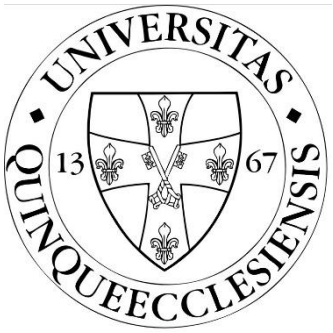
The analysis of modern radiation techniques in the treatment of childhood cancer craniospinal, and cervix cancer patients dose-escalation Simultan integrated boost irradiation.

Phd – Thesis

University of Pécs Doctoral School of Clinical Medical Sciences



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1. Chapter

Assessment of the results and hematological side effects of 3D conformal and IMRT/ARC therapies delivered during craniospinal irradiation of childhood tumors with a follow-up period of five years

Introduction

Special radiation treatment for the childhood cancer patient (medulloblastoma, PNET, Ependimoma) is craniospinal axis irradiation. With the development of radiation techniques, new opportunities occurred for the delivery of the treatment, which could hardly carried out and planned. With intensity modulated and image guided therapy, a more homogenous dose and a more accurate treatment could be achieved. Further optimization on dose homogeneity was achieved by adding sliding radiotherapy (Rapidarc, IGRT/ARC) to the treatment. Precise and fast treatment delivery is mandatory in the previously with chemotherapy pretreated central nervous system childhood cancer patient's treatment. After the installation in 2011 of Varian, Novalis TX linear accelerator, a new treatment option with Rapidarc technique was offered for our patients. With the introduction of supine positioning we solved the challenges of treatment positioning what couldn't modified during 3D-conformal radiotherapy (3D-CRT). The comfort of the long treatment was better without general anesthesia. However, during close oncological control, we observed more severe laboratory changes (white blood cells, platelets), what was controlled without any treatment break.

In our study we observed retrospectively for 3D-CRT and IGRT/ARC treated patient's hematologic laboratory changes. Prospectively we followed our patients after treatment to asses they survival difference between the two techniques.

Patient and Methods

Full CSI was carried out in 14 children and young adults with primary intracranial brain tumors, with a mean age of 14.64 years (3-33 years of age) at our institute between 2007 and 2014. We included each and every consecutive pediatric brain tumor patient who was treated during the study period. Each patient signed an informed consent form to participate in the retrospective data analysis. Guardians or parents signed for patients under the age of 18. In accordance with Hungarian regulations, no ethical approval was obtained for the analysis of our data. The treatment of patients before 2011 was performed with the 3D conformal technique and field alignment in a prone position.

Subsequently, patients were treated with IGRT and the RapidArc technique in a supine position. 3D conformal treatments were delivered with the Elekta Eclipse PreciseTS device, while the RapidArc treatments were carried out with the Varian Novalis TX linear accelerator.

Retrospectively, seven patients were identified separately in both groups, and our patients were followed in a partially prospective manner. Based on the histological types, predominantly medulloblastoma (11 cases), PNET (1 case), atypical rhabdoid tumor (1 case) and glioblastoma (1 case) were observed. All patients, except the glioblastoma patient, underwent primary surgery and adjuvant chemotherapy in accordance with the Hungarian National Cranial Protocol. A vacuum bed and head mask were used during positioning. It was decided to use an open-face mask during the treatment in a supine position; additionally, in order to be able to reproduce the positioning of the entire body, the patient's arms were fixed beside their body.

During radiotherapy, a median of 35.2 Gy (30.4-36.8 Gy) was delivered to the whole spine and the skull, followed by a posterior fossa boost of a median dose of 19.8 Gy (19.2-24 Gy). The CTV for the spine was defined cranially from the C1 vertebral body caudally to the S2 vertebral body. The vertebral body and spinous process in an antero-posterior direction and the transverse foreman latero-laterally were used as borders. A CTV PTV expansion of 4 mm was used. For posterior fossa irradiation, the primary tumor was defined as the GTV and extended by 1 cm to the CTV. The tumor bed was included in this CTV. A PTV was generated with a 3 mm margin from the previous structure. Low doses of oral steroids were used for short time if our patient developed cranial pressure elevation symptoms. Due to childhood treatment protocols our patient were with chemotherapy pretreated and received after radiotherapy further cycles, and maintenance vincristine therapy was performed during the radiation.

