Assessment of the results and the haematologic side effects of the 3D conformal and the IMRT/ARC therapies delivered during the craniospinal irradiation of childhood tumors, in a follow-up period of 5 years

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Abstract

Objectives

The craniospinal irradiation (CSI) of childhood tumors with Rapidarc technique is a new way of treatment. Our objective was to compare the acute haematologic toxicity pattern during 3D conformal radiotherapy with the application of the novel techniques.

Materials and methods

Data from patients treated between 2007 and 2014 has been collected and seven patients were identified in each of both treatment groups. The acute blood toxicity results were obtained, after establishing a general linear model, by using the SPSS software. Furthermore, the dose exposure of the organs-at-risk has been compared. Patients have been followed-up for a minimum of five years, then progression-free survival and overall survival data were assessed.

Results

After the assessment of the laboratory parameters of the two groups, it may be concluded that no significant differences were detected in terms of the mean dose exposures of the normal tissues or the acute hematological side-effects during the IMRT/ARC and the 3D conformal treatment. Laboratory parameters significantly decreased compared to the baseline values during the treatment weeks. Nevertheless, no significant differences were detected between the two groups. No remarkable differences were confirmed between the two groups regarding the five-year progression-free survival and overall survival, and no signs of serious irradiation organ toxicity were observed during the follow-up period in either of the groups.

Conclusion

Rapidarc technique can be used safely even for the treatment of childhood tumors, as the extent of normal tissue dose exposures and that of acute hematological side effects is not higher.

Background

Based on their incidence, tumors of the central nervous system rank second in the statistics of childhood neoplastic diseases in most of the European countries, just as well in Hungary[1]. Radiotherapy is of great importance as part of postoperative treatment. Full craniospinal axis irradiation (CSI) is performed postoperatively in medulloblastomas/PNET tumors and for the treatment of some of the more rare tumors for example atypical rhabdoid tumors, or ependymomas that have already disseminated in the CSF space. During routine craniospinal radiotherapy, the full neural axis is irradiated, most commonly at a dose of 35–36 Gy, then the boost treatment of the tumor nest with a minimum of 54 Gy. This doses are described by the Hungarian National Cranial Protocoll[2–7].

Acute side effects may occur during radiotherapy, which may lead to the discontinuation of the treatment. These side effects may be of neurological origin, they may be of hematological origin but other types of side effects may also occur as well. Side effects affecting the quality of later life can be expected of doses delivered to organs not located in the central nervous system.

With the advances in modern radio therapeutic technology like intensity modulated radiation therapy, but mainly with that of the arc therapeutic radiation treatment, the question may come up for side effects. Whether the integrated dose exposure, which can even be higher theoretically, caused by the field entries from multiple directions or the more extensive radiation exposure, although with a lower dose, of the normal tissues, organs causes more of the acute - predominantly hematological - toxicities. Naturally, it is also a question whether the dose exposure of the parenchymal organs is genuinely higher with the use of the new techniques.

For this purpose, we assessed the effects of both types of treatment techniques in terms of both the bones important for hematopoiesis, and the parenchymal organs. In addition, based on the changes in hematological parameters obtained during the treatment, we attempted to draw some conclusions in terms of additional bone marrow toxicity.

Due to the extent of the treated volume, positioning is essential during CSI treatments, therefore, it is also an objective to decrease the daily uncertainty of the setup. The easier and more precise delivery of treatment can be expected from IMRT/ARC therapy and from the image guidance, which is obligatory on these occasions. Another purpose of using these novel technologies might have been the aim to decrease the acute side effects related to the treatment, since even the airways (trachea, bronchi) might receive a lower dose rate when using IMRT/ARCT. Our experiences gathered with IMRT/ARC treatment are presented in this publication.

Methods

Full craniospinal irradiation was carried out in 14 children and young adults with a mean age of 14.64 years (3–33 years of age) at our Institute, between 2007 and 2014. Each patient has signed an informed concent to participate in the retrospective data analysis. Gurdians or parents signed for patients under the age of 18. Due to Hungarian regulation no ethical approval was obtained. The treatment of the patients before 2011 was performed with the 3D conformal technique and field alignment in a prone position. After that, patients were treated with IGRT and Rapidarc technique in a prone position. 3D conformal treatments were delivered with the Elekta Eclipse PreciseTS device, while the Rapidarc treatments were done with the Varian Novalis TX linear accelerator. Retrospectively, 7 patients were identified separately in both groups then our patients were followed-up in a partially prospective manner. Based on the histological types, predominantly medulloblastomas (11 cases), and PNET (1 case), atypical rhabdoid tumor (1 case) and glioblastoma (1 case) were observed. All patients had primer surgery and adjuvant chemotherapy due to the Hungarian National Cranial Protocol, except the glioblastoma patient. Vacuum bed and head mask were used during the positioning. An open-face mask

