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FULL PAPER

Influence of interfraction motion on margins for radiotherapy of gastric cancer

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Objective: The aim of this study was to evaluate interfraction uncertainties using kilovoltage (kV) radiographs for patients with gastric cancer during chemoradiotherapy and to calculate the planning target volume (PTV) margins.

Methods: 1284 measurements of set-up errors were analysed for treated patients. The measurements of craniocaudal (axis *y*), laterolateral (axis *x*) and antero-posterior (axis *z*) shifts in kV radiographs were performed. Interfraction clinical target volume (CTV)–PTV margins for all directions were calculated using the van Herk formula.

Results: The main shift for the *y*-axis was 0.7 mm [standard deviation (SD), ± 7.6], for the *x*-axis was 0.4 mm (SD, ± 3.7) and for the *z*-axis was 0.6 mm (SD, ± 3.5). The

CTV–PTV margin in the *x*, *y* and *z* directions was 8.3, 15.5 and 8.0 mm, respectively. We observed that the interfractional motion for patients increased approximately 0.0034 cm along the *x* direction with each subsequent fraction, whereas a 0.0058-cm reduction in length along the *y*-axis was observed. No time effects for the *z* direction were noticed.

Conclusion: According to our experience, a PTV margin of 9 mm along the *x*-axis, 16 mm along the *y*-axis and 8 mm along the *z* direction should be considered in the absence of image-guided radiotherapy.

Advances in knowledge: This knowledge concerning PTV set-up margins could be particularly useful for centres without a kV on-board imaging system.

In the treatment of gastric cancer, local recurrence is a major problem and occurs in 40–65% of the patients treated.^{1,2} Radical surgery is the gold-standard therapy,^{3,4} yet, still promotes suboptimal survival. Surgery itself provides long-term survival (5-year survival rate) for only 20–30% of patients.⁵ Adjuvant chemoradiotherapy has been provided to produce a reduction in locoregional relapses and an improvement in survival.⁶ A novel gastric cancer treatment strategy consisting of neoadjuvant chemoradiotherapy and surgery demonstrated a high rate of R0 resection, pathological complete response (PCR) and a low level of local recurrences.^{7,8} Radiotherapy (RT) has become an important part of gastric cancer treatment. However, the anatomic accuracy of RT depends on the ability of a positioning system to reproduce a patient's geometry during simulation, CT scanning and treatment procedures, precision in delineation especially can cause better outcomes, which is why the contouring should be completed by two radiation oncologists with a special interest in gastrointestinal malignancies. Accurate patient positioning between and during each fraction of RT is very important

for adequate tumour treatment, especially for intensity-modulated radiation therapy (IMRT) of gastric cancer. This type of treatment may reduce the radiation dose to normal adjacent tissue structures surrounding the stomach, such as bowel, the liver, the kidneys, the spinal cord, the heart, the pancreas and the lung. If this procedure is carried out imprecisely there can be a local control reduction. With the introduction of image-guided RT (IGRT), geometric variations such as set-up error and organ motion can be measured and used in correction protocols. This allows a reduction in the additional margins around the clinical target volume (CTV), or the internal tumour volume (ITV), which are added to form the planning target volume (PTV). This procedure may reduce complications and potentially improve local control through dose escalation. There are four types of systems for the correction of patient position during RT: electronic portal imaging devices; an ultrasound system; and kilovoltage and megavoltage cone beam CT (CBCT). Data from these systems permit the accurate measurement of systematic and random set-up errors. The International Commission on Radiation Units and Measurements

Table 1. Minimum, maximum, mean and median shifts in the *x*, *y* and *z* directions (cm)