Regarding the retrospective assessment of acute toxicity, the results of the follow-up laboratory tests performed during treatment were reviewed. The counts of white blood cells, platelets and red blood cells as well as the levels of hemoglobin and hematocrit were analyzed during treatment. Version 25 of SPSS software was used for the calculations. 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 sample t-tests were used. Furthermore, assessments were completed regarding the exposure dose of the organs-at-risk to determine whether IMRT/ARC therapy would eventually be associated with a higher exposure dose, 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, spleen and liver were contoured. The doses delivered to the heart, left ventricle, kidneys and lungs were also determined to assess exposure doses affecting the quality of later life. It was also noted that, on many occasions, it was necessary to suspend treatment for over one week due to the acute side effects caused by the treatment. Our study

also reviewed the treatment results using data obtained from the local pediatric oncological care center after the treatment in order to evaluate the progression-free and overall survival data. We also used long-term care data to check whether any delayed organ toxicity associated with radiotherapy had occurred in any child.

Results

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

The first point of analysis of the side effects caused by radiotherapy was the extent of exposure dose in the normal tissues. The mean exposure dose of the organs at risk responsible for the hematopoietic side effects in the case of the 3D conformal and 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, and liver: 708/917 cGy. No significant differences were observed in the bones near the target area between the two types of radiation therapy; however, the exposure dose of the sternum decreased and that of the spleen increased during IMRT/ARC.

The exposure doses of the nonhematopoietic 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, and left lung: 441/845 cGy. An increase regarding the organs at risk was detected with Arc therapy; however, these changes are well within the tolerability criteria according to the QUANTEC dose charts.

While the exposure dose of organs at risk is caused by a single direct field directed at the spine when using the 3D conformal technique, the characteristics of the rotating field of Arc irradiation during IMRT/ARC therapy means that more organs at risk may be affected by a lower dose. Thus, a slight dose increase may be experienced with this technique compared to the 3D conformal technique; however, this is tolerable.

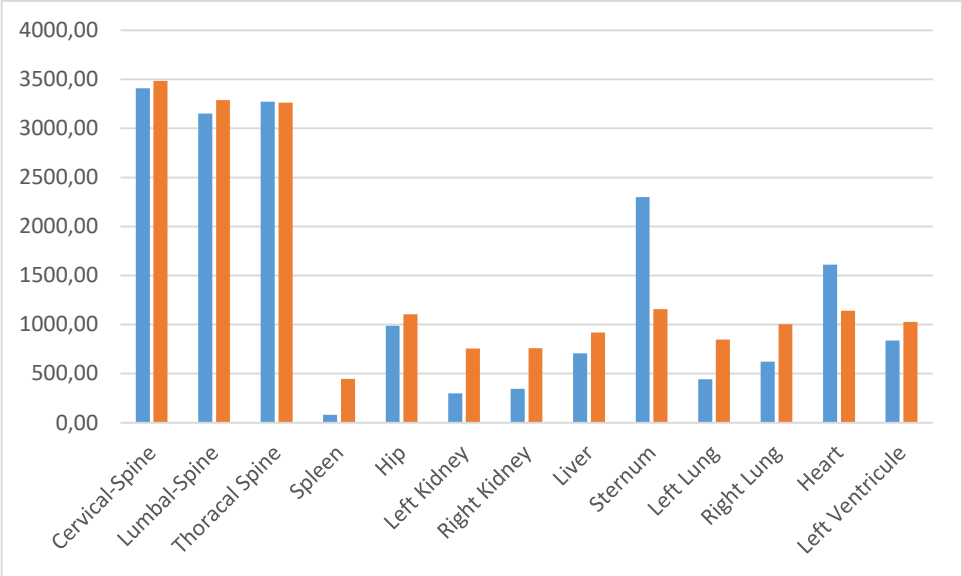

Figure 1: OAR dose exposures (cGy) during the treatments carried out with the two radiotherapeutic modalities. 3DCRT in blue and IMRT/ARC therapy in orange.

