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Original research article

Can we obtain planning goals for conformal techniques in neoadjuvant and adjuvant radiochemotherapy for gastric cancer patients?

Wojciech Leszczyński[a,*], *Paweł Polanowski*[b], *Paulina Leszczyńska*[b], *Leszek Hawrylewicz*[a], *Iwona Brąclik*[a], *Rafał Kawczyński*[b], *Jerzy Wydmański*[b]

[a] *Department of Radiotherapy and Brachytherapy Planning, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland*
[b] *Department of Radiotherapy, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland*

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ABSTRACT

Aim: The purpose of this study was to compare conformal radiotherapy techniques used in the treatment of gastric cancer patients. The study is dedicated to radiotherapy centres that have not introduced dynamic techniques in clinical practice.
Background: The implementation of multi-field technique can minimise the toxicity of treatment and improve dose distribution homogeneity in the target volume with simultaneous protection of organs at risk (OaRs). Treatment plan should be personalised for each patient by taking into account the planning target volume and anatomical conditions of the individual patient.
Materials and methods: For each patient, four different three dimensional conformal plans were compared: 2-field plan, 3-field plan, non-coplanar 3-field plan and non-coplanar 4-field plan. Dose distributions in a volume of 107% of the reference dose, and OaRs such as the liver, kidneys, intestines, spinal cord, and heart were analysed.
Results: The mean volume of the patient body covered using the isodose of 107% was 3004.73 cm^3, 1454.28 cm^3, 1426.62 cm^3, 889.14 cm^3 for the 2-field, 3-field, non-coplanar 3-field and non-coplanar 4-field techniques, respectively. For all plans the minimum dose in the PTV volume was at least 95% of the reference dose. The QUANTEC protocol was used to investigate doses in OaRs.
Conclusions: Comparison of 3D conformal radiotherapy techniques in gastric cancer patients indicates that none of the plans can fulfil simultaneously all of the criteria of the tolerance dose in the organs at risk. The implementation of the multi-field technique can minimise

* *Corresponding author at*: Department of Radiotherapy and Brachytherapy Planning, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, ul. Wybrzeże Armii Krajowej 15, 44-101 Gliwice, Poland. Tel.: +48 784 981 877.
E-mail address: wleszczynski@io.gliwice.pl (W. Leszczyński).
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the toxicity of treatment and improve dose distribution homogeneity in the target volume with additional protection of organs at risk (OaRs).

1. Background

Gastric cancer is the third most frequent cause of death from cancer worldwide, with 723,027 deaths registered in 2012.[1] The primary treatment modality of gastric cancer is surgery.[16] This treatment strategy is frequently employed in the early stage of cancer. Radical operation (R0) can be performed in approximately 50% of patients because of the diagnosis of cancer in the locally advanced or dispersal stage. Since the INT-0116 study was published, the standard for $pT_{2\text{-}4}\ N_{0\text{-}3}$ or $pT_1N_{1\text{-}3}$ gastric cancer is postoperative radiochemotherapy.[2,6] At some oncology centres, R1 surgical resection is also an indication for postoperative radiochemotherapy.[3] Implementation of this scheme enhances both local cure and the 5-year survival by approximately 15% compared with independent surgery treatment.

Initially, at many radiotherapy departments, a recommended two dimension (2D) technique using two opposing fields was applied for gastric cancer treatment. The constraint of 2D radiotherapy for the abdominal area is the close localisation of organs at risk such as the kidneys, liver, intestines and spinal cord. Consequently, this radiotherapy induced high hematologic toxicity of the digestive system and was completed earlier than planned in 17% of patients.[4] With recent advances in technology, computer dose distribution calculations have been shown to allow the introduction of three dimension (3D) conformal techniques (conformal radiotherapy; CRT) in common applications. These techniques turn out to be more effective in achieving high, homogeneous dose distribution in the target volume with simultaneous sparing of normal tissues. In the 3D conformal technique the shape of the planning target volume (PTV), mutual localisation of the target volume and organs at risk are all considered.[5] Dose distribution in the 3D technique allows the acquisition of more information than that in 2D planning. 3D planning exposes the local maximum of the dose distribution (hot spots) or allows localised regions of PTV that are not covered by the reference dose (cold spots).

