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Original research article

Feasibility of intensity-modulated radiotherapy to treat gastric cancer

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ARTICLE INFO

Article history:
Received 4 July 2017
Received in revised form
13 July 2018
Accepted 25 October 2018
Available online 16 November 2018

Keywords:
Gastric cancer
IMRT
2DkV image
Set-up errors
Patient positioning

ABSTRACT

Aim: To present a proposed gastric cancer intensity-modulated radiotherapy (IMRT) treatment planning protocol for an institution that have not introduced volumetric modulated arc therapy in clinical practice. A secondary aim was to determine the impact of 2DkV set-up corrections on target coverage and organ at risk (OAR).

Methods and Materials: Twenty consecutive patients were treated with a specially-designed non-coplanar 7-field IMRT technique. The isocenter-shift method was used to estimate the impact of 2DkV-based set-up corrections on the original base plan (BP) coverage. An alternative plan was simulated (SP) by taking into account isocenter shifts. The SP and BP were compared using dose-volume histogram (DVH) plots calculated for the internal target volume (ITV) and OARs.

Results: Both plans delivered a similar mean dose to the ITV (100.32 vs. 100.40%), with no significant differences between the plans in internal target coverage (5.37 vs. 4.96%). Similarly, no significant differences were observed between the maximal dose to the spinal cord (67.70 and 67.09%, respectively) and volume received 50% of the prescribed dose of: the liver (62.11 vs. 59.84%), the right (17.62 vs. 18.58%) and left kidney (29.40 vs. 30.48%). Set-up margins (SM) were computed as 7.80 mm, 10.17 mm and 6.71 mm in the left-right, cranio-caudal and anterior-posterior directions, respectively.

Conclusion: Presented IMRT protocol (OAR dose constraints with selected SM verified by 2DkV verification) for stomach treatment provided optimal dose distribution for the target and the critical organs. Comparison of DVH for the base and the modified plan (which considered set-up uncertainties) showed no significant differences.

1. Introduction

Standard treatment for resectable gastric cancer is partial or total gastrectomy, followed by adjuvant chemotherapy to completely eliminate residual disease.[1,2] However, postoperative radiation therapy (RT) may also be beneficial. The Southwest Oncology Group (INT0116) reported significantly lower locoregional relapse rates in patients treated with postoperative RT (19% vs, 29% in the control group) and a significant survival benefit.[3,4] A follow up study confirmed this strong persistent benefit from adjuvant radiochemotherapy.[5] Despite these good results,

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https://doi.org/10.1016/j.rpor.2018.10.006

treatment-related toxicity remains a concern.[6,7] Moreover, it is still not clear whether three-dimensional conformal radiotherapy (3DCRT) or intensity-modulated radiotherapy (IMRT) should be preferred for this tumor site.[7] Although IMRT theoretically provides more precise tumor coverage with better sparing of organs at risk (OARs) than 3DCRT,[7,8] it is less commonly used in gastric cancer due to difficulties with beam arrangements.

In recent years, however, some studies have demonstrated the feasibility of using IMRT to treat gastric cancer, with toxicity rates that are comparable to 3DCRT.[9] Compared to 3DCRT, IMRT treatment plans are more complex, as they must tailor the dose distribution more closely to the target volume with the parallel intention of minimizing the dose to OARs.[8,10,11] The highly conformal dose of IMRT implies steep dose gradients outside the target volume, which can be dangerous for locations with large intra-fractional organ movement, such as occurs in gastric cancer. As a result, there is an important risk of local over- and under-dosing, which can cause severe toxicity and, consequently, even treatment failure.[12] Image-guided radiotherapy (IGRT) techniques, which offer the possibility of real-time organ tracking, can help to improve accuracy; however, uncertainties related to patient setup (e.g., reproducibility and displacement) during fractionated radiotherapy delivery are still an important issue, even with IGRT.[12,13]

All image-guided modalities present two types of set-up errors: systematic and random errors,[14,15] and the potential effects of these two errors on the target dose must be considered to determine margin rules.[16] However, the complicated nature of geometrical uncertainties, combined with other factors (target volume delineation, organ motion, and set-up errors) make it very difficult to select appropriate margins.[15,17,18] One approach to this problem is to adopt fixed margins based on the published literature and later verify and correct these margins in the patient after each treatment session.[17,18]

Given the situation outlined above, the present study was carried out to assess the impact of set-up uncertainties on target coverage and normal tissue sparing in multiple-field non-coplanar IMRT in the treatment of gastric cancer. A second aim is to present a proposed gastric cancer IMRT treatment planning protocol for institution that have not introduced volumetric modulated arc therapy in clinical practice.