After analyzing weekly changes in the laboratory parameters, the following conclusions were made despite the low number of cases. The repeated measures ANOVA test revealed the following regarding the observed laboratory parameters. The total white blood cell counts significantly decreased compared to the baseline values over the weeks ($p=0.0029$), while the neutrophil counts initially increased then also decreased ($p=0.007$). The same significant decrease was observed in the platelet counts ($p=0.0004$). No changes were observed in the red blood cell counts ($p=0.107$) or in the hematocrit levels ($p=0.140$); however, a slight difference was observed in the hemoglobin levels ($p=0.045$). Nevertheless, no significant differences were observed between the two groups regarding the total white blood cell count ($p=0.449$), neutrophil ($p=0.754$), platelet ($p=0.815$), red blood cell ($p=0.506$), hematocrit ($p=0.489$) or hemoglobin ($p=0.360$) parameters.

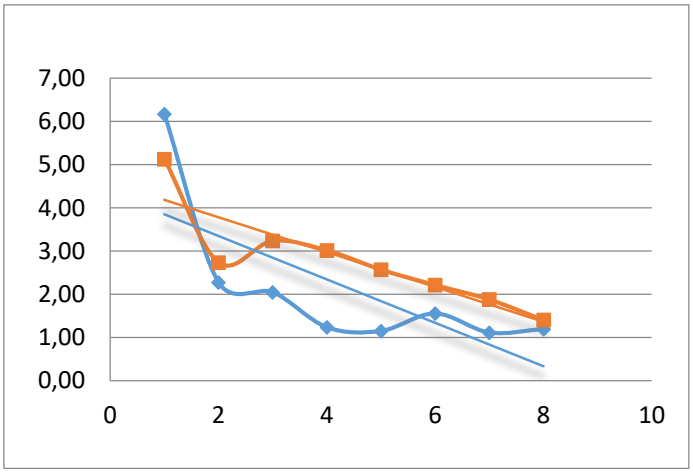

Figure 2: Neutrophil counts for all patients (G/l) during the treatment weeks. The decrease in the weekly mean value of neutrophil granulocytes during the treatment. A significant decrease can be observed during the treatment weeks; however, there is no difference between the two groups. (Orange: 3D-conformal plan, Blue: IMRT/ARC plan)

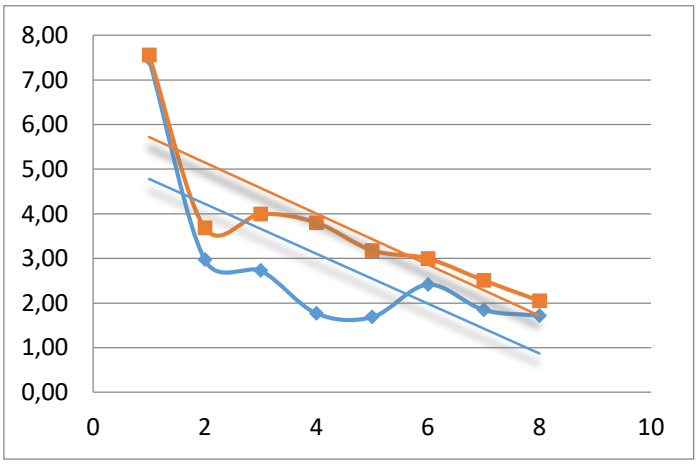

Figure 3: White blood cell counts for all patients (G/l) during the treatment weeks. The decrease in the weekly mean value of white blood cell counts during treatment. A significant decrease can be observed during treatment weeks; however, there is no difference between the two groups. (Orange: 3D-conformal plan, Blue: IMRT/ARC plan)

