RESEARCH ARTICLE

Delineation of Margins for the Planning Target Volume (PTV) for Image-Guided Radiotherapy (IGRT) of Gastric Cancer Based on Intrafraction Motion

Paulina Leszczyńska[1]*, Wojciech Leszczyński[1], Jerzy Wydmański[1], Dębiec Kinga[2], Agnieszka Namysł Kaletka[1], Andrzej Tukiendorf[3], Leszek Hawrylewicz[1]

Abstract

Background: Application of the image-guided radiotherapy (IGRT) system for gastric cancer involving daily verification of patient positioning on the treatment machine allows minimisation of geometrical errors as a consequence of intra- and inter-fraction motion. The purpose of this study was to define the intrafraction motion in gastric cancer patients during a treatment session based on the IGRT system and designation of margins around the clinical target volume CTV (internal target volume ITV) necessary to delineate the planning target volume (PTV). **Methods:** Twenty gastric cancer patients were analysed. The total radiation dose for each was 45Gy in 25 fractions within 5 weeks. The margins for the PTV were calculated according to van Herk (2004), Stroom and Heijmen (2002) and the International Commission on Radiation Units and Measurements (ICRU) Report 62 formulas based on craniocaudal (Y axis), laterolateral (X axis) and anteroposterior (Z axis) shifts. **Results:** Delineated margins for the PTV in gastric cancer with the three formulas applied were respectively 0.2, 0.2, and 0.2cm in the lateral plane, 0.3, 0.3, and 0.3cm in the craniocaudal plane and 0.3, 0.3, and 0.2cm in the anteroposterior plane. **Conclusions:** Recommended margins for the PTV in gastric cancer calculated in this study based on intrafraction motion are 0.3cm, 0.2cm and 0.3cm in the craniocaudal, lateral and anterioposterior directions, respectively. Use of the IGRT system corrects for the motions between factions and allows reduction in ITV-PTV margins. The main advantage of the smaller margins in comparison to the non-IGRT radiotherapy is a reduction in the probability of radiation complications.

Keywords: Gastric cancer radiotherapy- IGRT- intrafraction motion- margins for PTV

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Introduction

In the USA and Europe, postoperative radiotherapy is an approved method of treatment in patients with gastric cancer (Macdonald et al., 2001). The application of preoperative radiotherapy or chemoradiotherapy for locally advanced gastric cancer has undergone intensive research (Zhang et al., 1998; Wydmanski et al., 2007). Radiotherapy is also used for inoperable or unresectable gastric cancer (Saikawa et al., 2008; Wydmanski et al., 2014). Because the location of the tumour is in close proximity to radiation sensitive organs at risk (OAR) such as the kidneys, liver, intestines, pancreas, lungs, heart, and spinal cord, radiotherapy planning is challenging. The application of dynamic techniques such as intensity modulated radiotherapy (IMRT), volumetric arc therapy (VMAT) or Tomotherapy allows an effective reduction of the dose in OAR in comparison to the conformal techniques (Wang et al., 2013). However, high dose gradients and conformal avoidance require precision in preparing patients for treatment, delineation of the target regions and accurate positioning of the patient during each radiotherapy session. For accurate radiotherapy treatment, the image-guided radiotherapy (IGRT) system is applied which uses three–dimensional images that give precise information on patient positioning (Drabik et al., 2007). Application of the IGRT system involving everyday verification of patient positioning on the treatment machine using 2D kV orthogonal X-ray images allows minimisation of the geometrical error as a consequent of intra- and interfraction motion. Reduction of interfraction systematic and random errors allows minimisation of the margins between the internal tumour volume (ITV) and the planning target volume (PTV) (Perkins et al., 2006). Determination of margins of the ITV-PTV based on interfraction motion are particularly very important in radiotherapy departments that do not have IGRT system. However, IGRT does not eliminate the intrafraction motion during each radiotherapy session. The intrafraction motion is the foundation in the designation of the margins for the

*[1]Department of Radiotherapy Planning, [2]Radiotherapy and Chemotherapy I Clinic, [3]Department of Epidemiology, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland. *For Correspondence: Paulina.Leszczynska@io.gliwice.pl*

ITV-PTV based on the IGRT system. The intrafraction motion should be designated independently for specific tumour localisation and individually for each system of patient immobilisation.

The basis for safe radiotherapy, both in conformal and dynamic techniques, is high precision of reproducibility of the treatment plan geometry. Therefore, delineation of the gross tumour volume (GTV), the ITV and margins for the PTV are crucial. Definition of the target volume significantly influences treatment success. Usually the GTV and the ITV can be precisely defined on diagnostic images, although the PTV is based on a geometric concept which depends on the changes in the shape of the target volumes caused by motion of the organs at risk and both random and systematic errors (Drabik et al., 2007). Defining the optimal PTV is very important in treating the tumour adequately and at the same time minimising irradiation of the OAR and reducing the risk of radiation complications (Astreinidou et al., 2005).