The application of two opposing fields in gastric cancer radiotherapy, even in 3D conformal radiotherapy, promotes a high risk of radiation complications of the 3rd and 4th degrees.[2] The implementation of multi-field technique can considerably minimise the toxicity of treatment and improve dose distribution homogeneity in the target volume with simultaneous protection of organs at risk, such as the liver, kidneys, spinal cord and intestines. Selection of the appropriate three dimension (3D) conformal technique should be personalised to each patient by taking into account the target volume PTV and anatomical conditions of the individual patient.[19]

The idea of conformal radiotherapy is not new; however, recently, 3D treatment planning has allowed the introduction of this technique in clinical practice. Currently, in many countries, 3D conformal techniques for gastric cancer radiotherapy are commonly used, where the shape of the treatment fields fits the PTV, which is defined based on CT imaging (and other helpful imaging modalities, such as PET-CT or MRI).[8] At our department, postoperative radiochemotherapy has been the standard treatment for 15 years, and neoadjuvant radiochemotherapy has been the subject of research for 10 years.[7]

2. Aim

The aim of this study was to compare the 3D conformal techniques used in gastric cancer patients who qualified for adjuvant or neoadjuvant radiochemotherapy. The study is dedicated to radiotherapy centres that have not introduced dynamic techniques in clinical practice.

3. Material and methods

A retrospective analysis was performed on 20 gastric patients. For each patient, four different plans were performed. 3D techniques of two opposing fields (AP-PA) (2F), three coplanar fields (3F), three non-coplanar fields (3nF) and four non-coplanar fields (4nF) were used (Fig. 1a–d). Figures show the example of the beam orientation for the radiotherapy plans. However, the number of beams was constant but the beam angles were personalised for each patient because of anatomy of the patient and localisation of the target. Patients were stabilised using thermoplastic masks that covered the chest and abdominal regions. For treatment planning, computed tomography (CT) data sets with a 3-mm slice thickness were acquired. During the study, contrast agent was applied to the patient's vein for better visualisation of blood vessels on CT images and to facilitate contouring of the nodal regions. Additionally, each preoperative patient had to drink 500 ml of water to fill the stomach for imaging of the tumour. The volume of this liquid was equivalent to a light breakfast. Data sets were imported to the treatment planning system (TPS), where the target volumes (gross tumour volume – GTV, clinical target volume – CTV, planning target volume – PTV) and organs at risk (spinal cord, kidneys, liver, intestines, lungs, and heart) were contoured. The GTV was delineated based on the CT and gastroscopy results. The CTV volume includes the postoperative stomach lodge or stomach and regional lymph nodes (celiac trunk, splenic, pancreatic duodenal, pancreatic, portal vein, para-aortic, para-oesophageal and perigastric nodes). The PTV volume was defined as a 1-cm margin around the CTV. The planned total dose was 45 Gy in 25 fractions.

The main purpose throughout planning of the dose distribution was to cover the entire PTV using 95% of reference

