RESEARCH ARTICLE

Dosimetric Comparison of Three Different Radiotherapy Techniques in Antrum-Located Stomach Cancer

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Abstract

Background: The current optimal radiotherapy (RT) planning technique for stomach cancer is controversial. The design of RT for stomach cancer is difficult and differs according to tumor localization. Dosimetric and clinical studies have been performed in patients with different tumor localizations. This may be the main source of inconsistencies in study results. For this reason, we attempted to find the optimal RT technique for patients with stomach cancer in similar locations. **Methods:** This study was based on the computed tomography datasets of 20 patients with antrum-located stomach cancer. For each patient, treatments were designed using physical wedge-based conformal RT (WB-CRT), field-in-field intensity-modulated RT (FIF-IMRT), and dynamic intensity-modulated RT (IMRT). The techniques were compared in terms of expected target volume coverage and the dose to organs at risk (OAR) using a dose-volume histogram analysis. **Results:** FIF-IMRT was the most homogenous technique, with a better homogeneity index than WBCRT ($p<0.001$) or IMRT ($p<0.001$). However, IMRT had a better conformity index than WBCRT ($p<0.001$) or FIF-IMRT ($p<0.001$). Additionally, all OAR, including the kidneys, liver, and spinal cord, were better protected with IMRT than with WBCRT ($p=0.023$ to <0.001) or FIF-IMRT ($p=0.028$ to <0.001). **Conclusions:** In comparison to FIF-IMRT and WBCRT, IMRT appears to be the most appropriate technique for antrum-located stomach cancer. To establish whether IMRT is superior overall will require clinical studies, taking into account differences in both tumor localization (cardia, body, and antrum) and organ movement in patients with stomach cancer.

Keywords: Conformal radiotherapy- dosimetry- field-in-field radiotherapy-intensity-modulated radiotherapy

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Introduction

In Turkey, stomach cancer (SC) is generally (75%) diagnosed in locally advanced stages, where it is more often (77–82%) seen in distal portions of the stomach (non-cardia: 31.6% body and 45.4% antrum) (Selcukbiricik et al., 2013; Tural et al., 2013). Postoperative radio-chemotherapy has been the standard practice in patients with non-metastatic stage IB and higher SC since the Intergroup 0116 study (Macdonald et al., 2001).

The radiotherapy (RT) volume of distally located SC is quite large and includes radiosensitive dose-limiting organs such as the kidneys and the liver. Radiation-induced kidney and liver disease may result in organ failure, failure-related clinical manifestations, and death (Pan et al., 2010; Ma et al., 2013; Yavas et al., 2014). In addition, early and late radiation-induced side effects are directly associated with irradiation technique (Murty et al., 2010). Therefore, the development of an effective irradiation technique with limited toxicity remains an area of active interest.

Dosimetric and clinical studies of SC have compared two-dimensional RT (2DRT), three-dimensional conformal RT (3DCRT), and inverse-planned intensity-modulated RT (IMRT). These studies have generated conflicting results, and, in current practice, the optimal RT technique remains controversial. The National Comprehensive Cancer Network recommends 3DCRT. However, if a radiation dose reduction to organs at risk (OAR) cannot be achieved with 3DCRT, IMRT is recommended (Ajani et al., 2016). The most important advantage of IMRT over 3DCRT is an increase in conformity by adjusting the beamlet intensity. Thus, IMRT allows higher doses to be delivered to a tumor while reducing the doses to OAR. However, IMRT increases the healthy tissue volume receiving doses <10 Gray (Gy), which may increase the risk of secondary malignancies. Additional disadvantages of IMRT compared to 3DCRT are lower homogeneity, the need for expensive devices, prolonged treatment planning times, longer treatment delivery times, and complicated pretreatment quality-assurance procedures (Sasaoka and Futami; 2011).

