladder, and pancreas), there is an involvement of irregularities which avoids a homogenous dose distribution (4,5). Thus, in radiotherapy of the upper abdominal targets, beam shaping devices such as wedges must be applied to compensate the tissue irregularities (2). The general protocols that have been used for treatment of the pancreatic cancer are anterior and posterior (AP/PA) arrangements and the 3D conformal radiation therapy (3DCRT) (1,3). However, it has reported that protection of the OARs is not correctly satisfied with the AP/PA opposing field arrangements. Thus, it is recommended to use the multiple fields such as three fields with compensating wedges (3WF) and four-field box (FFB) to avoid the radiobiological complications of the AP/PA opposing fields (3-5). In this regard, it is reported that the intensity modulated radiation therapy (IMRT) technique results in reducing the dose received by the liver and kidneys (6). Additionally, Ringash et al, has been applied a five-field technique for postoperative radiotherapy of the gastric cancer (7).

On the other hand, although the physical or dynamic wedges are commonly applied to obtain homogeneous dose distribution in the PTV, increased dose hotspots about 10% are typically generated in final plans (2,3). However, uniformity of the dose distribution over the target volume as well as hotspot formation prevention can be achieved using the multi-leaf collimator (MLC) sub fields (8-11). This new 3DCRT approach called field-in-field is implemented in clinical studies of the different sites (e.g., breast, brain, gastric, and etc) (8,12,13). Prabhakar et al has been evaluated the dosimetric parameters of the FIF technique for various sites in comparison with the W3F

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■ Implication for health policy/practice/research/medical education

There is increasing concern regarding the radiation-induced secondary cancers following radiotherapy of the pancreatic cancer in cases where there is an overlap between the target and organs at risk (OARs) (e.g., left kidney). In this work, the radiobiological parameters of two 3D conformal radiotherapy (3DCRT) techniques including the wedge-based three fields (W3F) and field in-field (FIF) were compared.

method (9). Moreover, Tanaka et al (10) has been shown that using lung field blocks in the breast radiotherapy with the FIF technique leads to a significant reduction in the lung dose.

Nevertheless, the studies on the FIF have been generally based on the physical dose-volume statistics. Consequently, only the physical aspects of the 3D dose distribution can be described (9,12,14). To our knowledge, evaluation of the FIF treatment plans in the radiation therapy of the pancreatic cancer based on the radiobiological parameters has not yet been performed.

The main goal of the present study was to carry out a radiobiological comparison between the W3F and FIF techniques of treatment planning for the pancreatic cancer in the complicated cases with an overlap between the left kidney and PTV. The radiobiological evaluation was performed using the numerically calculated equivalent uniform doses (EUDs) obtained from the dose volume histograms (DVHs) of the two different treatment plans (15).

Materials and methods

Patients

Twenty-five patients with malignancy in the pancreas were selected. This study was approved by the research committee of the Kurdistan University of Medical Sciences (MUK).

Treatment-planning techniques

The computed tomography (CT) scans of all cases were acquired with 512×512 pixels at 5mm slice spacing on a flat tabletop of a GE LightSpeed CT Scanner. Then, the CT datasets were transferred to the *Isogray* treatment planning system (TPS) (Dosisoft, Cachan, France). The treatment volumes were contoured according to the published Radiotherapy and Oncology Group (RTOG) guidelines (16). The planning target volume (PTV) was created using a 10 mm wide isotropic expansion of the clinical target volume (CTV). The OARs (OARs) (i.e., kidneys, liver, and spinal cord) were contoured on the axial CT images. All cases were planned using two techniques including the W3F (plan 1: an anterior and two lateral wedged fields), and FIF (plan 2: by a copy of the plan 1 in the absence of the wedges) with the 15X mode of the 300 MU/min dose rate in the linear accelerator (Elekta synergy platform) equipped with 40 pairs of the multileaf collimators (MLC). Two different treatment plans employed in the present study are

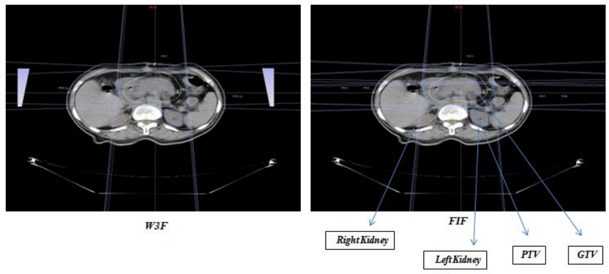

Figure 1. W3F and FIF techniques for treating pancreas cancers.

shown in Figure 1. The treatment planning was carried out such that at least 95% of the PTV received the prescription dose of 45Gy in 25 fractions. In order to perform the FIF treatment planning, we used the approach previously described by Prabhakar et al (9). Subsequently, the high-dose regions, above 105% of the maximum dose, were shielded with the MLCs in steps of 3%-5% dose levels using beam's eye views of the planning target volume. The weights of the MLC segments were manually adjusted to achieve the optimal dose homogeneity in the PTV as well as decrease in the hotspot.