Measure	Number of fractions	<i>x</i> -axis	<i>y</i> -axis	<i>z</i> -axis	Vector
Minimum	1	−1.5	−3.3	−1.3	0
First quartile	7	−0.2	−0.5	−0.1	0.4583
Median	13	0	0	0	0.7071
Mean	12.93	0.0366	−0.075	0.06044	0.7918
Third quartile	19	0.3	0.4	0.3	1.005
Maximum	28	1.8	2.2	2.1	3.3302

guidelines require the determination of the PTV. PTV margins have been defined by van Herk *et al.*⁹ However, results could be different for each calculation. Most studies have used van Herk formula, linking the PTV margin with systematic and random errors. Still, the PTV margin in the case of stomach cancer is not well defined. Scientists from the Princess Margaret Hospital showed that the median interfraction displacement was approximately 6 mm in the craniocaudal (CC) direction and 2 mm in the other directions, and they recommend a minimal internal margin of 1 cm superiorly and inferiorly, 5 mm anteriorly, posteriorly and to the right and left.¹⁰ Other authors^{11,12} have recommended a 1-cm addition to the CTV, but there are no calculations to confirm those. Thus, the purpose of the present study was to determine the connection between PTV margins and interfraction motion for our adaptive procedure according to the van Herk formula using calculations. Currently, there are no data concerning the set-up of margin calculations for RT of gastric cancer. Our study could be particularly useful for RT departments with lack of IGRT.

METHODS AND MATERIALS

1284 set-up error measurements from 57 patients with gastric cancer who were treated with pre-operative or post-operative chemoradiotherapy between 2010 and 2011 were evaluated. Set-up patient verification was performed using a two-dimensional (2D)/2D kilovoltage (kV) system [on-board imaging (OBI)] based on radiography (Varian Medical Systems, Palo Alto, CA). Combined treatment (chemo-RT) was used for patients diagnosed with stage pT2–4N0M0 or pT1–4N1–3M0. In all cases, total gastrectomy with D2 lymphadenectomy was performed. 48 patients underwent standard adjuvant chemoradiotherapy.¹³ Nine of them were qualified for pre-operative chemoradiotherapy, followed by surgery with adjuvant chemotherapy, according

to a prospective randomized trial comparing pre-operative chemoradiotherapy followed by operation and adjuvant chemotherapy to standard treatment.⁷ The fractionation dose per fraction was 1.8 Gy for a total dose of 45 Gy. In the case of R1 resection, the dose was increased to 50.4 Gy for the infiltrated margin. The CTV included gross tumour and the entire stomach with 5 cm for the upper and middle third of the stomach and 3 cm for the distal third for neoadjuvant treatment, the stomach bed and anastomoses for adjuvant treatment and draining locoregional lymph nodes, such as the perigastric, suprapyloric, infrapyloric, suprapancreatic, celiac, splenic hilar, porta hepatic or pancreatoduodenal,^{14–16} because in each case inspiration and expiration CT scans were acquired at planning, individual ITV was included in treatment planning. During RT, patients were given two cycles of chemotherapy consisting of 5-fluorouracil plus or minus leucovorin. In the adjuvant treatment group, four additional 5-day cycles of fluorouracil plus leucovorin were given. In the neoadjuvant radiochemotherapy group, radical surgery was performed at least 4 weeks after the end of RT. After surgery, chemotherapy was continued using fluorouracil plus leucovorin for up to six cycles.

Each patient was treated in the supine, head-first position using thermoplastic masks (by Orfit Industry, Belgium) and plates

Table 2. Mean, standard deviation (SD) and Shapiro-Wilk normality statistics

Deviation	Mean (cm)	SD	W statistic	<i>p</i> -value
<i>x</i>	0.037	0.367	0.9752	0.0000
<i>y</i>	−0.0750	0.756	0.9887	0.0000
<i>z</i>	0.060	0.355	0.9750	0.0000
Vector	0.792	0.465	0.9141	0.0000

Figure 1. Distribution of isocenter displacement in the *x*, *y* and *z* axes and a vector for bone structure verification (minimum, maximum, lower and upper quartile, median and outliers).

Table 3. Margins for the clinical target volume (cm) for the van Herk formula

Deviation	van Herk formula, $2.5\Sigma + 0.7\sigma$
<i>x</i>	0.83
<i>y</i>	1.55
<i>z</i>	0.80
Vector	0.87

Σ , total standard deviation of preparation (systematic) errors; σ , total standard deviation of execution (random) errors.