Field-in-field intensity-modulated RT (FIF-IMRT) is a forward planning technique. FIF-IMRT has advantages

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over wedge-based conformal RT (WB-CRT) in patients with breast cancer, endometrial cancer, and lymphoma: it does not require a pretreatment quality-assurance procedure, achieves better homogenity and conformity, reduces the dose to healthy tissues, and shortens treatment delivery times. However, the effects of FIF-IMRT in patients with SC are unknown (Gursel et al., 2011; Sasaoka and Futami; 2011; Yavas et al., 2013; Yamashita et al., 2015).

In this study, we investigated the applicability of FIF-IMRT and determined the most appropriate RT technique for patients with antrum-located SC. We used WB-CRT, FIF-IMRT, and IMRT techniques for treatment plans for patients with antrum-located SC and compared them dosimetrically.

Materials and Methods

Ethics statement

This study was approved by the local ethics committee of the Faculty of Medicine of Ondokuz Mayis University, Samsun, Turkey (acceptance date and number: 08/12/2016; 2016/364). Written informed consent was obtained from all participating patients.

Patients

Twenty patients with antrum-located SC were included in this comparative planning study. All patients were in stage T1–3 and were node positive after subtotal-distal gastrectomy according to the TNM staging classification for SC in the seventh edition (2010) of the American Joint Committee on Cancer (Ajani et al., 2016).

Simulation

RT planning was performed using a computed tomography (CT) simulator (Asteion Super 4; Toshiba Medical Systems, Otawara, Japan). All patients underwent CT scanning after at least 6 h of fasting. No oral contrast was used. Patients were immobilized in a supine position with both arms raised above the head. Intravenous contrast material was administered. CT imaging was performed with free breathing, at a slice thickness of 3 mm. The datasets were transferred to a treatment planning system (TPS, Eclipse 8.6; Varian Medical Systems, Palo Alto, CA, USA) via a Digital Imaging and Communications in Medicine network.

Target volumes and the delineation of OAR

The target volumes and OAR were contoured on individual axial CT slices in all patients by the same radiation oncologist. RT fields were customized for each patient according to Tepper and Gunderson (Tepper and Gunderson., 2002). In addition, International Commission on Radiation Units and Measurements reports 50 and 62 were taken into consideration for RT planning (Purdy, 2004). The clinical target volume (CTV) was planned to encompass the remaining stomach, tumor bed, and draining lymph node stations (perigastric, pancreaticoduodenal, porta hepatis, celiac, and suprapancreatic) (Tepper and Gunderson., 2002). The planning target volume (PTV) was defined by adding a 1-cm margin around the CTV. OAR included the spinal cord, liver, and kidneys.

RT planning

WB-CRT, FIF-IMRT, and IMRT plans were generated for delivery on a linear accelerator (Varian DHX SN-3149) using the Eclipse TPS, considering inhomogeneity corrections. The accelerator was equipped with a millennium multileaf collimator (MLC) with 120 ILO leaves. The width, maximum speed, and transmission of a leaf were 5 mm, 2.5 cm/min, and 2.5%, respectively.

For WB-CRT, four coplanar radiation fields with angles of 0˚, 90˚, 180˚, and 270˚ covering the target volumes with physical wedges and MLC leaves were generated to achieve the best plan. An 18 megavolt (MV) photon beam was used.

For FIF-IMRT, first, a copy of the WB-CRT plan was generated and calculations made without physical wedges. Thereafter, eight additional subfields (two subfields per field) were generated by blocking radiation >105% of the maximum dose with MLC leaves, in steps of 5%, using beam's eye view planning (Prabhakar et al., 2009). An 18 MV photon beam was used.

For IMRT, nine non-coplanar fields were generated with a dynamic wedge technique and inverse planning. A 6 MV photon beam was used. Priority was given to maintain coverage of the PTV. Optimization was run in beamlet mode for approximately 1,000 iterations, by which point the cost function had converged. Following the optimization of IMRT planning, final dose calculations were performed using Pencil Beam Convolution, Version 8.6.14. Quality control of the prepared IMRT treatment plans was performed by both IMRT solid phantom and electronic portal imaging dosimetry. IMRT solid phantom measurements were performed using an electrometer (PTW UNIDOS E, Freiburg, Germany) and an ionization chamber (PTW Farmer 0.6 cm^3, Freiburg, Germany). The values obtained from the Eclipse TPS were compared with the values obtained by portal irradiation. Differences <3% were accepted.

