Consideration of doses to some OARs depending on differently chosen CTV margins of lymph nodes in EBRT treatment of the stomach cancer

H Osmić¹, E Đedović¹, ² and G Marošević³, ⁴

¹ University Clinical Center Tuzla, Prof. dr. Ibre Pašića bb, 75000 Tuzla, Bosnia and Herzegovina
² University of Tuzla, Department of Physics, Univerzitetska 4, 75000 Tuzla, Bosnia and Herzegovina
³ Affidea Center for radiotherapy Banja Luka, Dvanaest beba bb, Banja Luka, Bosnia and Herzegovina
⁴ University of Banja Luka, Faculty of Medicine, Save Mrkalja 14, Banja Luka, Bosnia and Herzegovina

E-mail: edis.djedovic@yahoo.com

Abstract. Based on the computed tomography (CT) images it is not possible to see all the lymph nodes that belong to the stomach. In radiotherapy, for a clinical target volume (CTV) delineation based on CT images, it is necessary to determine the appropriate margin around the corresponding blood vessels to make sure that all the required lymph nodes will be irradiated. The larger margin will certainly cover all the lymph nodes but it can also produce an increase of the received dose in the normal tissues. While a smaller margin can eventually spare the normal structures as a consequence it brings a higher risk of missing the suspected lymph nodes. The aim of this study was to analyse the radiation doses received by some organs at risk (OARs) in the case of the three-dimensional conformal radiotherapy (3DCRT) treatment of the gastric cancer, for lymph node CTV margin sizes 5 mm, 7 mm and 10 mm. The study included 40 patients undergo the external beam radiotherapy (EBRT) treatment of gastric cancer. The one-way analysis of variance (ANOVA) with repeated measures test and Friedman's nonparametric test have been used for testing the statistical significance of differences among the examined groups. The difference between the examined groups has been considered significant if \( p < 0.05 \). The statistically significant differences in the dose contributions to the observed OARs (spinal cord, heart, small bowel and colon), among the examined CTVs, were found.

1. Introduction

Gastric cancer is one of the most common malignant neoplasms of the gastrointestinal tract. It is the fourth most common cause of death in the world [1]. In the United States, gastric cancer is currently the 15th most common cancer [2]. It is rarely found in people under the age of 30. About 10% of patients are people under the age of 50, and the average incidence is between 55 and 65 years. Male patients are more often affected by the disease than women, in a ratio of 2:1 [3].
Radiotherapy is used as a local or loco-regional therapeutic method in the gastric cancer treatment. During the treatment the surrounding normal tissues receive unnecessary an amount of the radiation dose which can lead to the occurrence of the unwanted therapeutic complications. The probability of cure of a malignant disease increases if the tumor is more radiosensitive and if the radio-tolerance of the normal tissues surrounding a target volume is increased. A radio-tolerance of a normal tissue can be a limiting factor for the indication and successful implementation of radiotherapy, due to the risk of the therapeutic complications.

The determination of the contours of the clinical target volume (CTV) is a complex task which requires an extensive theoretical and clinical oncological experience since it is necessary to determine the volume whose boundaries cannot be recognized on the diagnostic images. The sensitivity of the computed tomography (CT) in detection of the suspected lymph nodes is variable and certain diagnostic criteria are missing [4]. It is also useful to have preoperative CT to assess the tumor site. It is necessary to assess the distance from the blood vessels to include the lymph nodes in CTV. Given that organs at risk (OARs) are located next to the target volume, it is very difficult to avoid an irradiation of OARs during a dose deliver to CTVs. The biggest challenge is to determine at what distance from the corresponding blood vessels is the largest number of lymph nodes. It has been shown that 99% of lymph nodes of the pelvic area are located within 7 mm distance from blood vessels [5, 6]. Such studies do not exist for abdominal blood vessels and lymph nodes. Therefore, it is important to investigate the dosimetric effects of different sizes of CTV margins to the OARs in the three-dimensional conformal radiotherapy (3DCRT) treatment of the gastric cancer.

2. Materials and methods

In this work a sample of 40 patients was used, 30 men and 10 women. Each of the patients was simulated, for a need of treatment planning, on a CT simulator using the standard protocol: layer thickness 5 mm, pitch factor 1, field of view (FOV) 500, standard resolution and Lung Detail filter. The area from Th10 to L2 / 3 was scanned. On the FOCAL system for radiotherapy treatment planning, a delineation of the CTVs was performed. The CTVs included a tumor bed and anastomosis. Then, three CTVs of lymph nodes at 5 mm, 7 mm and 10 mm around the corresponding blood vessels were delineated. The OARs were also delineated for each patient: liver, heart, spinal cord, kidneys, small intestine and colon.