(by Stanley, Poland) with head support and four fixation points to minimize movement during RT, and to ease patient positioning. All patients had a CT planning scan performed. Intra-vein contrast was used, and in all cases, one glass of water was given to fill the stomach after a light meal. Conformal RT (3- to 4-field irradiation method) or IMRT was used. The applied treatment planning system was Eclipse™ by Varian® Medical Systems, Palo Alto, CA. All patients were positioning using an IGRT system called 2D/2D kV. At the beginning of each fraction, patients were positioned using laser alignments to marks on their thermoplastic mask. Afterwards, pre-treatment images in the lateral and anteroposterior projections were taken using radiography. Collected images were manually matched to the corresponding digitally reconstructed radiographs generated during planning, and the position of bony (the thoracic, lumbar vertebral column or coxal bone) anatomy was accessed. Displacements were evaluated in the lateral plane (*x*-axis), CC plane (*y*-axis) and anteroposterior plane (*z*-axis) in all cases. The patient's positioning was corrected automatically using a treatment couch. The images were reviewed by RT technicians. If the case of shifts more than 1 cm radiation oncologists check the cause of the shifts. Moreover, a three-dimensional (3D) vector of shifts was calculated for all patients with a root sum of squares.

The population systematic and random errors were calculated considering each axis. The population systematic error was defined as standard deviation (SD) from values of average shifts for all individual patients. The population random error was determined as the root mean square.¹⁷ The computation was conducted in R platform (www.R-project.org/).

RESULTS

Our analyses included data from 57 patients. 80% of the patients were treated with IMRT and 20% with 3D plans. In total, 1284

measurements of interfractional motion were performed. Descriptive statistics of patients are provided in Table 1.

The average 3D vector of shifts was 7.9 mm. In the *x*, *y* and *z* axes, it occurred in the range of −15 to 18, −33 to 22 and −13 to 21 mm, respectively. The population distribution of shifts in all axes was not consistent with a gaussian distribution.

The average value of absolute shift and SD for the *x*, *y* and *z* axes were 0.37 mm (SD, ± 3.67 mm), 0.75 mm (SD, ± 7.56 mm) and 0.6 mm (SD, ± 3.55 mm). Means and SDs of patients' displacement together with Shapiro–Wilk test statistics. The analysis of variance test for normality from complete samples and biometrics are reported in Table 2. The numbers given in Table 2 show an apparent decentralization of data (the smallest one is observed for the *x*-axis, while the highest for the *y*-axis). Moreover, the estimated *p*-values of the Shapiro–Wilk test indicate an abnormality of measurements.

The estimated *p*-values of the Shapiro–Wilk test indicate that measurements did not follow a standard path. Distribution of the *x*, *y* and *z* displacements together with vector deviation is shown in combined box plots in Figure 1. A rough analysis of Figure 1 provided evidence of larger deviations for the *y*-axis. Relatively, wide ranges for the *x*, *y* and *z* displacements resulted in a number of vector outliers (Figure 1).

The CTV–PTV margins for the van Herk formula calculated on the basis of shift values measured in the 2D/2D kV system were 8.3 mm for the *x*-axis, 15.5 mm for the *y*-axis and 8.0 mm for the *z*-axis. Margins for CTV based on systematic and random errors (Table 3) were calculated.

To evaluate the final effect of subsequent irradiations during treatment on the interfractional motion deviations in patients, we conducted multilevel, hierarchical modelling of data with differentiated effects. The estimations of a possible influence of the order of fractions are given in Table 4.

Table 4 provides the evidence of significance of fraction order on deviations in the displacement along the *x*- and *y*-axes during consecutive irradiations. However, the interfractional motion of patients increased approximately 0.0034 cm along the *x*-axis with each subsequent fraction, whereas a 0.0058-cm length reduction was observed along the *y*-axis. Although differences were very small, were corrected daily and only had insignificant impact on patient's positioning, we did not observe time effects

Table 4. Time effect on deviations (multilevel linear regression)

Deviation	Intercept (cm)	SE	<i>p</i> -value	Slope (cm)	SE	<i>p</i> -value
<i>x</i>	−0.0075	0.0363	0.8354	0.0034	0.0011	0.0018
<i>y</i>	0.0084	0.0666	0.8997	−0.0058	0.0024	0.0179
<i>z</i>	0.0628	0.0352	0.0745	−0.0007	0.0010	0.4992
Vector	0.7983	0.0371	0.0000	−0.0010	0.0016	0.5468

SE, standard error.

for the *z* direction. Graphical representations of significant changes are presented in Figures 2–4.