Next, the dose–volume histograms (DVHs) of the both W3F and FIF plans were obtained for the PTV, liver, spinal cord, right kidney, and left kidney in all patients.

Equivalent uniform dose

The generalized EUD was calculated and compared between the two different treatment plans. The EUD is defined as the dose which produces the equal biological effect if distributed homogeneously through the total volume of the structure of interest as the inhomogeneous dose distribution (15,17).

According to the Niemierko's model, the equation for the EUD is specified as:

$$EUD = \left(\sum_{i=1} (v_i EQD_i^a) \right)^{\frac{1}{a}} \quad (1)$$

In equation (1), a is a unit-less model parameter that is specific to the normal organ or tumor, and v_i is unit less and represents the i^{th} partial volume receiving dose D_i in Gy (15,17,18).

The relative volume of the total structure of interest corresponds to 1, then the sum of all partial volumes v_i will equal 1 (15,17,18). Furthermore, in equation (1), the EQD is the biological equivalent physical dose of 2Gy and defined as:

$$EQD = D \times \left(\frac{\frac{\alpha}{\beta} + \frac{D}{n_f}}{\frac{\alpha}{\beta} + 2} \right) \quad (2)$$

In the equation 2, n_f and $d_f = D/n_f$ are the number of fractions and dose per fraction size of the treatment course, respectively (18). The α/β is the tissue-specific linear-quadratic (LQ) parameter of the exposed organ (15,17). The EUD calculations were performed using the MATLAB and Simulink Student Version-R2010a (The MathWorks, Inc., Natick, Massachusetts).

First, the dose-volume histograms (DVHs) of the W3F and FIF plans were exported from the *Isogray* TPS. Then, the EUDs were calculated using the Niemierko method (15,17). The alpha-beta ratio for the pancreas tumor, kidney, liver, and spinal cord were considered as 10, 1, 1.5, and 2, respectively (18,19) (Table 1). Finally, the differences in the EUD values were compared between the W3F and FIF plans.

Moreover, several parameters were considered in analyzing the DVHs of the different OARs. For the kidneys, the mean dose and V_{28Gy} (volume receiving greater than or equal to 28Gy of the prescribed dose); in case of the liver, the mean dose and the V_{30Gy} (volume receiving greater than or equal to 30Gy of the prescribed dose); and for the spinal cord, the maximum dose and the maximum dose received by 2cc volume (D_{2cc}) were used (9, 14). Finally, the above-mentioned parameters were compared between the plan 1 and plan 2.

Data analysis

Statistical analyses were conducted with SPSS (version 16) for Windows. A Paired Student's *t* test based on the mean ± standard deviation (SD) values of the EUD was employed to test the statistical significance of the differences between the two plans. The *P* value <0.05 was considered statistically significant.

Results

The parameters extracted from the DVHs of the plans are shown in the Table 2. For the PTV, the EUD values in the FIF plans were slightly lower than the W3F with an average difference of 2%. Similarly, it is clear that there is a statistically significant reduction in the EUD, mean dose, and maximum dose values (mean ± SD) of the right kidney, left kidney, and spinal cord in the FIF plans compared to those of the W3F.

The EUDs of the right kidney, left kidney, and the spinal cord in the FIF plans were significantly ($P<0.05$) lower than the W3F by 55% (12.14 ± 1.12 Gy vs. 5.47 ± 1.35 Gy), 23% (19.44 ± 5.41 Gy vs. 22.79 ± 5.69 Gy), and 18.35% (6.14 ± 0.47Gy vs. 7.52 ± 0.68 Gy), respectively.

The EUD of the liver in the FIF plans was higher than the W3F plans by 6.79% (12.21 ± 1.78Gy vs. 13.04 ± 1.77Gy). Nevertheless, this difference was not significant ($P>0.05$).

The mean dose value of the PTV in the FIF plans (44.63 ± 2.37 Gy) was slightly ($P>0.05$) lower than the W3F technique (44.60 ± 2.48 Gy). Furthermore, the FIF plans significantly ($P<0.05$) produced smaller values of the mean dose for OARs including the right kidney: 43.79% (2.58 ± 0.52 Gy vs. 4.59 ± 0.45 Gy), the left kidney: 35.65% (7.58 ± 1.89 Gy vs. 11.78 ± 2.15 Gy), and the spinal cord: 32.91% (7.84 ± 2.80 Gy vs. 5.26 ± 1.11 Gy) than the W3F plans.

Figure 2 shows the dose–volume histogram comparison of the W3F technique versus the FIF technique in a typical case of pancreas cancer. The V_{28Gy} analysis for the bilateral kidneys showed a significant dose reduction ($P<0.05$) as 35% for the FIF plans versus the W3F plans. In addition, there is a significant reduction ($P<0.05$) in the dose received by 2 cc of the spinal cord by 8.02% with the FIF

Table 1. The parameters used to calculate the EUD using the Niemierko's method*

Tissue	Volume type	100% dose per fraction	No. of fractions	a	Alpha-beta ratio (Gy)
Pancreas (PTV)	Tumor	1.8	25	-13	10
Kidney	Normal	1.8	25	1	1
Liver	Normal	1.8	25	3	1.5
Spinal cord	Normal	1.8	25	13	2

Abbreviations: EUD, equivalent uniform dose, PTV, planning target volume.
*The parameters are obtained from the published papers (18-22).