2. Material and methods

Twenty consecutive patients (15 males and 5 females) diagnosed with gastric cancer and treated surgically were selected for study inclusion. All patients were scheduled for post-operative adjuvant RT. The dose protocol described by Macdonald et al. was utilized in all cases.[1] Histology and stage characteristics were as follows: 8 pts with stage IIIB tubular adenocarcinoma; 8 pts with stage IIIA mucinous adenocarcinoma IIIA; and 4 pts with stage IIIB mucinous adenocarcinoma.

2.1. *Treatment planning*

Patient preparation, planning, and treatment procedures were carried out according to typical protocol for gastric cancer, which we describe here.[1] To assure reproducibility during simulation and treatment of gastric lymphomas, we implemented the following procedures to reduce uncertainties caused by respiratory motion and variation in stomach filling: patients were instructed to avoid deep breathing during CT, simulation, and treatment and not to eat any meals or drink three hours before the planning CT and before all treatment fractions. Free-breathing CT scans were acquired with the patient in the supine position with hands up using thorax positioning system for immobilization devices. The patients underwent a CT scan (3 mm slices) encompassing the area from the 7th thoracic vertebrae to the 4th lumbar vertebrae.

The clinical target volume (CTV) consisted of the stomach bed, left diaphragm, and regional lymph nodes around the stomach, splenic artery, hepatoduodenal ligament, and the para-aortal and paracaval lymph nodes up to level L3. The lower part of esophagus with regional lymph nodes was also treated in patients with gastroesophageal junction cancer. According to the ICRU 50/62 recommendation, the internal target volume (ITV) was created.[19] ITV was created by adding 0.5 cm margin to CTV in transverse and sagittal directions and 1.0 cm margin in longitudinal axis.[20] The larger margin was necessary due to diaphragmatic breathing motion. The same values of asymmetric margins for setup variation were added to the ITV to create the planning target volume (PTV). The IMRT plan with the sliding window technique was prepared using Eclipse Treatment Planning System (TPS) (Varian Medical Systems, Palo Alto, USA) with the inverse planning algorithm available in the Helios module.

2.2. *Treatment and patient set-up verification procedure*

All patients were treated on a Clinac 2300C/D (Varian Medical Systems, Palo Alto, USA) linear accelerator equipped with Orthovoltage Beam Imager. The IGRT procedure for gastric cancer used in the study requires acquiring the 2DkV images over the entire treatment course.[18,21] The on-line adjustment of bony structures from 2DkV images to digitally reconstructed radiographs (DRRs) for set-up fields was used. Thus, based on two orthogonal (0 and 270 degree) 2DkV images, displacements in the anterior–posterior (AP), cranio-caudal (CC), and lateral (left-right; LR) directions were determined.

2.3. *Evaluation of the effect of set-up uncertainties on dose-volume histograms*

CT-based treatment planning has a significant drawback as it does not consider the changes that can occur in the shape and position of the tumor from one day to the next. However, because image-guided techniques allow us to collect and provide set-up information, 'pseudo-adaptive' plans based on this information were generated for all patients. The new partial plan was prepared for each verification fraction by moving the isocenter from its initial position. The new dose distributions were calculated and summed, finally presented in the relative

values (%).[18,22] The field geometry, number of monitor units, and multi-leaf collimator (MLC) motions were locked for the analyzed IMRT plans to simulate the doses delivered to the patient using the base plan (BP) parameters and taking into account the set-up error values.[16,22]