Treatment plans were prepared on the Elekta’s XiO treatment planning system. To deliver the dose, three 15 MV photon radiation fields were used. A criterion has been established according to which the coverage of CTVs were at least 95% of the prescribed dose. The prescribed dose was 45 Gy.

For the analysis the data were collected on the basis of dose volume histograms (DVHs). Statistical analysis was performed by using the SPSS program for statistical processing and analysis of data (IBM® SPSS® Statistics, Version 23). The one-way analysis of variance (ANOVA) test with repeated measurements was applied in the analysis. The Bonferroni test was used for post hoc analysis. To test the hypothesis for variables whose results do not satisfy the assumption of normal distribution, for one of the related groups (CTV$_{5\text{ mm}}$, CTV$_{7\text{ mm}}$, or CTV$_{10\text{ mm}}$), the t - test was used. For variables which do not meet the normal distribution assumption, a nonparametric Friedman hypothesis test was used. For post hoc analysis in the Friedman test, the Wilcoxon rank test was used. In cases when the condition of symmetry of distribution is not met the non-parametric sign test was applied.

3. Results

The analysis included 40 patients undergoing the postoperative external beam radiotherapy (EBRT) treatment for gastric cancer. The mean age of the patients was 59.4 years (standard deviation = 9.2 years) with a range from 37 to 78 years. The ratio of male patients in comparison to female patients was 3:1. Further analysis showed that the most common age is 50-70 years. The lowest contribution of patients was between the ages of 30 and 40 years.

The results of the single-factor ANOVA test for repeated measurements with Greenhouse - Geisser correction, has showed that there is a statistically significant influence of a margin size of the
CTV lymph nodes on the value of $V_{30}$ in the case of heart ($F(1.253, 48.906) = 224.145, p < 0.05$, $\eta^2 = 0.852$). The Bonferroni post hoc tests has showed a statistically significant differences between the $V_{30}$ values for the 5 mm compared to the 7 mm and 10 mm margins but also a statistically significant difference between the $V_{30}$ values for 7 mm and 10 mm margins. The results of the Friedman test has showed that there is a significant influence of the margin size of CTV lymph nodes on the value of $V_{40}$ in the heart ($\chi^2 (2) = 79.038, p < 0.05$). The sign test in the post hoc analysis has showed a statistically significant difference in the median values for $V_{40}$ for the 5 mm and 7 mm ($Z = -6.002, p < 0.05$), 5 mm and 10 mm ($Z = -6.166, p < 0.05$), and 7 mm and 10 mm ($Z = -6.166, p < 0.05$) margins.

The results of the Friedman test has showed that there is a statistically significant influence of a margin sizes of the CTV lymph nodes on the $D_{max}$ values in the spinal cord ($\chi^2 (2) = 49.950, p < 0.05$). The sign test in the post hoc analysis has showed a statistically significant difference between the median values for $D_{max}$ for the 5 mm and 7 mm ($Z = -4.585, p < 0.05$), 5 mm and 10 mm ($Z = -5.534, p < 0.05$), and 7 mm and 10 mm ($Z = -3.637, p < 0.05$) margins.

The results of the Friedman test has showed that there is a statistically significant influence of a margin size of the CTV lymph nodes on the $V_{45}$ values in the small intestine ($\chi^2 (2) = 61.016, p < 0.05$). The sign test in the post hoc analysis has showed a statistically significant difference in the median values for $V_{45}$ for the 5 mm and 7 mm ($Z = -5.127, p < 0.05$), 5 mm and 10 mm ($Z = -5.480, p < 0.05$), and 7 mm and 10 mm ($Z = -5.295, p < 0.05$) margins.

The results of the Friedman test has showed that there is a statistically significant influence of a margin size of the CTV lymph nodes on the $V_{45}$ values in the colon ($\chi^2 (2) = 66.652, p < 0.05$). The sign test in the post hoc analysis has showed a statistically significant difference between the median values for $V_{45}$ for the 5 mm and 7 mm ($Z = -5.071, p < 0.05$), 5 mm and 10 mm ($Z = -5.833, p < 0.05$), and 7 mm and 10 mm ($Z = -5.659, p < 0.05$) margins.

4. Discussion and conclusion

The performed analysis has showed that there was a statistically significant difference in the value of the maximum dose received by the spinal cord between all examined groups CTV$_{5\text{ mm}}$, CTV$_{7\text{ mm}}$, and CTV$_{10\text{ mm}}$ (34.19 Gy, 36.84 Gy and 39.55 Gy, respectively, $p < 0.05$). For all groups, the dose received by the spinal cord was below its constrain value [7].