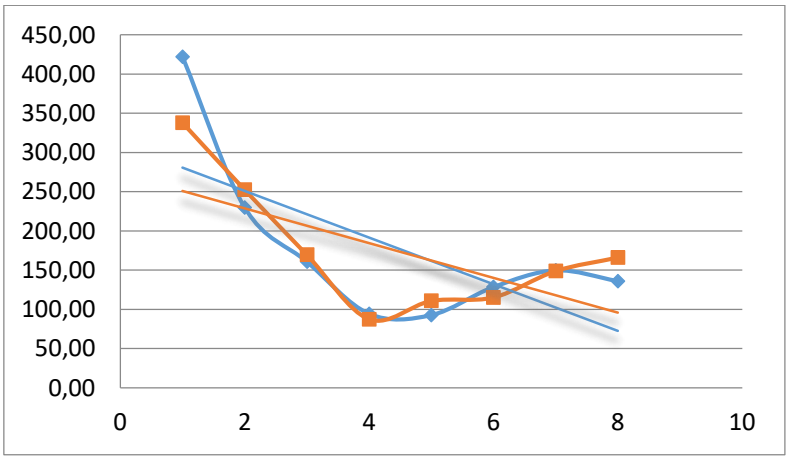

Figure 4: Platelet counts for all patients (G/l) during the treatment weeks. The decrease in the weekly mean value of platelets during treatment. A significant decrease can be observed during treatment weeks; however, there is no difference between the two groups. (Orange: 3D-conformal plan, Blue: IMRT/ARC plan)

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

We have been following our patients for twelve years. The median follow-up duration in the 3D conformal group was ten years compared to five years in the RapidArc group.

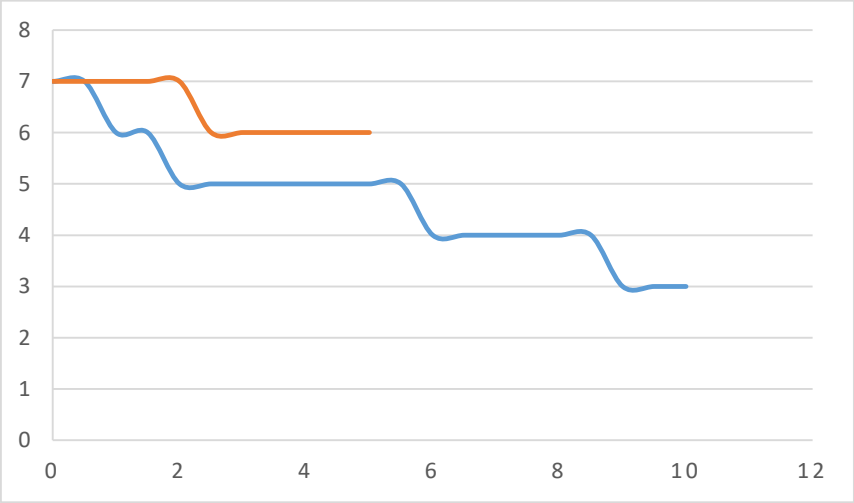

Figure 5: Progression-free survival. All patient curves over the years. 3DCRT in blue and IMRT/ARC in orange.

In terms of progression-free survival, the development of local recurrence or new organ manifestations in patients with a poorer prognosis affected the development of the curves in both groups.