2.4. Plan evaluation

For each patient, an alternative simulated plan (SP), which took isocenter shifts into account, was created. SP plans were created based on IGRT procedure performed during fraction delivery. The IGRT procedure provided verification only on the basis of bone structures. However, through the new calculation of dose distribution, an information was obtained whether the recalculated dose distribution cover the target adequately due to inter-fractional movement. Mathematically, SP represented the sum of all fractional dose distributions, in the relative values (%), in the same way as it was done for the BP. Similarly, the cumulative dose-volume histogram (DVH) for the SP was plotted in the same way as for BP. The DVH for both the SP and BP were then compared. On the basis of that comparison, normal tissue doses were evaluated using the following criteria: percent of the volume of the kidney and liver receiving 80%, 50% and 20% of the prescribed dose ($V_{80\%}$, $V_{50\%}$ and $V_{20\%}$); for the spinal cord, the maximum dose (D_{max}) was analyzed. Target coverage determined for the SP and BP plans was analyzed using the ITV and PTV doses, as follows: 1) ($V_{95\%}$): the percentage of the ITV/PTV volume receiving at least 95% of the prescription dose; 2) ($D_{95\%}$): the dose received by 95% of the ITV/PTV; 3) ($D_{5\%}$): the dose received by 5% of the ITV/PTV; and 4) (D_{mean}): the mean ITV/PTV dose.

In addition, for the ITV and PTV, we calculated the internal target coverage (ITC) according to the following formula: $ITC = (D_{5\%} - D_{95\%})/D_{95\%}$. Dose differences, expressed as relative percentage difference (R%D), were calculated using the formula:[1]

$$R\%D = \frac{D^{BP}_{mean} - D^{SP}_{mean}}{D^{BP}_{mean}} \times 100 \quad (1)$$

The comparison between the BP and SP was made using a paired two tailed Student's t test ($p \leq 0.05$ for significant differences).

2.5. Statistical analysis of set-up errors

To evaluate the geometrical uncertainties arising during patient set-up, the systematic [$\sum$] and random [σ] errors were calculated. The vector length obtained for the whole group of displacements was calculated.

The displacement values in three directions for the entire group of patients were included in determination of the $\sum$ and σ components of the setup margin (SM). Based on the calculated components of the set-up errors, we calculated the margin from ITV to PTV. Thus, we verified assumed margins for the ITV, based on our uncertainties: 0.5 cm for the lateral and anterior-posterior directions and 1 cm for the craniocaudal axis using DVH analyses. To calculate the margins, the formula proposed by van Herk at different confidence intervals (CI) was used.[16] The recipe for SM presented as follows: $SM = 2.5\sum + 0.7\sigma$ for the 95% CI.

3. Results

3.1. Treatment planning protocol

The prescribed dose was 45 Gy delivered in 1.8 Gy per fraction for 5 days per week.[1] The normalization method used for the IMRT plans required that at least 95% of the PTV received the prescription dose or higher. The most challenging problem was to meet the criteria described above while providing sufficient sparing of normal structures, especially the kidneys. Dose constraints for healthy tissues were defined for the following organs/structures: the right and left kidney, liver, spinal cord, heart, and lung. The dose-volume restrictions were as follows: <12 Gy to 25% of the right kidney; <22.5 Gy to 33% of the left kidney; < 30 Gy to 60% of the liver; < 40 Gy to 10% of the spinal cord; < 40 Gy to 30% of the heart; and < 20 Gy to 50% of the lung.[1,20,23] Based on these criteria and restrictions, the beam arrangements were developed, consisting of seven non–coplanar beams spread around the PTV volume. The detailed beam geometry and energy are presented in Table 1.

Because of the complicated shape and diverse distances between the PTV and the contours of the body, a mix of two energies (6 and 20 MV) was used.[10,24] The typical dose distribution for the IMRT plans is shown in Fig. 1.

3.2. Comparison of 'pseudo-adaptive' plans using DVHs

Characterization of the study parameters are summarized in Table 2 for the ITV and PTV and in Table 3 for OARs. For this group of patients, the ITV D_{mean} with standard deviations was 100.32 ± 0.44% for the BP versus 100.40 ± 0.40% for the SP. No significant differences ($p < 0.05$) were found between these two values, indicating that the coverage of the target volume was similar for both BP and SP. Similarly, the target comparison of ITV doses ($D_{95\%}$, $D_{5\%}$ and D_{mean}) showed no differences (Table 2).