has been decided to be used during the treatment in a supine position, and for the sake of reproducibility of positioning the entire body, the patient's arms were fixed beside their body. During the radiotherapy a median of 35.2 Gy (30.4–36.8 Gy) were delivered to the whole spine and the skull, followed by a posterior fossa boost of a median of 19.8 Gy (19.2–24 Gy). The CTV for the spine was defined cranially from the C1-, caudally from the S2 vertebral body. In antero-posterior direction the vertebral body and the spinous process, latero- laterally the transverse foreman were used as borders. A CTV PTV expansion of 4 mm were used. For posterior fossa irradiation the primary tumor was defined as GTV, and extended with 1 cm to CTV. The tumor bed was included to this CTV. A PTV was generated with a 3 mm margin from the previous structure.

As for the retrospective assessment of the acute toxicity, the results of the follow-up laboratory tests performed during treatment were reviewed. The counts of white blood cells, platelets, red blood cells, the levels of hemoglobin and hematocrit were analyzed during treatment. For our calculations, version 25 of the SPSS software was used. Repeated ANOVA tests were performed for all values except for the difference between the age values and during the calculation of hemoglobin levels, where independent samples t-tests were used. Furthermore, assessments were completed regarding the dose exposure of the organs-at-risk, in order to determine, whether IMRT/ARC therapy is eventually associated with a higher dose exposure, predominantly regarding the hematopoietic organs. The entire bony spine was divided into three segments, thus the cervical, thoracic and lumbar spine segments were contoured. In addition, the sternum, pelvic bones, the spleen and the liver were contoured. For the assessment of dose exposures affecting the quality of later life, the doses delivered to the heart, the left ventricle, the kidneys and the lungs were also determined. It has also been surveyed that on how many occasions it became necessary to suspend the treatment for more than 1 week due to the acute side effects caused by the treatment. The results of treatment were also reviewed as an additional feature of our study, using data obtained from the local pediatric oncological care center after the treatment, for the evaluation of progression-free and overall survival data. We used the long-term care data also to check, whether any delayed organ toxicity associated with radiotherapy has occurred in any child.

Results

The mean age of the patients in the 3D conformal population was 15.71 years (± 9.69 years), while in the IMRT/ARC arm, it was 13.57 years (± 11.77 years). Using the independent sample-t test, no significant difference was noted between the mean age ($p = 0.710$).

The first point of analysis of the side effects caused by the radiotherapy was the extent of dose exposure in the normal tissues. The mean dose exposure of organs-at-risk responsible for the hematopoietic side effects in case of the 3D conformal and the IMRT/ARC treatments were as follows: Cervical spine: 3408/3484 cGy, Thoracic spine: 3271/3261 cGy, Lumbar spine: 3152/3288 cGy, Sternum: 2299/1156 cGy, Pelvic bone: 987/1104 cGy, Spleen: 81/460 cGy, Liver: 708/917 cGy. While no significant differences were seen in the bones near the target area between the two types of radiation therapy,

nevertheless, the dose exposure of the sternum decreased and that of the spleen increased during IMRT/ARC treatment.

The dose exposures of the non-hematopoietic organs-at-risk were as follows: Heart: 1612/1140 cGy, Left ventricle: 827/1025 cGy, Right kidney: 343/757 cGy, Left kidney: 298/755 cGy, Right lung: 623/1003 cGy, Left lung: 441/845 cGy. An increase was detected with the Arc therapy regarding the organs-at-risk, however, these changes are well within the tolerability criteria according to the QUANTEC dose charts.

While the dose exposure of organs-at risk is caused by a single direct field directed at the spine when using 3D conformal technique, due to the characteristics of the rotating field of the arc irradiation during IMRT/ARC therapy, more organs-at-risk may be affected by a lower dose, thus, a slight dose increase may be experienced compared to the 3D conformal technique, nevertheless it is tolerable.

Analyzing the weekly changes in the laboratory parameters, the following conclusions can be made despite having a low number of cases. The repeated measures ANOVA test revealed the followings regarding the observed laboratory parameters. The total white blood cell counts significantly decreased compared to the baseline values during the weeks ($p = 0.0029$), the neutrophil counts initially increased then they also decreased ($p = 0.007$). The same significant decrease was observed in the platelet counts ($p = 0.000$). No changes were observed in the red blood cell counts ($p = 0.107$) and in the hematocrit levels ($p = 0.140$), however, a slight difference could be observed in the hemoglobin levels ($p = 0.045$). Nevertheless, no significant differences were observed between the two groups regarding the total white blood cell counts ($p = 0.449$), the neutrophils ($p = 0.754$), the platelets ($p = 0.815$), red blood cell ($p = 0.506$), hematocrit ($p = 0.489$) and hemoglobin ($p = 0.360$) parameters.