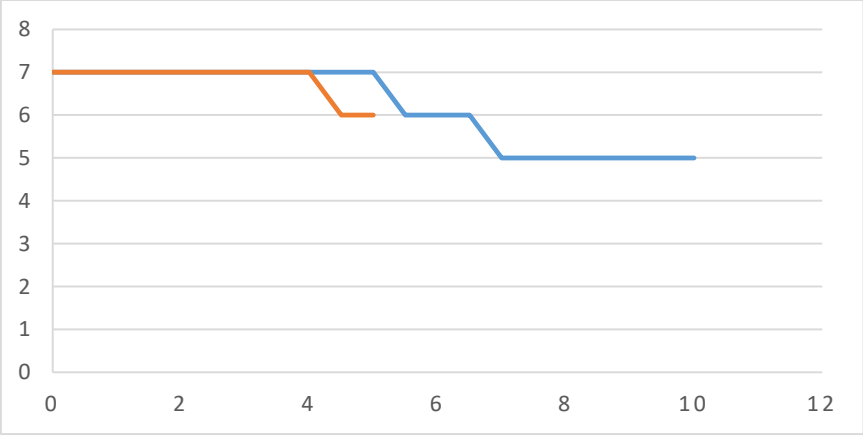

Figure 6: Overall survival data. All patient curves over the years. 3DCRT in blue and IMRT/ARC in orange

There was no significant difference between the development of the overall survival curves of the two populations in the first five years. A trend could not have suggested. For late toxicity assessments further observation is needed.

Discussion

CSI irradiation is a challenging treatment, not only due to patient age but also because of the many challenges of its practical application. While planning 3D conformal radiotherapy, it is difficult to align the entire cranial irradiation with the field treating the spine and to align the spinal fields with each other. The cranial field is usually covered by two lateral fields, while the spinal fields consist of single posterior fields. The development of “hot spots”, dose inhomogeneities, increases at the alignment points, thus increasing the risk of overdosing. Sebestyén et al. demonstrated the technique used on eight patients at their institute to avoid overdosing. By using segments in the field, no overdosed areas developed at the points of field alignment. This may be reduced by using the intensity modulate technique (IMRT). Using the IMRT, Kuster et al. managed to decrease the homogeneous dose distribution while increasing coverage of the target area and protection of the organs at risk.

With further advancements in radiotherapeutic techniques and planning options and with volumetric arc therapy (VMAT) becoming increasingly widespread, it became necessary to study how much gentler this treatment modality is compared to conventional stationary field IMRT. Rolina et al. analyzed the plans of ten patients. They improved 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 exposure doses of the organs at risk between the two techniques. These results were supported by other studies conducted at other institutes. In the SIOP-E-BTG group study, the same cases were sent to 15 institutes for planning to compile the best 3D-CRT, IMRT, VMAT and proton therapeutic plans. The modern radiotherapeutic techniques resulted in improvements in dose conformity and dose homogeneity compared to 3D-CRT. The dose exposure of organs at risk also improved; however, significant differences were only obtained with proton therapy.

Hideghéty et al. assessed the benefits and disadvantages of prone and supine patient positioning in twelve patients. No differences were observed regarding dose homogeneity or coverage. However, the supine position was more advantageous in terms of patient comfort and achieving a simple treatment.

The side effects of the treatment may be acute or delayed. In the current study, we essentially dealt with the acute side effects and sought an explanation for their development. While using

IMRT and other modern techniques in the St. Claire study, the dose limits of organs at risk were not approached compared to 3D-CRT; thus, they believed that the side effects may decrease. During the prospective study of Cox conducted between 2010 and 2014, acute side effects were analyzed in ten patients. Gastrointestinal side effects, such as vomiting and diarrhea, occurred predominantly during the treatments. However, these side effects are well tolerated with appropriate supportive care, unlike the significantly more therapy-resistant side effects of alopecia and headache. As an effect of dose modulation during IMRT, the dose delivered towards the abdominal organs is well controllable; therefore, the side effects are also more tolerable[14]. In the HIT-91 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 in 35% of patients who received chemotherapeutic regimens before and after their radiotherapy and in 19.3% of patients who only received maintenance therapy. The hematological side effects were especially prolonged in young adults. By eliminating the direct field, the dose of the sternum - an organ at risk - was successfully reduced by 57% using IMRT. This was also supported by our results, as the dose for the sternum was 2299/1156 cGy. We demonstrated the safety of rotating field arc radiation therapy, with no remarkable myelosuppressive side effects observed.