The greatest difference between the two plans for calculated doses for the ITV results was found for the ITC parameter. Taking into account the other indices assessed, the greatest difference detected for $D_{5\%}$ was 0.25%. In contrast, the smallest differences (0.15% and 0.18%), were obtained for ITV

Table 1 – IMRT beam arrangement with set-up geometry and energy for twenty gastric cancer patients. The beam arrangement is based on the author's treatment planning protocol.

Field no.	Couch angle [°]	Gantry angle [°]	Energy [MV]
1	0	110	6
2	345	40	6
3	270	335	20
4	90	335	6
5	5	295	20
6	350	260	20
7	10	210	20

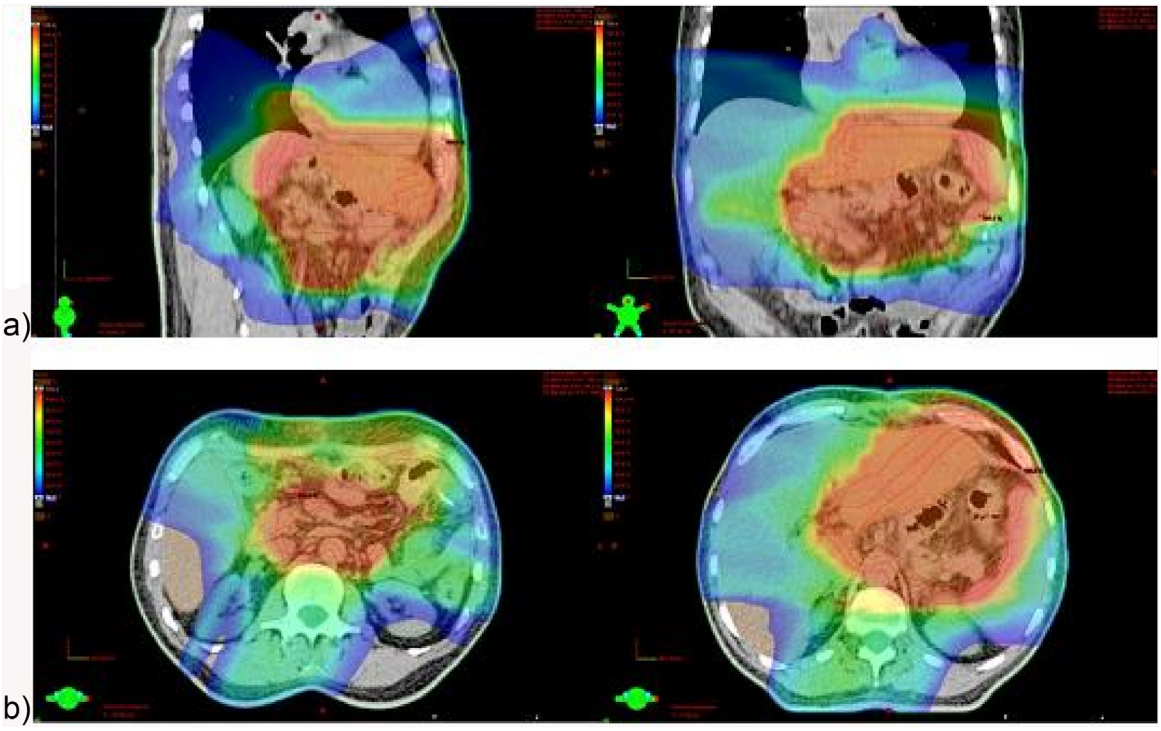

Fig. 1 – IMRT dose distribution for gastric cancer on: (a) the sagittal and coronal plane; (b) the transversal plane on the lower and upper section of the PTV.

Table 2 – Evaluation of ITV and PTV doses for BP and SP* for the IMRT plans of the twenty patients.