For all treatment techniques, a 2.5 mm grid size and pencil-beam convolution algorithm were applied to the planning calculations. Heterogeneity corrections were turned on during all dose calculations. The center of PTV was taken as the center of irradiation. The prescribed dose to the PTV was 45 Gy in 25 fractions; the dose rate was 3 Gy/min. The aim of the target coverage was to deliver at least 95% and 100% of the prescribed dose to the PTV and CTV, respectively. Attention was paid to maintain a difference between the maximum and prescribed doses of <10%. Accepted dose constraints for OAR were as follows: 70% of the liver was to receive <30 Gy, the mean dose (D-mean) for liver was <25 Gy, 70% of each kidney was to receive <20 Gy, the D-mean for each kidney was <18 Gy, and the maximum spinal cord dose was <45 Gy (Czito et al., 2013; Zhang et al., 2015; Ajani et al, 2016).

Evaluation of RT planning

All treatment plans were evaluated according to the dose-volume histogram. The evaluated dosimetric parameters were the D-mean, maximum dose (D-max), volume of the PTV receiving 95% of the prescription

dose (V95%), volume receiving <95% of the prescribed dose (V<95%), dose received by 2% of the target volume (D2), dose received by 98% of the target volume (D98), volume receiving >107% of the prescribed dose (V>107%), conformity index (CI), and homogeneity index (HI); the D-mean and volume receiving ≥20 Gy of the prescribed dose (V20) for kidneys; the D-mean and volume receiving ≥30 Gy of the prescribed dose (V30) for liver; and the D-max for the spinal cord (Prabhakar et al., 2009). Because this was a dosimetric study, we did not compromise PTV coverage, even where OAR would be exposed to doses above the dose constraints.

The CI was defined as: $CI = (TV_{ref} / TV) \times (TV_{ref} / V_{ref})$, where TV_{ref} is the target volume (cm^3) covered by the reference isodose, TV is the target volume (cm^3), and Vref is the volume (cm^3) covered by the reference isodose. The values ranged between 0 and 1. Values closer to 1 indicate higher dose conformity to the target (Gursel et al., 2011).

HI was defined as: $HI = [(D2-D98) / D_{pres}] \times 100$, where D_{pres} is the prescribed dose. The value should be <15 for an acceptable plan. Lower HI values mean more homogeneous dose distributions (Gursel et al., 2011).

Statistical analysis

Statistical analyses were performed using SPSS software (Ver. 16.0; SPSS Inc., Chicago, IL, USA). The values for all dosimetric parameters noted above for each treatment planning method were recorded and compared. Paired, two-tailed Wilcoxon signed-rank tests were applied. A value of $p<0.05$ was considered to indicate statistical significance.

Results

The PTV dose was similar for all three techniques in terms of V95%, V<95% and D98 ($p>0.05$). The most homogenous dose distribution, with better HI, D-max, D2, and V>107% values, was achieved with FIF-IMRT, as compared to WBCRT ($p=0.012$ to <0.001) and IMRT ($p<0.001$). FIF-IMRT had a higher CI than did WBCRT ($p<0.001$); however, IMRT had a higher CI than WBCRT ($p<0.001$) or FIF-IMRT ($p<0.001$) (Table 1).

The kidneys and the spinal cord were not protected better by FIF-IMRT than by WBCRT ($p>0.05$). The liver was better protected with FIF-IMRT than with WBCRT ($p<0.001$ for the mean liver dose; $p=0.005$ for V30). However, with FIF-IMRT, dose constraints for the liver were exceeded in 65% of patients. Finally, IMRT was the most successful technique in terms of protecting all OAR. It was superior to WBCRT ($p=0.005$ for the V20 for the right kidney; $p=0.001$ for the D-mean in the left kidney; $p=0.023$ for the V20 for the left kidney; $p<0.001$ for the D-mean and V30 for the liver; $p=0.001$ for the D-max for the spinal cord) and to FIF-IMRT ($p=0.006$ for the V20 for the right kidney; $p=0.001$ for the D-mean in the left kidney; $p=0.028$ for the V20 in the left kidney; $p<0.001$ for the D-mean and V30 for the liver; and $p=0.001$ for the D-max for the spinal cord). Although protecting the liver was difficult with all three techniques, the overdose rates dropped from 70% with WBCRT and 65% with FIF-IMRT to 20% with IMRT (Tables 2 and 3).