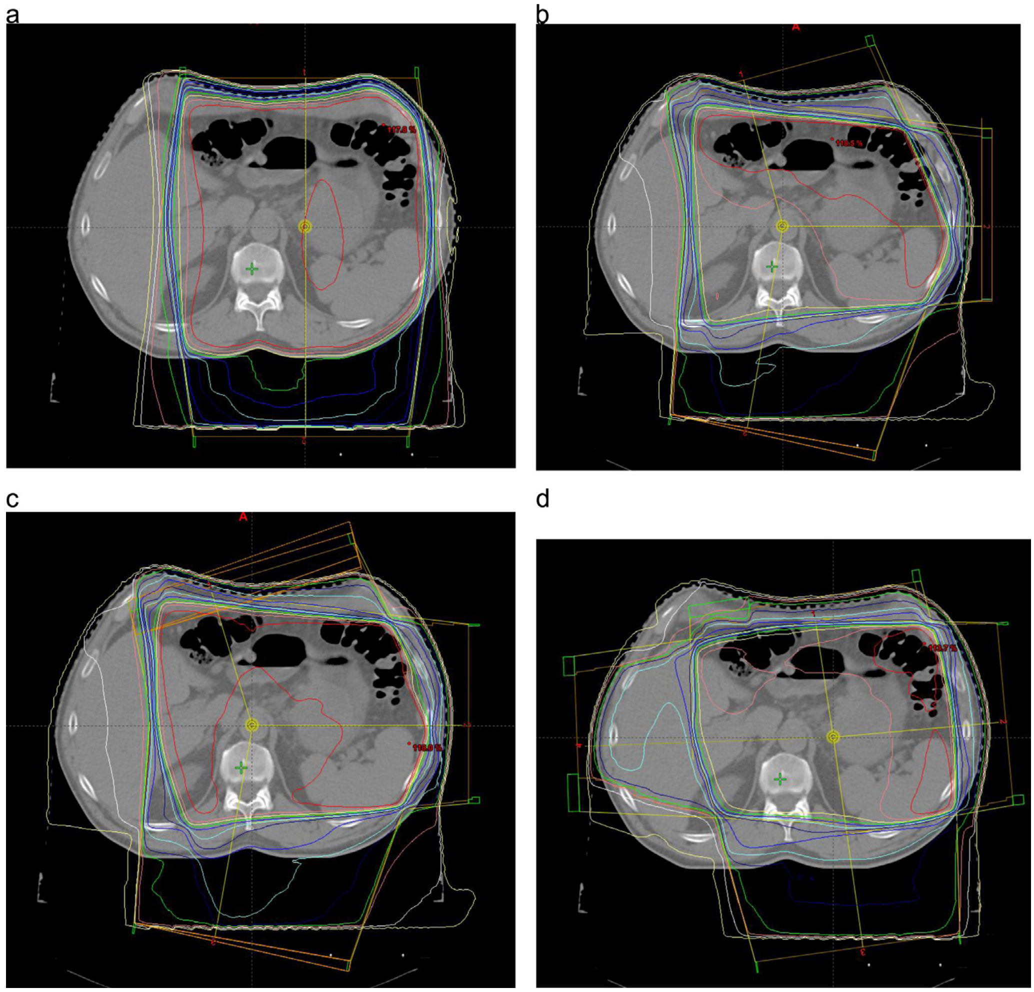

Fig. 1 – (a) Two-field technique (2F). (b) Three-field technique (3F). (c) Non-coplanar three-field technique (3nF). (d) Non-coplanar four field technique (4nF).

dose. During the comparison analysis of 3D conformal plans, the maximum dose to the patient's body, maximum dose to the spinal cord, volume of the right and left kidneys covering the isodose of 20 Gy and the mean dose for both kidneys, the mean dose for the liver, the mean dose for the right and left lungs, and the mean dose in the heart were investigated. All the tolerance criteria for organs at risk were analysed according to the Quantec protocol.[15] In each plan, the isodose volume of 107% of the reference dose was examined. Additionally, the conformity index (CI) and homogeneity index (HI) were calculated[9] using the following benchmarks:

$$CI = \frac{V_{RI}}{TV}$$

where V_{RI} = 95% isodose volume; TV = target volume.

The conformity index describes the dose distribution in the target volume and surrounding normal tissues. When the value of the index is 1, the dose distribution is precisely conformal. A value of the index greater than 1 indicates that the radiation dose also covers surrounding normal tissues – the 95% isodose of the reference dose volume is larger than the PTV volume.

$$HI = \frac{I_{max}}{RI}$$

where I_{max} = maximum dose in PTV; RI = reference dose.

Regarding statistical analysis, the Shapiro–Wilk normality test and Levene's homogeneity test were performed. The normality condition was not fulfilled; therefore, the non-parametric ANOVA Friedman test and then Duncana post hoc test were used to compare and analyse the described conformal radiotherapy techniques. The importance level of performed statistic was $\alpha = 0.05$.