Two cases of grade 3 leukopenia were seen in the 3D conformal arm, however, only grade 1 side-effects were noted in the IMRT/ARC arm. However, several cases of grade 2 thrombocytopenia were seen in the IMRT/ARC arm and the results of these patients essentially did not affect the mean values of corpuscular cell parameters for the given week. One week breaks in the therapy became necessary on two occasions in each of the 2 groups, either due to leukopenia or due to thrombocytopenia. Furthermore, no delayed organ toxicities were noted.

We have been following-up our patients for 12 years. Median follow-up duration in the 3D conformal group is 10 years, while in the Rapidarc group it is 5 years.

In terms of the progression-free survival, the development of local recurrences or new organ manifestations at the patients with a condition of a poorer prognosis affected the course of the curves.

There is a minimal difference between the courses of the overall survival curves of the two populations in the first five years.

Discussion

CSI irradiation is a challenging treatment, not only due to the age of the patients but also because of the many challenges of its practical realization. During the planning of 3D conformal radiotherapy it is a difficult task to align the whole cranial irradiation with the field treating the spine, and to align the spine fields with each other. The cranial field is usually covered by two lateral fields, while the spine fields consist of single posterior fields. The development of the so called ”hot spots”, dose inhomogeneities increases at the points of alignment, thus, the risk of overdosing increases[8 – 11]. Sebestyén et al. demonstrated the technique utilized at their institute for avoiding overdosing, on 8 patients. By using segments in the field, no overdosed areas developed at the points of field alignment[12]. This may be reduced by using the intensity modulate technique (IMRT)[13]. Kuster et al., using the IMRT technique, managed to decrease inhomogeneous dose distribution, they increased the coverage of the target area and the protection of the organs at risk[14].

With the further advancements in the radiotherapeutic techniques and the planning options and with the volumetric arc therapy (VMAT) becoming more and more widespread, the need emerged for studying how much more gentle is this treatment modality compared to the conventional stationary field IMRT treatment. Rolina et al analyzed the plans of 10 patients. They were able to improve the coverage of the target area by using the VMAT technique, however, this did not result in significant differences. No remarkable differences were seen in terms of the dose exposures of the organs-at-risk between the two techniques[15]. These results were supported by other studies conducted at other institutes[16 – 18]. In the study of the SIOP-E-BTG group, the same cases were sent to 15 institutes for planning, in order to compile the best 3D-CRT, IMRT, VMAT and Proton therapeutic plans. The modern radiotherapeutic techniques resulted in the improvement of the dose conformity and the dose homogeneity compared to 3D-CRT. The dose exposure of organs-at-risk also improved, however, significant differences were only obtained with the proton therapy[19].

Hideghéty et al. assessed the benefits and disadvantages of prone and supine patient positioning with 12 patients. No differences were seen regarding dose homogeneity, and coverage. However, supine position was more advantageous in terms of patient comfort and easier treatment realization. While using this positioning, general anesthesia of the patients became avoidable and due to the better stability of this position we achieved better reproducibility during online verification compared to applying prone patient positioning.

The side effects of the treatment can be acute or delayed. In the current study we essentially dealt with the acute side effects, and we were looking for an explanation for their development. In the study of St. Claire, during the use of IMRT and other modern techniques, the dose limits of organs-at-risk were not approached compared to the 3D-CRT, thus, according to their opinion, the side-effects may decrease[21]. During the prospective study of Cox conducted between 2010 and 2014, the acute side effects were analyzed in 10 patients. During the treatments, gastrointestinal side effects occurred predominantly, such as vomiting and diarrhea. However, these side effects are well tolerable with appropriate supportive care, unlike the much more therapy resistant alopecia and headache[22]. As an effect of the dose modulation

during the IMRT treatment, the dose delivered towards the abdominal organs is well controllable, therefore, the side effects are also more tolerable[14]. In the HIT91 study, according to the description of Kortman et al.treatment interruptions became necessary due to the occurrence of myelosuppressive side-effects. Notable (> grade 3) myelosuppression was seen at 35% of the patients who received chemotherapeutic regimens before and after their radiotherapy, and at 19.3% of patients who received maintenance therapy only. The hematological side-effect was prolonged especially in young adults. With the elimination of the direct field, the dose of the sternum - being an organ-at-risk - was successfully reduced by 57% using the IMRT treatment[23]. This was supported by our results as well, as the dose of sternum was 2299/1156 cGy. We demonstrated the safety of the rotating field arc radiation therapy, and no remarkable myelosuppressive side-effects were observed.