Table 1. Dosimetric Parameters for Planning Target Volumes with Three Planning Techniques

	Mean±SD (minimum-maximum)			*P*-value		
	WB-CRT	FIF-IMRT	IMRT	WB-CRT vs. FIF-IMRT	WB-CRT vs. IMRT	FIF-MRT vs. IMRT
Mean dose (cGy)	4,640.95±27.74 (4,601-4,709)	4,606.80±22.84 (4,563-4,648)	4,657.05±27.67 (4,611-4,729)	0.0002	0.059	0.0001
Maximum dose (cGy)	4,830.70±50.39 (4,755-4,971)	4,741.60±32.61 (4,677-4,812)	4,913.75±64.22 (4,780-4,970)	0.00008	0.001	0.00008
V95 (%)	97.07±1.5 (95.00-99.50)	97.07±1.61 (95.00-99.40)	96.89±1.63 (95.00-96.60)	0.823	0.614	0.852
D2 (cGy)	4,771.85±37.93 (4,712-4,858)	4,697.30±29.20 (4,644-4,737)	4,814.25±54.25 (4,722-4,879)	0.00008	0.006	0.00008
D98 (cGy)	4,487.00±29.57 (4,434-4,538)	4,485.45±32.35 (4,435-4,543)	4,466.65±44.58 (4,397-4,530)	0.538	0.173	0.247
V > 107 (%)	0.74±1.91 (0.00-7.82)	0.00 (0.00-0.00)	3.61±3.69 (0.00+11.35)	0.012	0.003	0.0002
V < 95 (%)	2.87±1.58 (0.50-5.00)	2.88±1.60 (0.60-5.61)	3.10±1.63 (0.40-5.00)	0.823	0.575	0.808
Homogenity index	6.32±0.76 (5.31-7.67)	4.70±0.84 (2.93-6.29)	7.72±1.96 (4.49-10.53)	0.0001	0.021	0.0002
Conformity index	0.58±0.04 (0.50-0.67)	0.60±0.05 (0.49-0.71)	0.75±0.03 (0.68-0.83)	0.0003	0.00008	0.00008

SD, standard deviation; WB-CRT, wedge-based conformal radiotherapy; FIF-IMRT, field-in-field intensity modulated radiotherapy; IMRT, intensity modulated radiotherapy; cGy, centigray.

Table 2. Dosimetric Parameters for Organs at Risk with Three Planning Techniques

	Mean±SD (minimum-maximum)			*P*-value		
	WB-CRT	FIF-IMRT	IMRT	WB-CRT vs. FIF-IMRT	WB-CRT vs. IMRT	FIF-MRT vs. IMRT
Right kidney Dmean (cGy)	1,095.5±542.05 (219-2265)	1,086.45±540.94 (218-2189)	1,196.9±278.77 (538-1764)	0.211	0.108	0.117
Right kidney V20 (%)	28.12±17.50 (1.32-64.70)	28.05±17.67 (1.32-64.32)	17.54±6.98 (7.37-34.90)	0.396	0.005	0.006
Left Kidney Dmean (cGy)	998.15±441.77 (199-1863)	1,000.90±441.45 (202-1876)	1,334.20±230.14 (840-1689)	0.059	0.001	0.001
Left Kidney V20 (%)	27.04±15.62 (1.08-57.90)	27.15±15.69 (1.08-58.10)	18.82±5.58 (8.27-29.00)	0.244	0.023	0.028
Liver Dmean (cGy)	2,589.55±303.98 (2,057-3024)	2,556.20±292.86 (2,035-2955)	2,244.40±223.77 (1,951-2635)	0.0002	0.0001	0.0001
Liver V30 (%)	35.07±11.48 (16.00-64.08)	33.77±10.82 (16.00-60.95)	23.75±4.99 (17.50-32.93)	0.005	0.0001	0.0002
Spinal cord Dmax (cGy)	2,927.55±575.21 (2,422-4652)	2,956.30±566.38 (2,424-4631)	3,758.70±337.06 (3,144-4333)	0.057	0.001	0.001