Structure	Parameter	MEAN [%]		SD [%]		MIN [%]		MAX [%]	
		BP	SP	BP	SP	BP	SP	BP	SP
ITV	$V_{95\%}$	99.76	99.94	0.39	0.41	99.63	99.28	100.00	100.71
	D95%	97.70	97.85	0.81	0.83	96.98	96.59	98.65	99.08
	$D_{5\%}$	102.94	102.69	1.07	0.93	101.93	101.66	104.84	104.20
	D_{mean}	100.32	100.40	0.44	0.40	99.76	99.84	100.96	100.98
	ITC	5.37	4.96	1.86	1.80	3.31	2.92	8.37	7.87
	R%D	0.21	0.21	0.08	0.62				
PTV	V95%	99.55	98.29	0.42	1.21	98.89	96.34	99.99	99.69
	D95%	97.49	96.93	0.77	0.96	96.38	95.61	98.50	98.17
	D5%	103.25	102.85	1.04	1.00	102.20	101.97	104.80	104.61
	D_{mean}	100.41	100.19	0.43	0.36	99.90	99.85	101.02	100.42
	ITC	5.92	6.13	1.84	2.04	3.75	4.01	8.73	9.18
	R%D	0.25	0.25	0.07	0.62				

*BP indicates base plan; SP, the sum of partial plans; SD, standard deviation; ITV, internal target volume; PTV, planning target volume; ITC, internal target coverage; R%D, relative percentage differences.

Table 3 – Dosimetric parameters for the right and left kidneys, liver and spinal cord for BP and SP* for twenty patients.

Structure	Parameter	MEAN [%]		SD [%]		MIN [%]		MAX [%]	
		BP	SP	BP	SP	BP	SP	BP	SP
Right kidney	$V_{80\%}$	10.58	10.84	5.49	5.50	5.50	5.05	18.13	14.49
	$V_{50\%}$	17.62	18.58	3.71	3.99	13.84	12.73	23.04	23.54
	$V_{20\%}$	29.51	29.36	4.33	4.72	19.42	21.83	33.42	35.23
Left kidney	$V_{80\%}$	17.34	18.34	3.72	3.94	10.48	10.73	23.32	23.66
	$V_{50\%}$	29.40	30.48	4.71	4.60	18.57	19.91	34.22	33.90
	$V_{20\%}$	56.79	59.68	10.02	11.44	40.49	43.64	65.23	76.28
Liver	$V_{80\%}$	36.80	35.93	6.84	7.18	26.88	23.37	44.42	43.21
	$V_{50\%}$	62.11	59.84	11.43	10.93	38.47	37.89	70.14	70.14
	$V_{20\%}$	98.12	96.08	3.91	6.37	88.80	81.55	100.30	100.00
Spinal cord	D_{max}	67.70	67.09	6.20	7.18	61.60	61.52	81.10	83.48

*BP indicates base plan; SP, the sum of partial plans; SD, standard deviation.

Table 4 – Patient set-up errors, mean displacement, systematic error, and random error for the entire group of patients.

Parameter	Direction		
	L-R	C-C	A-P
Mean displacement [mm]	−2.57	0.46	−0.24
Systematic error [mm]	−2.57	0.45	−0.24
Random error[mm]	2.22	2.74	1.58
Standard deviation [mm]	3.22	4.74	3.97
Set-up margin [mm]	7.80	10.17	6.71

L-R indicates left-right; C-C, cranio-caudal; A-P, anterior–posterior.

$D_{95\%}$ and ITV $V_{95\%}$, respectively. The greatest PTV difference (1.26%) was found for PTV $V_{95\%}$. The statistical analysis made with a paired two-tailed Student's t test, showed no significant differences among the various indices. The percent of the volume receiving 80%, 50% and 20% of the prescribed dose ($V_{80\%}$, $V_{50\%}$, and $V_{20\%}$) to the liver and each kidney, and D_{max} to the spinal cord are shown in Table 3. The dose distribution calculated for BP and SP revealed no significant differences between any of the parameters analyzed for the OARs.

3.3. *Set-up errors for gastric cancer*

Based on the results of 2DkV displacements, we calculated the systematic and random errors, which are summarized in Table 4. The SM values determined in the LR, CC, AP directions were 7.80, 10.17 and 6.71 mm, respectively. The calculated length vector was 6.75 mm for taken values of displacement V was 10.22 mm, so we are twice as low as our assumed tolerance level.