Bone marrow suppression as an acute side effect is typical during the treatment. Sung Zong-Wen outlined in his work that a large area of tissue is affected by a relatively low dose during the VMAT treatment. In addition, the main side effect in the treated patients was hematological toxicity, which did not exceed the decrease beyond the Grade (Gr) 3 value[24]. Wong et al. observed hematological toxicity with the following magnitude in 14 patients during VMAT treatment. Leukopenia Gr 2: 11%, Gr 3: 26%, Gr 4: 63%, Anemia Gr 2: 89%, Thrombocytopenia Gr 1–2: 16%, Gr 3: 26%, Gr 4: 37%[25]. Kumar et al. conducted a study involving 4 institutes between 2011 and 2014, and they analyzed the hematological causes of therapy discontinuation in 52 patients. Treatment was discontinued if a grade 2 side-effect developed, and, it was continued upon the appearance of grade 1 side-effects. The irradiation of the spine had to be interrupted at 73.1% of the patients, for which the cause was leukopenia in 92% of the cases, it was thrombocytopenia in 2.6% of the cases, and both were responsible in 5.3% of the cases[26]. In our study, we encountered milder side effects both in the 3D conformal arm and in the IMRT/ARC arm.

According to Fossati et al., a decrease in the development of delayed side effects can be observed in the case of the IMRT treatment, which include cardiac side-effects and hypothyroidism. However, with increasing doses, no additional delayed toxicities can observed regarding the lungs, kidneys, testicles, uterus and ovaries. For the final evaluation of the delayed side effects of the IMRT treatment we still do not possess enough data, due to the relatively short follow-up period. It may be noted at this point that IMRT carried out with arc irradiation has a benefit over the 3D conformal technique in the protection of the hypothalamus and the hippocampus, considering that the IMRT treatment provides better dose homogeneity. However, further observation is necessary according to Bernier et al.[28]. Further evaluation of our data is necessary for the assessment of the delayed side effects.

Salloum et al. processed mortality and morbidity data from patients treated with medulloblastomas between 1970 and 1999, thus these data covered three decades. The median time from diagnosis was 21 years at the 1311 enrolled patients. The 15-year mortality rates were 23.2% and 12.8% in patients treated in the 70 s and 90 s, respectively. Mortality rates due to recurrences were 17.7% and 9.6%, respectively. However, the rate of a second tumor was higher in patients treated with multiple modalities in the 90 s (56.6% vs. 39.9%). It was also indicated that patients, who have been treated due to highrisk

medulloblastomas had a greater need for services aiding learning[29]. Altogether, the role of advancing and developing techniques was highlighted, and we also set a similar objective in our study. Similarly good results were achieved during the follow-up of our patients with the use of these advanced techniques.

Conclusions

During the analysis of the treatments of our patients, we highlighted that there was no notable difference between the two treatment modalities in terms of the normal tissue dose exposure, even the dose exposures to certain organs and tissues can be reduced markedly with the use of modern technology. IMRT/ARC therapy can be carried out more reliably and more easily both from the aspects of patients and the radiotherapy technicians as well. There is no difference regarding the decrease in the laboratory parameters between the two groups, therefore, IMRT/ARC treatment is also safe from a hematological point of view. According to our experience, the different dose exposures do not affect the laboratory parameters markedly, nor do they cause acute complications. Longer follow-up intervals are necessary for the assessment of delayed side effects.

Abbreviations

3D
three dimension
IMRT/ARC
Intensity modulated radiotherapy with moving gantry
CSI
Craniospinal irradiation
SPSS
Statistical Package for the Social Sciences
PNET
primitive neuro-ectodermal tumor
Gy
Gray
GTV
gross tumor volume
CTV
clinical target volume
PTV
planning target volume
ANOVA
analysis of variance
cGy
centi Gray

QUANTEC
Quantitative Analyses of Normal Tissue Effects in the Clinic
OAR
Organs at risk
3D-C
3D-conformal plan
RA
IMRT/ARC plan
VMAT
volumetric arc therapy
3D-CRT
3 dimensional conformal radiotherapy
HIT-91
Hirmtumor-91 study
Gr
grade
SIOP-E-BTG
International Society for Pediatric Tumor – Europe – Brain Tumor Group

Declarations

Ethics approval and consent to participate

For retrospective data evaluation not necessary due to Hungarian regulation

Consent to publish

Informed consent was signed by each participant

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial, non-financial relationship that could be constructed as potential competing of interest.