SD, standard deviation; WB-CRT, wedge-based conformal radiotherapy; FIF-IMRT, field-in-field intensity modulated radiotherapy; IMRT, intensity modulated radiotherapy; Dmean, mean dose; Dmax, maximum dose; V20, the volume receiving greater than or equal to 20 Gy of the prescribed dose; V30, the volume receiving greater than or equal to 30 Gy of the prescribed dose; cGy,centigray

Table 3. Overdose Rates (Greater than Dose Constraints) for Organs at Risk with Each Technique

	WB-CRT	FIF-IMRT	IMRT
	n (%)	n (%)	n (%)
Right kidney Dmean	3 (15)	3 (15)	0 (0)
Right kidney V20	7 (35)	7 (35)	1 (5)
Left kidney Dmean	1 (5)	1 (5)	0 (0)
Left kidney V20	6 (30)	7 (35)	0 (0)
Liver Dmean	14 (70)	13 (65)	4 (20)
Liver V30	14 (70)	13 (65)	3 (15)
Spinal cord Dmax	1 (5)	1 (5)	0 (0)

WB-CRT, wedge-based conformal radiotherapy; FIF-IMRT, field-in-field intensity modulated radiotherapy; IMRT, intensity modulated radiotherapy; Dmean, mean dose; Dmax, maximum dose; V20, the volume receiving greater than or equal to 20 Gy of the prescribed dose; V30, the volume receiving greater than or equal to 30 Gy of the prescribed dose; n, number of patients

Discussion

In the past, 2DRT planning with anteroposterior-posteroanterior field arrangements was done based on preoperative CT images. Geometrical changes in the OAR postoperatively were not taken into account. With 3DCRT, postoperative delineation of radiation-sensitive organs was achieved (Morganti et al., 2013; Lee et al., 2015), and dosimetric studies comparing 2DRT and 3DCRT were performed.

In these studies, 3DCRT generally achieved superior PTV coverage, with lower doses to the spinal cord and at least one kidney. However, this superior protection was not observed for the liver in most cases (Leong et al., 2005; El-Hossiny et al., 2009; Morganti et al., 2013; Adas et al., 2014). In a single study, all dose volume parameters, including liver, were better with 3DCRT (Lee et al., 2015).

In clinical studies where planning was done with 2DRT or 3DCRT alone, there were reports of progressive decreases in kidney function (45.8–52%) and liver injury (50%), including the Child-Pugh grade progression with/without classical radiation-induced liver disease (Jansen et al., 2007; Yavas et al., 2014; Li et al., 2015). One study compared the clinical results of 2DRT and 3DCRT; however, no difference in kidney and liver parameters or survival time between the two treatment techniques was reported. However, this study assessed liver and kidney function only during the first four weeks after RT. There are no studies comparing later side effects between the two techniques (Lee et al, 2015).

It is impossible to compare the results of dosimetric studies of 3DCRT and IMRT due to the use of different dose constraints and RT planning methods. Alani et al., (2009) used 3DCRT (4-field) and IMRT (9-field) and reported similar CTV coverage, with lower kidney and spinal cord values with IMRT. However, the liver values were higher with IMRT. Additionally, they reported a marginal benefit of IMRT and suggested that IMRT should be used in patients at risk for kidney problems. Murthy et al., (2010) used 3DCRT (3- and 4-field) and IMRT (7-field); they found better PTV coverage, and lower liver and spinal cord values with IMRT. In addition, they showed that the percentage of volumes receiving more than their tolerance doses for all OAR was reduced with IMRT. Ma et al., (2013) used IMRT (5- and 7-field) and 3DCRT (4-field), and reported that better PTV coverage with lower spinal cord and liver values were achieved with 5-field IMRT. However, the D-mean for kidney was higher with both IMRT plans than with 3DCRT.