4. Results

For all of the prepared plans, the minimum dose in the PTV volume was at least 42.75 Gy that corresponds to 95% of the reference dose. The maximum dose in the PTV volume averaged 52.2 Gy (range: 49.9–54.4 Gy) for the 2F technique, 52.3 Gy (range: 49.5–53.3 Gy) for the 3F technique, 51.8 Gy (range: 49.1–56.1 Gy) for the 3nF technique and 51.4 Gy (range: 49.6–53.9 Gy) for the 4nF technique. The mean volume of

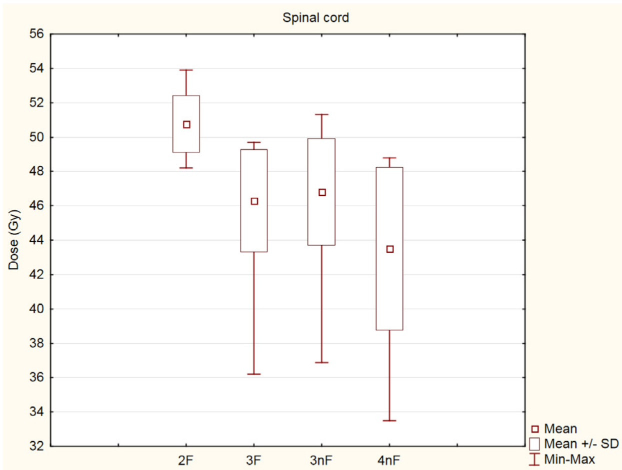

Fig. 2 – Minimum, maximum and mean values for the spinal cord.

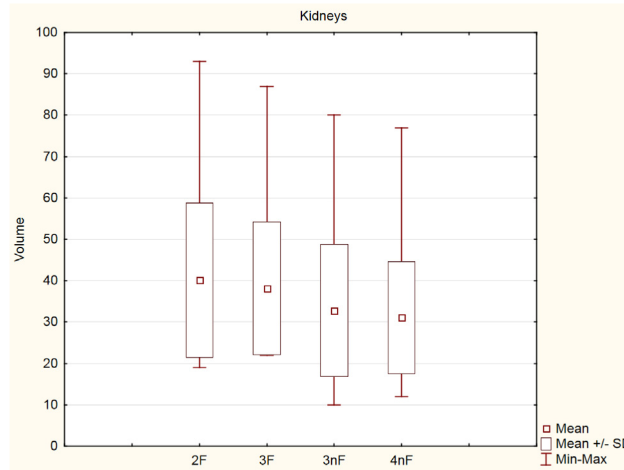

Fig. 3 – Minimum, maximum and mean values for kidneys.

the patient body covered using the isodose of 107% of the reference dose was 3004.73 cm^3, 1454.28 cm^3, 1426.62 cm^3, 889.14 cm^3 for the 2F, 3F, 3nF and 4nF techniques, respectively.

The maximum doses for the spinal cord using the 2F technique were exceeded in 65% of the plans. The acceptable maximum dose for the spinal cord is 50 Gy. This requirement was performed for 100% of the plans for the 3F technique, 95% for 3nF technique and 100% for the 4nF technique. The mean maximum doses in the spinal cord were acceptable for the 3F technique, the 3nF technique and 4nF technique and averaged as follows: 50.8 Gy for the 2F, 46.3 Gy for the 3F, 46.8 Gy for 3nF and 43.50 Gy for the 4nF techniques. Additionally, for all of the 4nF plans, the maximum doses in the spinal cord were not higher than 49 Gy. Results for the maximum doses in the spinal cord for particular radiotherapy planning techniques are shown in Fig. 2.

The mean values of the V20 parameter for the right and left kidneys were as follows: 40.2% for the 2F, 38.2% for the 3F, 32.8% for the 3nF and 31.1% for the 4nF techniques. The tolerance criterion for the kidneys was V20 – 32% of the volume. This value was obtained for 40% of plans for the 2F technique, 35% of plans for the 3F technique, 50% of plans for the 3nF technique, and 60% of plans for the 4nF technique ($p = 0.000$) (Fig. 3). Results are shown in Table 1. The mean dose for both kidneys for each technique were as follows: 2F: 19.5 Gy; 3F: 17.9 Gy; 3nF: 15.3 Gy; 4nF: 14.0 Gy. The mean dose for both kidneys should be <15 Gy. The values of the criterion were met for 40% of the plans for the 2F technique, 40% of the plans for the 3F technique, 55% of the plans for the 3nF technique, and 65% of the plans for the 4nF technique ($p \leq 0.001$). Results are shown in Table 1.