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

Salloum et al. processed mortality and morbidity data from patients treated for medulloblastomas between 1970 and 1999; thus, these data covered three decades. The median time from diagnosis in the 1311 enrolled patients was 21 years. The 15-year mortality rates were 23.2% and 12.8% in patients treated in the 70 s and 90 s, respectively; the mortality rates

due to recurrence were 17.7% and 9.6%, respectively. Altogether, the role of advancing and developing techniques was highlighted; we also set a similar objective for our study. Similarly, good results were achieved using these advanced techniques during the follow-up of our patients. Although the overall survival curves in our study developed in a very similar way, only a trend can be suggested. This result is a consequence of the low number of patients. Our study has some limitations due to the very small sample size and heterogeneity of the cohort.

Conclusion

The analysis of our patients' treatments highlighted that there was no notable difference between the two treatment modalities in terms of the normal tissue dose exposure; indeed, the dose exposures to certain organs and tissues can even be reduced markedly with the use of modern technology. IMRT/ARC therapy can be carried out more reliably and easily from the perspective of both patients and radiotherapy technicians. Although there were a small number of cases, there was no difference in the decrease in laboratory parameters between the two groups. Therefore, from the point of view of hematologic side effects, IMRT/ARC treatment is also safe. In our experience, the different dose exposures do not markedly affect the laboratory parameters, nor do they cause acute complications. Longer follow-up intervals and a larger number of patients are necessary to assess delayed side effects.

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2. Chapter

Substitution of brachytherapy boost by the use of simultan integrated boost with IMAT-IGRT technique, a single institutional, prospective, pilot study.

Background

Cervical cancer accounts for 30% of all gynecological malignancies in the developed world. The pathogenic role of HPV infection in the development of cervical cancer is well known with The macroscopic spread of the tumor is characterized according to FIGO and TNM classifications. Patients with cervical cancer classified as more advanced than FIGO stage Ib2 and stage T1b2 generally receive definitive radiochemotherapy (RCT). In these stages, treatment is performed most commonly using RCT as follows: percutaneous pelvic radiotherapy (RT) at a dose of 45 to 50.4 Gy using the 4-field box or IMRT (intensity modulated RT) technique at daily doses of 1.8 Gy per fraction, and pathological lymph nodes are boosted with SIB to 61,2 Gy with 2,2 Gy fractions, simultaneously with cisplatin chemotherapy at doses of 40 mg/m^2 weekly in 4 to 5 cycles. According to the globally approved "gold standard", 3 to 4 x 7 Gy image based intracavitary HDR-AL boost irradiation is performed at the end of the treatment. If the lesion is large combined intracavitary / interstitial implant is recomended.

However, in a proportion of the patients, brachytherapy (BT) is not feasible (due to anatomical factors, extreme scarring etc.), or some patients do not consent to the procedure. BT may also be limited by the inability of intracavitary techniques to provide appropriate tumor coverage. However, thanks to the impressive progress in teletherapy technology by the routine use of IGRT (Image Guided RT), IMRT and IMAT (Intensity Modulated Arc Therapy) methods, the possibility of developing an alternative external beam dose escalation model may also arise. With external beam radiotherapy using the SIB (simultaneous integrated boost) technique, this type of RCT is theoretically feasible. The aim of our study is to develop an alternative treatment method for our patients which is safe and is not different from the standard therapy in terms of its effect. In our present paper, we would like to share our first results.