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Figures

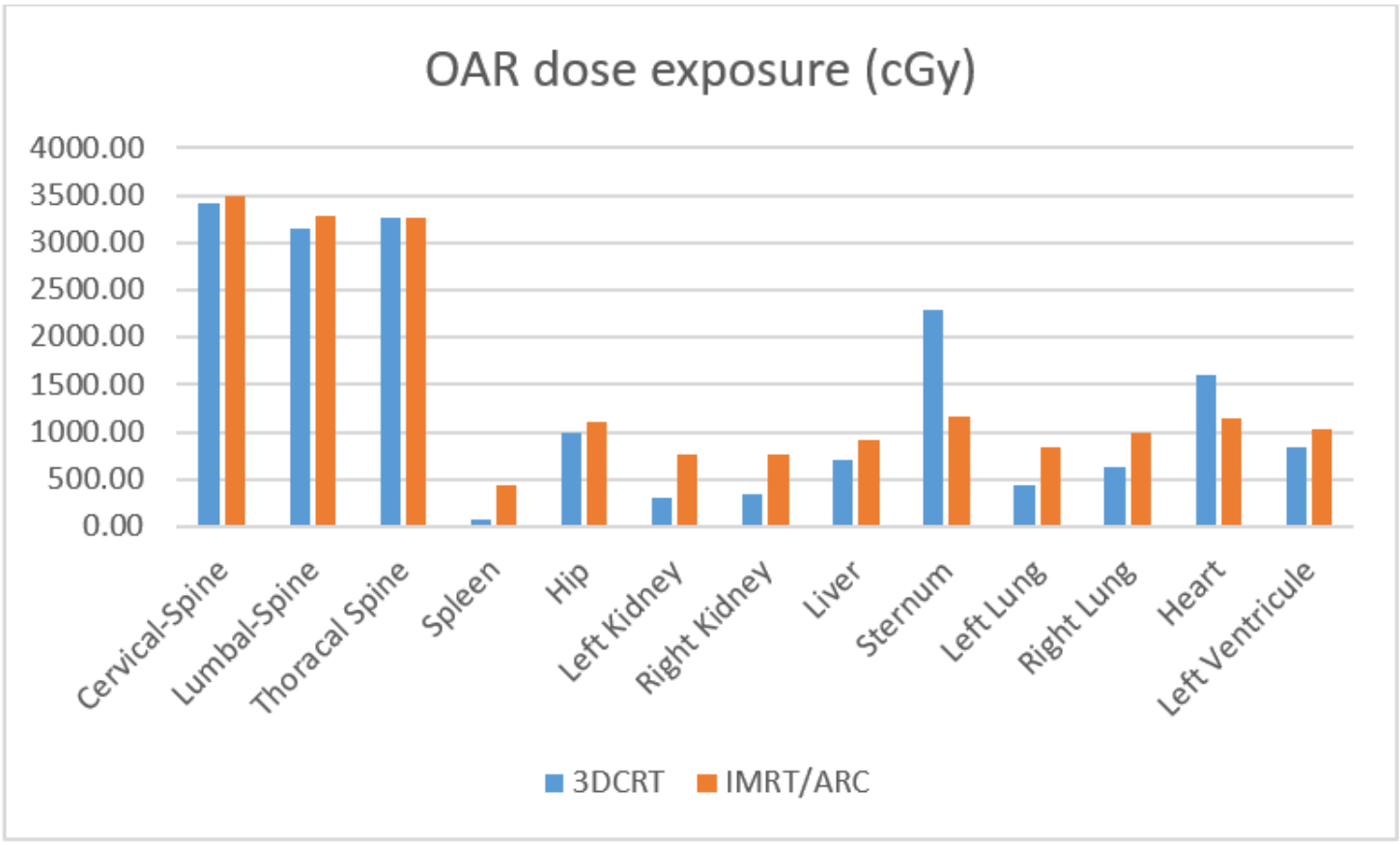

Figure 1

OAR dose exposures during the treatments carried out with the two radiotherapeutic modalities.