In a study by Leong et al. [8], the mean maximum dose received by the heart was 43 Gy, while in the study by Soyfer et al. the mean maximum dose received by the heart was 35 Gy [9]. To reduce the risk of pericarditis to less than 15%, it is recommended that the mean pericardial dose be $V_{30} < 46\%$ [10]. In this work a statistically significant difference in the $V_{30}$ among all examined groups ($p < 0.05$) was obtained. In none of the groups the $V_{30}$ was exceeded the value 46% (the obtained values among the groups were 13.6%, 15.2% and 20.58%). In a study by Leszczyński et al. the different conformal plans for postoperative gastric cancer radiotherapy were compared, with 2 fields, 3 fields, 3 non-coplanar fields, and 4 non-coplanar fields. Multi-field plans can reduce the dose to surrounding organs but no single plan can spare all organs simultaneously [11]. The $V_{30}$ for the heart in the 3-field plan was 18.1%, which coincides with the results obtained in this study.

The volume of the small intestine which received 45 Gy, for the CTV$_{5\text{ mm}}$, CTV$_{7\text{ mm}}$ and CTV$_{10\text{ mm}}$ groups, were 56.64 cm$^3$, 61.97 cm$^3$ and 72.75 cm$^3$, respectively. Although the $V_{45}$ value, for all examined groups, was below the dose limit ($V_{45} < 195 \text{ cm}^3$), there is a statistically significant difference between all groups, $p < 0.05$. The small intestine is anatomically located in the small pelvis and a very small volume is located in the upper abdomen which is the reason why the doses received by the small intestine in postoperative radiotherapy for gastric cancer were small.

The maximum dose that the colon can receive with the 50% chance of complications in the next 5 years is 55 Gy [12]. The dose prescribed for postoperative radiotherapy treatment of gastric cancer is 45 Gy in 25 fractions, so it is not possible to reach this dose limit. Nevertheless, there is a statistically significant difference among all examined groups in the colon volume which received 45 Gy, $p < 0.05$. 


The statistically significant differences in the dose contributions to the observed OARs (spinal cord, heart, small bowel and colon), among the examined CTVs, were found. This is in accordance to the results obtained for the other OARs (kidneys and liver) during the EBRT treatment of the gastric cancer [13].

5. References
[1] http://www.who.int/mediacentre/factsheets/fs297/en/
[2] http://seer.cancer.gov/statfacts/html/stomach
[3] https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/global-cancer-facts-and-figures/global-cancer-facts-and-figures-3rd-edition.pdf
[4] Kwee R M and Kwee T C 2009 Imaging in assessing lymph node status in gastric cancer Gast. Canc. 12 6–22
[5] Matzinger O, Gerber E, Bernstein Z, Maingon P, Haustermans K, Bossert J F, Gulyban A, Poortmans P, Collette L and Kuten A 2009 EORTC-ROG expert opinion: radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach Radiat. Oncol. 92 164-75
[6] Lim K, Small W Jr, Portelance L, Creutzberg C, Jürgenliemk-Schulz I M, Mundt A, Mell L K et al 2011 GynIMRT Consortium. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy for the definitive treatment of cervix cancer Int. J. Radiat. Oncol. Biol. Phys. 79 348-55
[7] Nashimoto A, Nakajima T, Furukawa H et al 2003 Randomized trial of adjuvant chemotherapy with mitomycin, fluorouracil, and cytosine arabinoside followed by oral Fluorouracil in serosa-negative gastric cancer: Japan Clinical Oncology Group 9206-1 J. Clin. Oncol. 21 2282-2287
[8] De Vita F, Giuliani F, Orditura M et al 2007 Adjuvant chemotherapy with epirubicin, leucovorin, 5-fluorouracil and etoposide regimen in resected gastric cancer patients: a randomized phase III trial by the GruppoOncoLogico Italia Meridionale (GOI 9602 Study). Ann. Oncol. 18 1354-1358
[9] Di Costanzo F, Gasperoni S, Manzione L et al 2008 Adjuvant chemotherapy in completely resected gastric cancer: a randomized phase III trial conducted by GOIRC J. Natl. Cancer Inst. 100 388-398
[10] Bang Y-J, Kim Y-W, Yang H-K et al 2012 Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial The Lancet 379 315-321
[11] Noh SH, Park SR, Yang HK et al 2014 Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial Lancet Oncol 15 1389-1396
[12] Kulig J, Kolodziejczyk P, Sierzega M et al 2010 Adjuvant chemotherapy with etoposide, Adriamycin and cisplatin compared with surgery alone in the treatment of gastric cancer: a phase III randomized, multicenter, clinical trial Oncol. 78 54-61
[13] Osmić H, Hasukić S, Hasukić B, Fazlić S and Đedović E 2018 Influence of lymph node clinical target volume margin size on liver and kidneys in three dimensional conformal radiotherapy of gastric cancer: A dosimetric analysis J. Nucl. Med. Radiat. Ther. 9(05) 1000374