4. Discussion

The primary aim of the present study was to assess the impact of set-up uncertainties on target coverage and normal tissue sparing in IMRT for gastric cancer. The main finding was that the selected set-up margin provided optimal dose distribution for the target and the critical organs. In the comparative analysis of the DVHs for the BP and SP (which considers set-up uncertainties), no significant differences were observed. This implies that set-up errors could be compensated for by adding a 0.5 cm margin to the CTV in the transverse and sagittal directions and 1.0 cm margin in the longitudinal axis) to create the PTV. When set-up errors determined during the course of treatment were taken into account, we did not observe any significant differences between the BP or SP. the DVH results for both plans were comparable in terms of target coverage and critical structure sparing. The small (non-significant) differences between the mean values (and standard deviations) of the analyzed indices, especially those which tracked the ITV and PTV results, showed that the BP and SP plans were nearly identical, a finding that is further confirmed by the small standard deviations for these indices. These are very good results and provide further support for the used margins.

Based on ICRU 83 recommendations, our aim was to generate treatment plans with a uniform dose prescribed to the target volume, delivering at least 95% of the prescribed dose to 98% of the volume.[24] We found that for the calculated values of the ITV and PTV, the relative percentage difference between BP and SP was very low, a finding that indicates the close similarity between the original plan and the plan that considered the impact of 2DkV uncertainties. However, agreement between plans for the ITC values calculated independently for the ITV and PTV was not as good, although the differences were not statistically significant; not surprisingly, the SDs were larger for these parameters compared to other target volume parameters. These findings are supported by the statistical verifications performed for OARs, in which standard deviations were significantly higher, as shown in Table 3. In fact, given this large variance in SD, we decided to check the anatomical characteristics of our patients (i.e., target volume size, the distance between the PTV and OARs, and the portion of the liver contained within the PTV volume). The large scatter of the $V_{80\%}$, $V_{50\%}$ and $V_{20\%}$ values may have occurred because this was the first group of patients treated with IMRT for gastric cancer at our center, and they were not required to meet any specific anatomical selection criteria. However, this situation provided us with an opportunity to verify our clinical procedures for non-anatomically selected patients, to check the optimal beam arrangement and constraints for IMRT plans, and to verify the fixed set-up margin.[25]

IMRT is becoming the treatment of choice to successfully deliver inhomogeneous dose distributions.[8,26] To compensate for the uncertainties that result from patient positioning and organ motion, a margin must be added to the CTV to create the final PTV.[17,18,27] However, determining the appropriate size of the margin is always an important question, as this aspect has a strong influence on potential target underdosing or OAR overdosing. In our study, an asymmetrical margin (10–20 mm) was applied for treatment planning and delivery. The additional calculations performed to verify the CTV to PTV extension based on set-up displacements proved our initial assumption that the largest margin should be added in the CC direction. Nevertheless, the measured displacement was much smaller than 20 mm in all directions (7.80 mm, 10.17 mm, and 6.71 mm in the LR, CC, and AP directions, respectively). Taking into account all the measured set-up uncertainties and the simulated agreement between the planned and delivered doses, the overall results of the examined treatment procedure were quite satisfactory.

5. Conclusions

IMRT treatment of gastric cancer allows for the delivery of a highly conformal dose to the large PTV with adequate sparing of OARs.[8,10] However, steep dose gradients outside the target volume and organ motion in the treated area make it necessary to verify the patient positioning more frequently.

In this study, we showed that IMRT treatment plans prepared with seven non-coplanar beams have the potential to deliver clinically appropriate doses to the PTV while reducing the doses received by OARs (especially kidneys). We found no significant differences in DVH data between the baseline IMRT plan and the simulated plan (created according to measured isocenter shifts,). This finding shows that real set-up errors

are smaller than the proposed set-up margin (10 mm in all directions, except 20 mm in the cranio-caudal direction).

Conflict of Interest statement

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Financial Disclosure statements

None declared.

Acknowledgements

None declared.

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