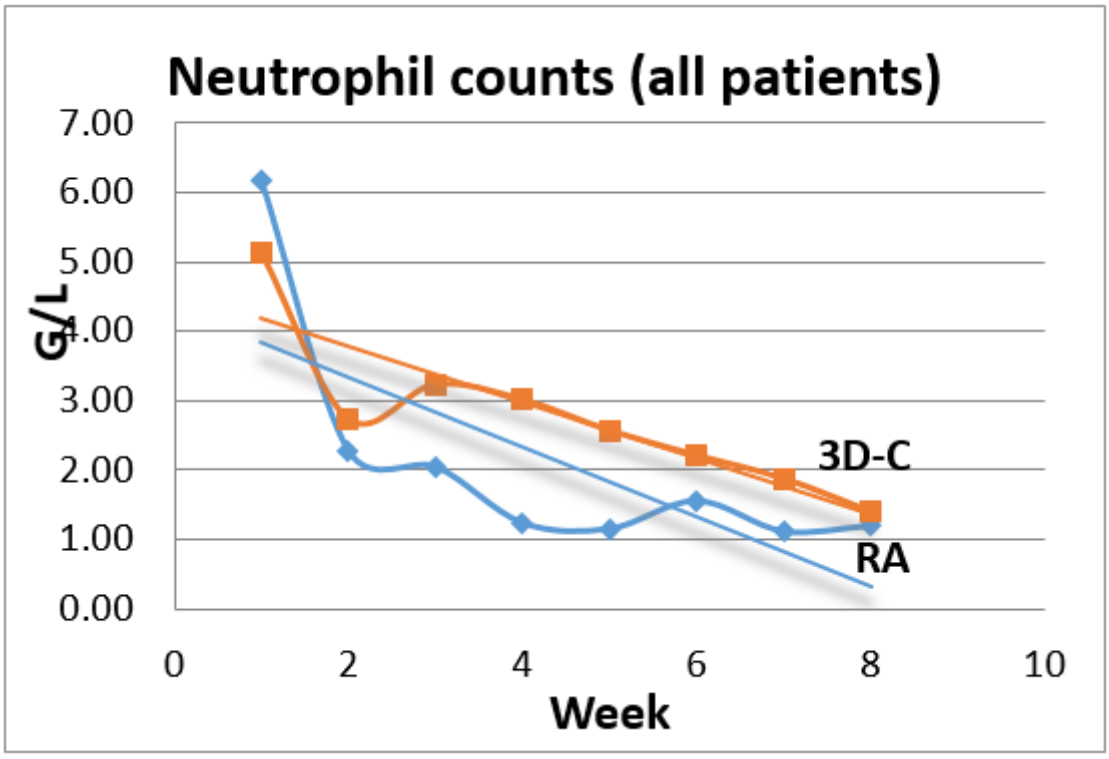

Figure 2

The decrease in the weekly mean value of neutrophil granulocytes during the treatment. A significant decrease can be observed during the treatment weeks, however, there is no difference between the two groups. (3D-C: 3D-conformal plan, RA: IMRT/ARC plan)

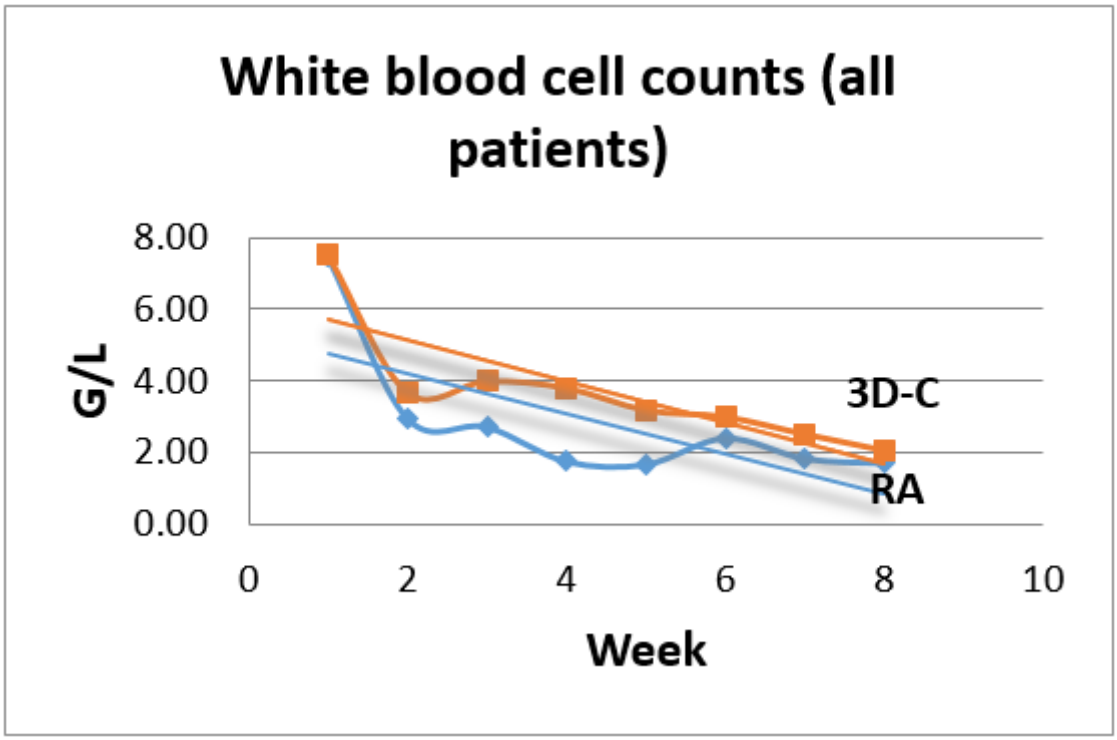

Figure 3

The decrease in the weekly mean value of white blood cell counts during treatment. A significant decrease can be observed during treatment weeks, however, there is no difference between the two groups. (3D-C 3D-conformal plan, RA: IMRT/ARC plan)