The results of clinical studies comparing 3DCRT and IMRT have been conflicting. Minn et al., (2010) observed a statistically significant increase in creatinine levels in

patients from a 3DCRT group, and they reported that IMRT protected kidney function better, without causing increased toxicity or a difference in survival, relative to 3DCRT. Liu et al., (2014) reported statistically similar toxicity results, including unchanged creatinine levels, without differences in survival, despite higher IMRT doses (50.4 Gy) compared to those with 3DCRT (45 Gy). Trip et al., (2014) reported late but less severe kidney toxicity, including clinical manifestations like hypertension in patients treated with IMRT, despite lower radiation doses to both kidneys. Chopra et al., (2015) reported that the kidneys were exposed to significantly less radiation with IMRT; however, no difference was found in toxicity, local relapse, or overall survival rates between IMRT and 3DCRT.

In two dosimetric studies, Prabhakar et al., (2008, 2009) compared FIF-IMRT to WBCRT in patients with various abdominal cancers. Abdominal malignancies were divided into upper (gastroesophageal junction, stomach, gall bladder, and pancreas) and lower (urinary bladder, rectum, and anal canal) categories. They found better homogeneity and conformity, a need for less monitor units, and lower kidney and spinal cord doses with FIF-IMRT for most sites. As a result, they recommended that FIF-IMRT should be employed in place of WBCRT in RT planning for abdominal malignancies.

Overall the dosimetric and clinical studies mentioned above report conflicting results. RT techniques were planned for different tumor locations (distal vs. proximal) and/or different nodal stages (node positive vs. node negative) and/or after different surgical procedures (subtotal gastrectomy vs. total gastrectomy) and/or different tumor sites (rectum vs. stomach). All of these parameters are important in field design for RT planning. As a result, these studies have limited usefulness in terms of selecting an appropriate RT technique. We therefore sought to make the current study more useful by investigating RT planning methods in patients whose cancers had similar characteristics.

In the present study, all patients had antrum-located tumors, lymph node involvement, and subtotal distal gastrectomy without splenectomy. For this reason, the target volumes were similar in all patients. We did not compromise on PTV coverage due to dose constraints for OAR. Thus, some values for the OAR were above the dose constraints. The comparison of WBCRT and FIF-IMRT plans demonstrated that the PTV dose coverage was similar. FIF-IMRT was found superior only in terms of homogeneity and conformity relative to WBCRT. However, the kidneys and spinal cord were not better protected with FIF-IMRT than with WBCRT. Although statistically the liver was better protected with FIF-IMRT than with WBCRT, high values (above the dose constraints) occurred in 65% and 70% of patients, respectively. Thus, for most (≥65%) patients with antrum-located SC, it is impossible to protect the liver without compromising PTV coverage using either FIF-IMRT or WBCRT. However, IMRT achieved the best dose conformity to the PTV, with a higher CI value, and protected all OAR better than either WBCRT or FIF-IMRT. Although the mean kidney doses with IMRT were higher than with the other two techniques, the dose constraint was not exceeded in any patient. For all three techniques, protection of the liver was more difficult than for other OAR. However, the risk of compromising the PTV ratio dropped from 70% with WBCRT and 65% with FIF-IMRT to 20% with IMRT.

In conclusion, this study demonstrates that in patients with antrum-located SC, FIF-IMRT does not protect OAR better than WBCRT, despite the achievement of better homogeneity and conformity. Secondly, IMRT achieved superior OAR protection with better conformity than did FIF-IMRT or WBCRT. IMRT seems to be the most appropriate technique for antrum-located SC RT. The use of IMRT should be examined further; moreover, these conclusions require support from clinical studies taking into account differences in tumor localization (cardia, body, and antrum) and organ movement in patients with SC.

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