In practice, there is the question of how large the margins in gastric cancer radiotherapy should be. The margins for the PTV in gastric cancer radiotherapy are not clearly defined. Some authors based on clinical experience, have proposed margins ranging from 0.5 to 1cm around the ITV, but these margins have not been confirmed by calculations (Milano et al., 2006; Leong et al., 2005; Wydmański and Mohanti, 2008; Matzinger et al., 2009). Previously published data on the PTV margins for gastric cancer indicated that these margins are asymmetrical and different for the lateral plane (X axis), craniocaudal plane (Y axis) and anteroposterior plane (Z axis) (Namysł-Kaletka et al., 2015). Moreover, for radiotherapy without IGRT, the margin for the Y direction far exceeds 1cm. However, there are no recommendations concerning the margins for application of the IGRT system.

This is an experimental study, which aims to define the intrafraction motion in gastric cancer patients during treatment sessions based on the IGRT system and designation of margins around the ITV necessary to delineate the PTV.

Materials and Methods

Twenty gastric cancer patients treated at Department of Radiotherapy Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Gliwice Branch, Poland were examined. The inclusion criteria for patients were: confirmed histologically gastric cancer stage pre- or postoperative and good performance status (Zubrod Scale 0-2). Patients were undergone chemoradiotherapy with the total dose 45Gy in 25 fractions within 5 weeks. All the patients were treated using IMRT or the RapidArc techniques, planning details are described in previous publications (Wydmański and Mohanti, 2008; Namysł-Kaletka et al., 2015).

The position in all examined patients was stabilised using a thermoplastic mask (Orfit Industry, Wijnegem, Belgium) for the chest and abdominal region. For each radiotherapy session, the patients were positioned on the isocentre which was previously marked on the X-ray simulator. Patients were positioned by application of the 2D/2D kV IGRT (Varian Medical Systems, Palo Alto, CA, USA) system before each radiotherapy fraction. The location of the patient was determined based on the bony structures on radiological images in the anteroposterior and lateral projections. Before the radiotherapy session, correction of the patient position was carried out using the couch movement. The shifts were noted in the lateral plane (X axis), craniocaudal plane (Y axis) and anteroposterior plane (Z axis). When the radiotherapy session was completed, the radiological images were obtained again using the 2D/2D kV IGRT system. It was expected 1500 data (500 measurements for each direction) but finally in seven hundred and eighty three measurements of setup errors were evaluated. Because of the time limitation the kV images after completed session were preformed average every second fraction. Based on differences between obtained images before and after session, intrafraction motion was determined for each patient. Moreover, based on the data from the IGRT system, the interfraction motion was examined for the same group.

The margins for radiotherapy planning took into account the effects of treatment and were calculated according to the Van Herk (2004), Stroom and Heijmen (2002) and ICRU Report 62 formulas which proposed that the margins for the PTV should be defined as follows:

$M = 2.5\,\Sigma + 0.7\sigma$ (Van Herk, 2004)

$M = 2.0\Sigma + 0.7\sigma$ (Stroom and Heijmen, 2002)

$M = \mathrm{sqrt}(\Sigma^2 + \sigma^2)$ (ICRU Report 62)

- Σ- SD of systematic errors
- σ- SD of random errors

The formula include both systematic and random errors resulting from motion of the skin with respect to the mask, motion of the internal anatomy which limits the reproducibility of the patient set up from the CT scanner and movement of organs during the course of radiotherapy.

The translation vector was also determined as follows:

$V = \mathrm{sqrt}(X^2+Y^2+Z^2)$

For the data obtained, statistical analysis was performed and the p-value was set as 0.05.

Results

The data, including intrafraction motion, of 20 patients were analysed. For intrafraction motion, the mean values and standard deviations for each direction: lateral (X), craniocaudal (Y), anteroposterior (Z) were as follows: 0.004±0.124cm; 0.057±0.133cm; 0.013±0.162cm, respectively. The 3D vector (V) of shift was 0.201±0.149cm. Margins for the PTV for the X, Y, and Z planes were calculated according the Van Herk (2004), Stroom and Heijmen (2002) and ICRU Report 62 formulas. The values obtained are shown in Table 1. Displacement of the X, Y, and Z directions and the translation vector are shown in Figure 1.

A multilevel modelling analysis of the data with mixed effects was used to investigate the effect of subsequent irradiations during treatment. For intrafraction motion, estimates of a possible influence in the order of the fractions are given in Table 2.