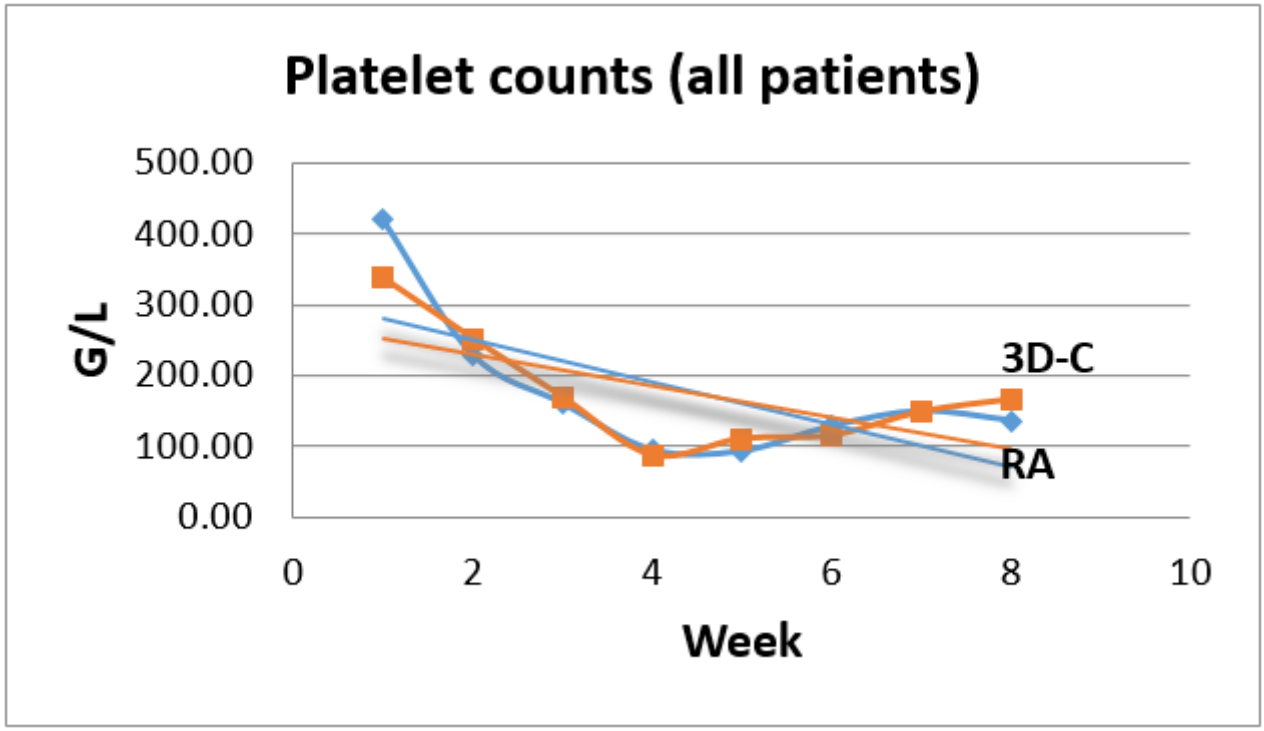

Figure 4

The decrease in the weekly mean value of platelets during treatment. A significant decrease can be observed during treatment weeks, however, no difference is present between the two groups. 3D-C 3D-conformal plan, RA: IMRT/ARC plan)