Regarding the liver, statistically significant differences were shown with comparison of the 3D techniques ($p \leq 0.001$). The assessment criterion for the liver was the mean dose <30 Gy. This criterion was obtained for 100% of the plans for the 2F technique, 100% of the plans for the 3F technique, 100% of the plans for the 3nF technique and 50% of the plans for the 4nF technique. The mean values of the mean dose were as follows: 18.8 Gy: 2F; 23.6 Gy: 3F; 23.4 Gy: 3nF; 29.2 Gy: 4nF.

Table 1 – Comparison of parameters among the 2-field, 3-field, non-coplanar 3-field and 4-field techniques.

OaR	2F mean (range)	3F mean (range)	3nF mean (range)	4nF mean (range)
D_{mean} kidneys (Gy)	19.5 (9.7–45.3)	17.9 (10.8–33.9)	15.3 (7.5–31.7)	14.0 (8.2–27.7)
$V_{20/32}$ kidneys R&L (%)	40.2 (19.0–93.0)	38.2 (22.0–87.0)	32.8 (10.0–80.0)	31.1 (12.0–77.0)
D_{mean} Liver (Gy)	18.8 (13.3–24.0)	23.6 (18.2–27.6)	23.4 (18.1–28.4)	29.2 (23.8–34.9)
D_{max} spinal cord (Gy)	50.8 (48.2–53.9)	46.3 (36.2–49.7)	46.8 (36.9–51.3)	43.5 (33.5–48.8)
D_{max} intestines (Gy)	51.4 (49.0–54.1)	51.8 (49.3–54.0)	51.7 (48.7–56.1)	51.1 (49.1–53.8)
D_{mean} lung L (Gy)	12.8 (8.3–18.5)	12.1 (7.3–20.3)	13.3 (8.9–22.0)	13.0 (8.9–20.5)
D_{mean} lung R (Gy)	3.0 (1–6.8)	5.6 (2–11.5)	6.7 (2.5–14.0)	7.7 (2.8–15.0)
D_{max} Body (Gy)	52.6 (50.5–54.4)	52.3 (49.5–54.3)	51.9 (49.1–56.1)	51.5 (49.6–53.9)
D_{mean} heart (Gy)	22.1 (5.4–43.5)	18.7 (4.4–34.8)	18.7 (4.4–34.8)	17.4 (4.2–28.4)

Table 2 – Conformity and homogeneity index values and the mean volumes of the 107% of the reference dose.

Parameter	2F	3F	3nF	4nF
CI index (range)	2.23–3.19	1.58–2.07	1.63–2.15	1.53–2.07
Mean CI	2.71	1.86	1.84	1.72
HI index (range)	1.11–1.21	1.10–1.21	1.09–1.25	1.10–1.20
Mean HI	1.16	1.16	1.15	1.14
Isodose volume 107% (cm^3) (range)	867.6–6116.5	130.3–3162.9	93.8–3885.4	128.4–2191.7
Mean	3004.73	1454.28	1426.62	889.14

The mean values of the maximum dose in the body for each technique were as follows: 52.59 Gy: 2F; 52.27 Gy: 3F; 51.93 Gy: 3nF; 51.93 Gy: 4nF ($p = 0.008$). The mean values for the heart for all of the plans were acceptable and averaged 22.1 Gy for the 2F technique, 18.7 Gy for the 3F technique, 18.7 Gy for the 3nF, and 17.4 Gy for the 4nF technique. The acceptable mean dose for the heart was <26 Gy.

The results for the conformity index calculations among the analysed plans were statistically significant ($p \leq 0.001$); results are shown in Table 2. The homogeneity index showed no statistically significant difference among the compared plans ($p > 0.2$); data are shown in Table 2.

5. Discussion

Comparison of 3D conformal radiotherapy techniques for gastric cancer patients does not answer the question of which of them should be the standard technique for radiotherapy treatment. To assess the dose distribution in organs at risk among particular techniques, it was established that the PTV volume should be 95% – 107% of the reference dose in each analysed plan. This requirement became a priority to further analyse the doses in organs at risk. The minimum dose – 95% of the reference dose in the PTV volume – was obtained in all of the plans. Conversely, the criterion for the maximum dose – 107% of the reference dose–the maximum acceptable dose in the PTV volume according to ICRU 50 and 62 – was not satisfied for any of the treatment plans.[10]

A meaningful aspect for the comparison of 3D radiotherapy techniques is the localisation of hot spots – regions where the maximum dose and volumes of isodoses exceed 107% of the reference dose.