DISCUSSION

In this study, we used kV OBI measures to calculate interfraction motion. The variability in couch shift correction reflected a combination of the accuracy and precision of the digital couch readout, variability in patient movement within the immobilization device and patient weight loss during treatment. Routine quality assurance testing indicated that couch repositioning variability was <1 mm. Some authors have observed a correlation between positioning errors and patients' weight loss.¹⁸ According to calculations, the interfractional motion increased along the *x*-axis during treatment, which could correlate with patient weight loss. Better patient preparation as well as remaining relaxed during treatment affects the correct positioning.

The PTV margin for stomach cancer is not well defined. A 1-cm addition to the CTV in all directions has been the standard procedure, but no data have been published to confirm this suggestion.¹⁹ Orfit Industries recommend adequate and stable fixation. However, there is still no information from the industry in terms of set-up uncertainties and margins, especially for patients with diseases located in the abdomen. It is very important to determine intra- and interfractional errors based on every department's experiences to deliver successful treatment for gastric cancers. The aim of our study was to calculate set-up margins. This knowledge, concerning PTV set-up margins, could be especially useful for centres with no kV OBI system.

In this study, margins were calculated using the van Herk formula (9 mm for the *x*-axis, 16 mm for the *y*-axis and 8 mm for the *z*-axis) to create the PTV around the CTV. Hawkins *et al.*²⁰ have reported the following numbers for oesophageal cancer margins: 5, 7 and 5 mm for the *x*, *y* and *z* axes, respectively. Using the van Herk ($M = 2.5\Sigma + 0.7\sigma$) formula, the CTV–PTV margins in the lateral, CC and anteroposterior directions were

Figure 3. Deviations along the *y*-axis vs number of fractions.

calculated. Σ represents the population systematic error and σ represents the population random error. This formula appears to be the most suitable because it ensures that 90% of patients receive a minimum cumulative CTV dose of at least 95% of the prescribed dose.²¹ In our opinion, van Herk calculations are the correct way of evaluating a treatment plan because they are based on detailed knowledge of the distribution of geometric errors in the patient population.⁹ In this article, we showed an error distribution of geometric uncertainties for parameters such as set-up error. According to our experience, the CTV–PTV margin in the *y*-axis should be >10 mm, as described in other articles,^{11,12} although larger margins for a non-IGRT approach can cause the delivery of a higher dose to adjacent normal tissue structures surrounding the stomach. Daily IGRT correction helps to protect at-risk organs and tissues.

Figure 2. Deviations along the *x*-axis vs number of fractions.

Figure 4. Deviations along the *z*-axis vs number of fractions.

Wysocka et al¹⁰ reported smaller interfraction displacement relative to the vertebral bodies (6 mm in the y -axis and 2 mm in the other directions). Jayachandran et al²² have shown the mean interfractional vector shift distance was 5.5 mm (95th percentile, 14.5 mm; range 0–19.3 mm), but the study analyses treatment of pancreatic cancer, which may result from another group of patients.

The mean of displacement in patients in the y and z axes was almost the same as reported by Hawkins et al²⁰ for oesophageal cancer and smaller in the x -axis (0.37 vs 0.80, respectively). An online, daily correction protocol reduces set-up errors, but our observed shifts are largely similar to those previously reported. SDs for the x and z axes according to our calculations were similar to those reported by Cranmer-Sargison et al²³ in patients with rectal cancer but were larger in the y -axis (7.56 vs 3.70 mm). However, displacements occurred in patients with different anatomical locations of the tumour. Our absolute values for the shift maximum in all directions were much smaller than the shifts verified by portal imaging (6 vs 10 mm in

x , 12 vs 18 mm in y and 13 vs 6 mm in z). The average values were similar in both reports.²⁴

Intrafraction errors were not included in our calculation. For abdominal sites, Xu et al²⁵ investigated the use of pre- and post-treatment CBCT imaging to minimize intrafraction motion. Next, we will investigate intrafractional patient movement and organ motion using a CBCT system.

CONCLUSION

To avoid geographical errors during RT of gastric cancer, an appropriate CTV–PTV margin should be calculated. According to our experience, a PTV margin of 9 mm along the x -axis, 16 mm on the y -axis and 8 mm in the z direction should be considered in the absence of IGRT.

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