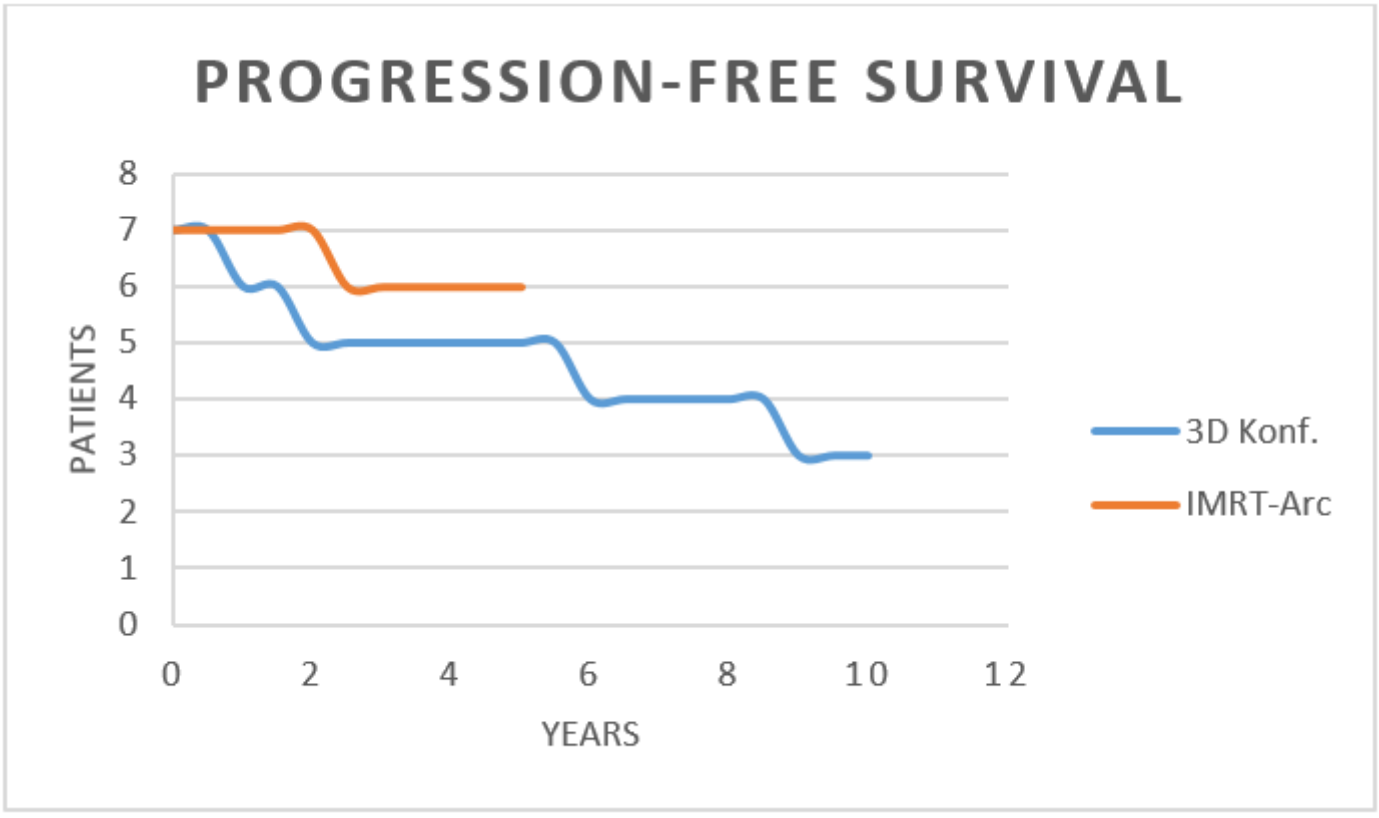

Figure 5

Progression-free survival.

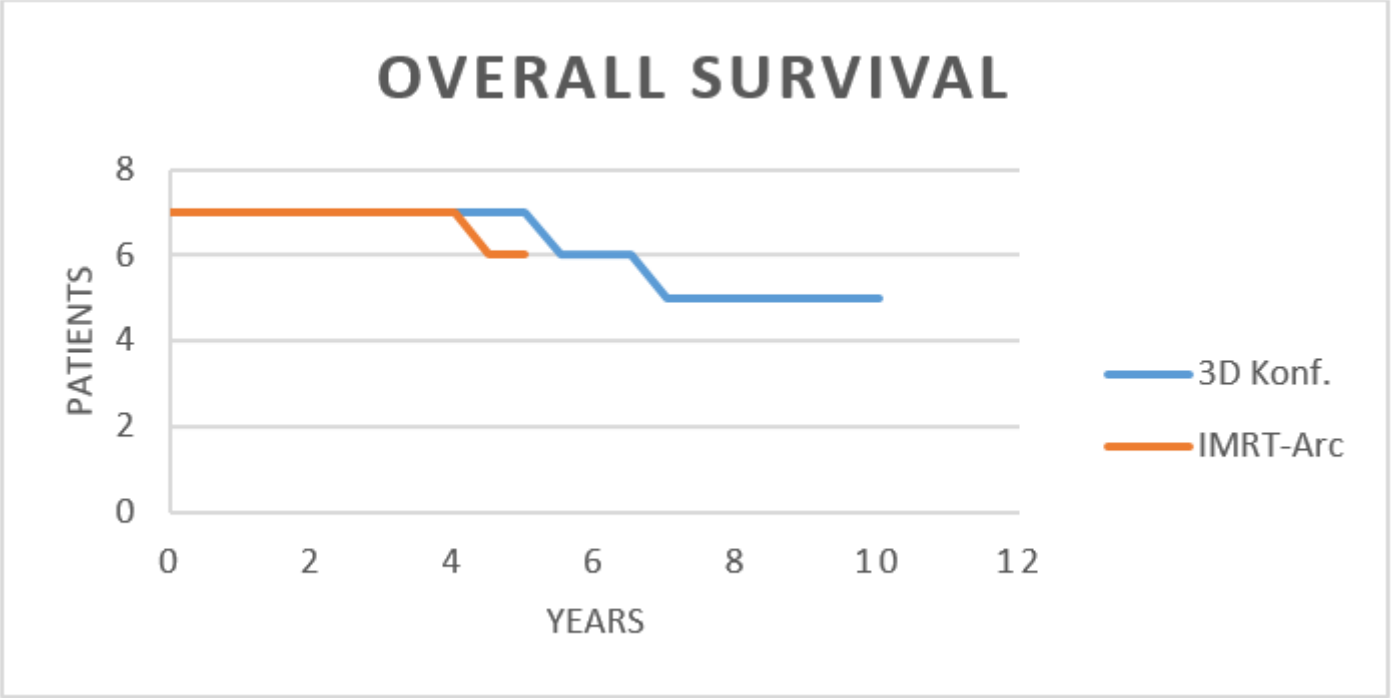

Figure 6

Overall survival data