The volume of the dose distribution above 107% seems to be an interesting parameter. This parameter describes the size of the tissue volume that is within the high-dose region and has significant meaning regarding the occurrence and intensity of radiation complications. Thus, it was found that the volume of this parameter is the smallest in the 4nF technique. Considering that this volume in the 2F and 3F techniques was, respectively, approximately 3.3 and 1.6 times higher than that in the 4nF technique.

The conformity index and homogeneity indices were calculated for all of the plans. The homogeneity index expresses the proportion of the maximum dose in the PTV to the planning reference dose, and its value describes the homogeneity of the dose distribution in the target volume. In this study, for all of the techniques obtained, the HI values were approximate, indicating that all techniques provide a similar dose homogeneity in the target volume.

However, the conformity index describes the relationship between the treatment volume (region covering at least 95% of the reference dose) and the entire volume of the PTV. It describes the dose distribution in the PTV volume and surrounding healthy tissues. The obtained results clearly indicated that, in the 2F technique, it is impossible to achieve conformal dose distribution. Other techniques, despite appreciably better CI values, deviate from unity; thus, not only the target volume was covered by isodose of the 95%. Those results revealed that none of the 3D conformal radiotherapy techniques can assure ideal adjustment of the dose distribution only to a target volume. For the 4nF technique, the CI value is the most beneficial.

Delineation of the target volumes and organs at risk is a significant step during treatment planning. Large differences in the stomach volume were observed particularly for neoadjuvant treatment patients. Additionally, substantial organ at risk motion was noticed, particularly intestines moving in the postoperative stomach lodge in gastrectomy patients following complemented radiotherapy.

Comparative analysis of 3D conformal radiotherapy techniques was performed based on the collation of the dose in organs at risk and values and locations of local maximum doses. The point of reference for the obtained doses is QUANTEC analysis (Quantitative Analysis of Normal Tissue Effect in the Clinic) which assesses the risk of radiation complications occurring in a healthy tissue data set.[15] Leong et al. showed the superiority of multi-field techniques (6-field) to the 2-field technique with 50% better target volume coverage and lower doses to organs at risk (kidneys, spinal cord) in their 15-patient study. Worse parameters were achieved for the liver in the 4-field technique; however, doses were still tolerable for this organ. Additionally, 95% of the reference dose covered 99% of the PTV volume in plans with applications of multi-field techniques compared with 93% coverage of the PTV volume in the 2-field plans.[11,14] Soyfer et al. in their 19-patient study confirmed the superiority of multi-field techniques to the 2-field technique, especially for doses to the kidneys and spinal cord. Similar to Leong's study, more beneficial dose distributions for the liver were obtained using the two opposing fields technique. Additionally, 95% isodose CTV coverage was achieved in all of the compared plans. However, there are no data describing doses in the PTV region where organ mobility and errors in patient positioning were considered. Exclusion of the PTV volume from consideration seems to have major consequences in target cold spots that are undesired because these regions should receive at least 95% of the reference dose.[11,13] The advantage of multi-fields (from 4 to 6 fields) to the AP-PA technique, particularly for the spinal cord and left kidney was demonstrated also by El-Hossiny for the analysis of 17 patients. The 2-field technique is more beneficial for the liver. It should be noted that only 25% of the PTV volume received a dose higher than 40 Gy from 45 Gy of the reference dose. It is not clear why authors have abandoned ICRU criteria for the PTV.[11,12] All of the patients were treated with a total dose of 45 Gy in 25 fractions (dose per fraction = 1.8 Gy). None of the cited studies performed CI and HI analysis.