The results shown in Table 2 indicate that there were

Table 1. The Mean Values and Standard Deviations for the X, Y, and Z Directions and the Margins for CTV Calculated According to the Van Herk (2004), Stroom and Heijmen (2002) and ICRU Report 62 Formulas for Intrafraction Motion

Direction	Mean	SD	Van Herk (2004)	Stroom and Heijmen (2002)	ICRU Report 62
X [cm]	0.004	0.124	0.2	0.2	0.2
Y [cm]	0.057	0.133	0.3	0.3	0.3
Z [cm]	0.013	0.162	0.3	0.3	0.2
V [cm]	0.201	0.149	0.3	0.3	0.3

SD, standard deviation

Table 2. Time Effect on Deviations (Multilevel Linear Regression) of Intrafraction Motion.

Direction	Intercept [cm]	SE	p-value	Slope [cm]	SE	p-value
X	-0.02	0.02	0.33	0.001	0.001	0.31
Y	-0.02	0.03	0.64	0.000	0.001	0.79
Z	0.04	0.03	0.14	0.001	0.001	0.27
Vector	0.20	0.03	0.00	0.000	0.001	0.74

SE, standard error

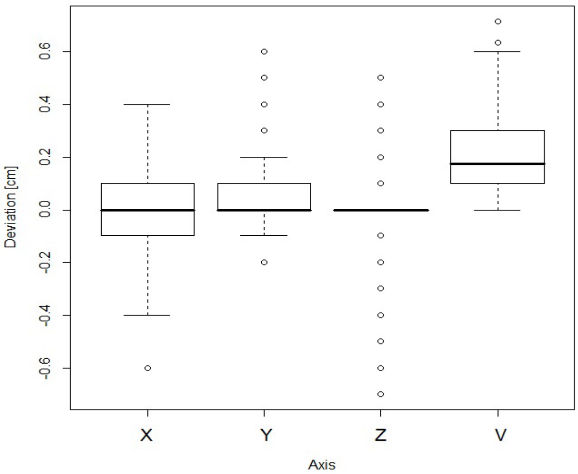

Figure 1. Distribution of the Shifts in the X, Y, and Z axes and 3D Translation Vector for 2D kV IGRT Verification (Minimum, Maximum, Lower and Upper Quartile, Median and Outliers) for Intrafraction Motion

no significant deviations for the X, Y, and Z axes during consecutive irradiations.

Discussion

Margins for the PTV in gastric cancer calculated in this study according to the Van Herk (2004), Stroom and Heijmen (2002) and ICRU Report 62 formulas were as follows: 0.2, 0.2, and 0.2cm in the lateral plane, 0.3, 0.3, and 0.3cm in the craniocaudal plane and 0.3, 0.3, and 0.2cm in the anteroposterior plane, respectively. This indicated that the results were similar, thus these formulas can be used for delineation of margins based on intrafraction motion. The intrafraction mean displacements were lower than 0.1cm in all directions. Our calculations confirmed that mean values and standard deviations of the intrafraction motions were much smaller than the interfraction motions. In our earlier study, the mean value of absolute shift and SD for the X, Y and Z axes were 0.037cm (SD, ±0.367cm), 0.075cm (SD, ±0.756cm) and 0.06cm (SD, ±0.355cm) (Namysł-Kaletka et al., 2015).

In our conception of treatment planning, the motions of stomach during each fraction of radiotherapy should be included in ITV. Such an approach is in line with the recommendations of ICRU Report 62. In modern radiation therapy based on this report, it is critical to the proper determination of the ITV. Accurate determination of the ITV allows to avoid the geographical errors. The intrafraction motions of the stomach due to breathing movements have been described previously. Watanabe et al. (2011) calculated the average intrafractional gastric motion using repeated CT scans. The results were -1.2 ± 1.3, 0.2 ± 0.7 and 0.5 ± 0.8 cm for the superior-inferior, lateral and ventro-dorsal directions, respectively. This study also showed that the average interfractional motions in the centre of the stomach were higher: 0.4, 0.2 and 0.1 cm for the craniocaudal, lateral and anterioposterior directions, respectively. Hashimoto et al., (2005) analysed the motion of organs at risk in the digestive tract using a fluoroscopic real-time tracking system to monitor the position of the implemented markers. The determined internal margins mean/standard deviation of the range of motion in the oesophagus were 0.3/0.2, 0.8/0.4, and 0.4/0.3 cm for the lateral, craniocaudal and anteroposterior directions, respectively, in patients with intrafractional tumour motion less than 1.0cm. Those calculations may be similar for tumour gastroesophageal junction. In our opinion, the ITV should include respiratory mobility of the stomach. The advanced technology like the IGRT system only eliminates displacements between fractions but does not influence on movements of patients during each fraction of radiation. However, better immobilisation system may reduce the movements during radiation therapy.