Table 2. Dosimetric parameters extracted from the DVHs for the PTV and OARs in the W3F and FIF plans

Structure	Dosimetric parameters			EUD_S	
		W3F	FIF	W3F	FIF
PTV	Mean dose (Gy)	44.60 ± 2.48	44.63 ± 2.37	56.32 ± 1.06	55.13 ± 1.20
	Max dose (%)	106.12 ± 2.52	107.55 ± 2.35		
Right Kidney	Mean dose (Gy)	4.59 ± 0.45*	2.58 ± 0.52	12.14 ± 1.12*	5.47 ± 1.35
	V_{28Gy} (%)	8. 78 ± 0.42*	2.91 ± 0.41		
Left Kidney	Mean dose (Gy)	11.78 ± 2.15*	7.58 ± 1.89	22.79 ± 5.69*	19.44 ± 5.41
	V_{28Gy} (%)	39.89 ± 3.89*	29.36 ± 2.78		
Liver	Mean dose (Gy)	8.60 ± 2.48	9.03 ± 2.56	12.21 ± 1.78	13.04 ± 1.77
	V_{30Gy} (%)	14.76 ± 1.11	15.53 ± 1.74		
Spinal cord	Mean dose (Gy)	5.26 ± 1.11*	7.84 ± 2.80	7.52 ± 0.68*	6.14 ± 0.47
	Max dose (%)	38.11 ± 4.41*	32.35 ± 4.39		
	Dose received by 2cc (Gy)	16.47 ± 5.96*	13.60 ± 3.14		

* Represents the significant difference between the W3F and FIF.

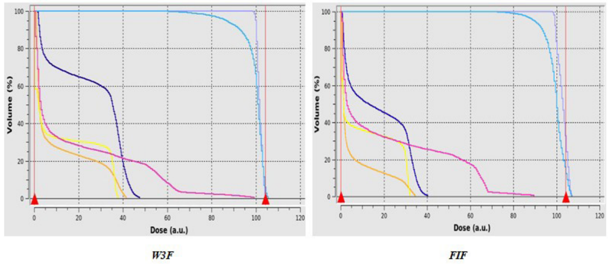

Figure 2. DVH comparison of the W3F, FFB, and FIF techniques in a pancreas cancer (Violet: GTV; Blue: PTV; Navy blue: Left kidney; Rouged: Liver; Yellow: Spinal cord; Orange: Right kidney).

technique as compared to the W3F technique.
The V_{30Gy} and mean dose analysis for the liver respectively showed the increases by 6.79% and 4.76% for the FIF plans versus the W3F plans (Table 2). However, these differences were not significant ($P > 0.05$).

Discussion

Reduction of the dose received by OARs is most important throughout the radiotherapy of pancreatic cancer; particularly in cases with an overlap between the OARs and PTV. Since the kidney and liver are relatively sensitive to the radiation, particular attention must be paid to their tolerances during radiation therapy of the pancreas (4,5,7). The tolerance doses are expressed as TD5/5 and TD50/5 indicating the doses at which late morbidity is seen in 5% and 50% in 5 years, respectively. TD5/5 and TD50/5 for whole kidney irradiation are 23Gy and 28Gy, respectively. In addition, TD5/5 and TD50/5 for the completely liver irradiation have been reported to be 30Gy and 40Gy, respectively (21). Recently, QUANTEC study has summarized the radiation exposure consequences for the kidneys and liver (23-26).
We performed this study to compare the radiobiological parameters between the W3F and FIF treatment planning techniques to establish the advantages of each method. The results of the present study showed that the FIF method has the superiority over the W3F method in the context of reducing the radiobiological difficulties through decreasing the doses received by the kidneys and spinal cord. Specially, reduction of the dose received by the kidneys in the FIF technique is critical for the possible future administration of the chemotherapy. Our results are in agreement with the previous studies (9,27) who reported decreasing of the kidney dose, following implementing the FIF technique in various sites of the abdominal malignancies.
It is well established that the patients with primary cancer of the pancreas have good prognosis as well as long-time survival (4). Therefore, in order to keep the satisfactory long-term renal functions, the dose to the kidneys should be kept even less than 15–18Gy (4,21). It would be beneficial to investigate the DVHs of the kidney and liver associated with the long-term adequate kidney and liver functions.

Conclusion

Advances in the treatment planning software as well as treatment machines lead to the significant improvements in the pancreas radiation therapy; particularly regarding the reduction of doses received by the OARs. In the present study, it was shown that the dose received by the OARs and radiobiological complications in the FIF treatment planning technique was smaller than the W3F technique. In summary, the FIF method can be considered for 3DCRT of the pancreas cancer regarding the treatment advantages such as the simplicity, straightforwardness, and harmlessness.

Authors' contribution

FA is the single author of this paper.

Conflict of interests

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author. Also, this article does not contain any studies with human or animal subjects.

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