Relying on Quantec analysis, the risk of radiation necrosis for the spinal cord is 0.2% after application of a total dose not higher than 50 Gy in conventional fractionation. In the present study, 50 Gy as the maximum dose for the spinal cord was accepted, but, for safety reasons, in practice we use in our Radiotherapy Department maximum dose 45 Gy. Accepted doses were obtained in 100% of the plans for the 4nF technique, 95% of the plans for the 3nF technique and in 100% of the coplanar fields plans. The 4nF technique is the only technique where the mean dose for the spinal cord did not exceed 45 Gy (Table 1). However, most importantly, in the 2F technique, 35% of the prepared plans fulfil the required criterion of acceptance; thus, it is not recommended to use the 2F technique in this group of patients.

Liver is an essential clinical organ during radiotherapy in gastric cancer patients. According to the Quantec protocol, the mean dose for the whole volume of the organ is 30 Gy. Above this dose, in 5% of patients, radiation damage of the liver occurs. The techniques that most effectively fulfil the mean dose statement are the 2F technique, the 3F technique and the 3nF technique. After application of these techniques, 100% of the plans achieved acceptable doses. However, only 50% of 4nF plans met this criterion, creating a serious constraint regarding the usage of this method.

The doses in both kidneys combined (as one organ) were compared. According to Quantec, the standard tolerance mean dose for the whole organ is 15 Gy. Above this value, a 5% risk of essential clinical dysfunction of the kidney exists. Second statement, regarding the analysis of a particular 3D radiotherapy conformal technique and the acceptable dose for the kidneys, is that 32% of the volume of the kidneys should not receive dose higher than 20 Gy. Thus, the dose distribution for both kidneys for the 4nF and 3nF techniques was satisfactory, respectively, in 60% and 50% of the plans. For both kidneys combined, the most effective is the 4nF technique, where the criterion to the mean dose is satisfied in 65% of the plans. The required criterion was fulfilled in 35% of the plans for the 3F technique and in 40% of the plans for the 2F technique. The technique with the least usage is the 3F technique with only 35% of plans results being satisfactory.

The maximum tolerated dose for intestines is 45 Gy. Above this value, there is a risk of occlusion occurrence or perforation when the irradiated volume exceeds 1957. The obtained results suggest that the 4nF technique is the most suitable for this organ. Usage of this technique allows the achievement of acceptable doses in 30% of the plans. Other techniques demonstrated poor results.

Regarding the heart, the analysis was collected at the mean value of the tolerance dose for this organ. The acceptable mean value of the dose was 26 Gy. In accordance with the Quantec protocol, it is the dose that involves 15% risk of pericarditis. The required criterion was met in 90% of the 4nF and 3nF plans, in 80% of the 3F plans and in only 65% of 2F plans.

Regarding the lungs, the Quantec protocol indicates that they have a 5% risk of pneumonia for the mean dose of 7 Gy for the whole organ and about 20% risk when the 30% volume of both lungs received 20 Gy. In this study, an acceptable criterion is mean dose of 7 Gy for the volume of one lung. For the right lung, this condition is met for all the plans of the 2F. The criteria are fulfilled for the 4nF technique in only 40% of the plans. Much worse results were obtained for the left lung where the acceptable mean dose was not fulfilled in any of the plans for each technique. Taken together, the above results indicate that the safest technique for the treatment of gastric cancer is the 2F plan.

Generally the study is dedicated to radiotherapy centres that have not introduced dynamic techniques in clinical practice. However, Milano MT et al. compared conformal techniques with dynamic IMRT techniques in gastric cancer radiotherapy. They showed that the dynamic technique significantly reduces the dose for the liver and one kidney. The study demonstrated excellent target coverage – 98% of PTV volume received 45 Gy.[17] Similar results were obtained by Ringash et al. They used the IMRT technique in postoperative radiotherapy in gastric cancer. The authors emphasised the mobility of the organs in the abdomen region and risks associated with the usage of highly conformal dynamic techniques.[18]

6. Conclusions

Comparison of 3D conformal radiotherapy techniques in gastric cancer patients indicates that none of the plans can fulfil simultaneously all of the criteria of the tolerance dose in the organs at risk. The implementation of a multi-field technique can minimise the toxicity of treatment and improve dose distribution homogeneity in the target volume with additional protection of organs at risk (OaRs).

Conflict of interest

None declared.

Financial disclosure

None declared.

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