Van Herk (2004) advocated that it was useful to separate the interfractional variations into systematic errors and random errors. To ensure a minimum dose to the ITV of 95% for 90% of patients, they determined that $2.5\,\Sigma + 0.7\sigma$ is required for a margin between the ITV and PTV. According to their formula, the stomach margins calculated in our study were 0.3cm, 0.2cm and 0.3cm in the craniocaudal, lateral and anterioposterior directions, respectively. With respect to the study by Yamashita et al.

(2012) who systematically evaluated the intrafractional gastric motion of metal markers using 4D-CT, the 95th percentile values for the cumulative distributions in the lateral, anterioposterior and craniocaudal directions were 0.63cm, 0.90cm, and 1.36cm, respectively. In our opinion, the calculations by Van Herk (2004) are correct for evaluating a treatment plan because they are based on detailed knowledge of the distribution of geometric errors in the patient population.

In comparison to the interfraction motion, Namysł–Kaletka et al., (2015) showed that the PTV margins for gastric cancer radiotherapy calculated according the Van Herk (2004) formula were 0.83cm in the lateral plane, 1.55cm in the craniocaudal plane and 0.87cm in the anteroposterior plane. This indicated that the margins can be minimised by use of the IGRT system. According to the study by Wysocka et al., (2010), who measured the interfraction and respiratory organ motion during conformal radiotherapy in gastric cancer, found that the median interfraction displacement was approximately 0.6 cm in the craniocaudal direction and 0.2 cm in the other directions during a 5-week period of postoperative RT in patients with resected gastric cancer. The estimated median respiratory amplitude was 1.6cm for all organs. A. Namysł–Kaletka et al., (2015) observed time effects for the interfractional motion for patients increased approximately 0.0034cm along the X direction with each subsequent fraction, whereas a 0.0058cm reduction in length along the Y-axis was observed. These effects may result from the decrease in body weight during radiotherapy. In this study, there were no significant deviations for the all axes during radiotherapy.

Adequate margins allow better local control and reduction of side effects. Understanding the intrafractional motion is still very important and adjustment of the treatment strategy based on the observed motion behaviour could be beneficial in patient treatment. It is well recognized that the stomach continually changes volume and position not only on a daily basis (interfractional variation) but also during radiotherapy (intrafractional variation). In this situation the PTV margin for stomach cancer is not well defined in the literature. The most common is added a 1cm margin for gastric cancer planning (Adas et al., 2014). However it is very important to determine intra- and interfractional errors based on each department and could result in the successful treatment of gastric cancer.

Knowledge on intrafraction and interfraction patient motion during treatment allows accurate delineation of PTV margins for radiotherapy planning. This is significant in the intensity modulated planning dose absorbed by the tumour and normal tissue sparing due to the conformal dose distribution and high dose gradients. Interfraction motion can be minimised using the IGRT system during each radiotherapy session, and intrafraction motion can be reduced by patient immobilisation. The definition of PTV margins in gastric cancer for each radiotherapy department improves effectiveness of the treatment.

Recommended margins for the PTV in gastric cancer calculated in this study based on intrafraction motion are 0.3cm, 0.2cm and 0.3cm in the craniocaudal, lateral and anterioposterior directions, respectively. Delineated margins for the PTV in gastric cancer can be used only in radiotherapy with the IGRT system. An important aspect of this study is that all the patients were immobilised using a thermoplastic mask for the chest and abdominal region. The use of IGRT system eliminates the motions between the factions and allows a reduction in the ITV-PTV margins. The main advantage of the smaller margins in comparison to the non-IGRT radiotherapy is a reduction in the probability of radiation complications.

Ethical consideration

Bioethics committee of Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Gliwice Branch, Poland agreement number KB/493-59/09.

Conflicts of interest statements

The authors indicated no potential conflicts of interest.

Authors' contributions

Conception and design: Paulina Leszczyńska, Wojciech Leszczyński, Jerzy Wydmański , Dębiec Kinga Provision of study materials and patients: Jerzy Wydmański , Dębiec Kinga, Agnieszka Namysł – Kaletka Collection and assembly of data: Paulina Leszczyńska, Wojciech Leszczyński, Dębiec Kinga, Agnieszka Namysł – Kaletka Data analysis and interpretation: Paulina Leszczyńska, Jerzy Wydmański, Andrzej Tukiendorf, Leszek Hawrylewicz

Manuscript writing: All authors

Final approval of manuscript: All authors

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