Patients and Methods

This study was performed according to the approval of the ETT TUKEB (Medical Research Council - Scientific and Research Ethics Committee) registration number 5620-3/2015/EKU on 21/01/2015 and the Regional Research Ethics Committee of the University of Pécs registration number. 5409. The study was registered to the German Clinical Trial Platform on 13/11/19 with the registration number DRKS00019044. In this study, patients with FIGO stages from IIB to IVA were enrolled. Patient enrollment was performed between January 2015 and September 2018, in which period 14 patients were treated. Most of the patients do not consent to BT due to psychological factors, BT was not feasible due to bladder involvement, or extreme

obesity. Their median age was 57.5 years (37 to 78). All procedures were performed in accordance with the relevant guidelines and regulations. All patients signed an informed consent form before study enrollment. The TNM classifications of the treated cervical cancers were stage from T2b to T4. In addition, lymph node involvement was observed in 9 patients (Table II/1.).

	SIB-Dose	TNM	Stage	Age
PT-001	67.2 Gy	T4N0M0	IVA	78
PT-002	67.2 Gy	T2bN0M0	IIB	60
PT-003	67.2 Gy	T2bN0M0	IIB	60
PT-004	67.2 Gy	T2bN1M0	IVA	55
PT-005	79.2 Gy	T4N0M0	IVA	37
PT-006	79.2 Gy	T4N1M0	IVA	44
PT-007	67.2 Gy	T2bN1M0	IVA	40
PT-008	79.2 Gy	T4N1M0	IVA	49
PT-009	79.2 Gy	T3bN1M0	IVA	46
PT-010	79.2 Gy	T4N1M0	IVA	43
PT-011	79.2 Gy	T3bN0M0	IIIB	66
PT-012	79.2 Gy	T3bN1M0	IVA	70
PT-013	67.2 Gy	T2bN1M0	IVA	75
PT-014	67.2 Gy	T4N1M0	IVA	75

II/1. Patient Characteristics

Diagnostics:

The generally applied physical examination was supplemented by an MRI scan within 6 weeks prior to treatment for the purpose of a more exact staging. Prior to the initiation of percutaneous RT, PET/CT scans were performed in radiotherapy treatment position to help to determine the exact GTV (“gross tumor volume”).

Target Volume delineation:

For the determination of the GTV-T, we used 3 noncontrast planning CT scans with 3-mm thickness. The first scan was performed with a full bladder, and the second scan with an empty bladder. After the second scan, the patient drank 300 ml water, and the third scan was performed after half an hour. An iodine-marked tampon was inserted in the patient’s vagina for all 3 scans to mark the bottom of the cervix. The T1, T2 and MPRAGE contrast-enhanced MRI sequences and the PET/CT scans were deformable registered to the planning CT. In all images, we defined the GTV-T and created an SIB-GTV as an ITV (internal target volume). Using a 3-mm safety margin, we created the SIB-PTV (planning target volume).

A CTV-N (clinical target volume of nodes) was determined according to institutional and RTOG protocols that included the mentioned SIB-GTV. We used a 5-mm margin for the pelvic PTV

Treatment planning:

Planning was performed on the third planning CT. The treatments were performed with RapidArc technique using a Novalis TX linear accelerator.

In 7 patients in whom the primary tumor was less than 5 cm in longest diameter as measured by MRI, SIB was delivered in 28 fractions at doses of 2.4 Gy per fraction during pelvic irradiation with a total dose of 50.4/1.8 Gy (the total dose to PTV-SIB was 67.2 Gy). Thus, the BED (biologically effective dose) of the dose delivered to the cervical tumor was 83.33 Gy, which was calculated with an α/β value of 10. During the treatment, the dose limits of the organs at risk (OAR) applied in BT has been used: rectal wall D2cc, 64 Gy; bladder wall D2cc, 85 Gy; sigmoid colon wall D2cc, 63 Gy, respectively. The treatment with SIB represents with an α/β value of 3 a BED of 120,96 Gy and 142.56 Gy. During the determination of normal tissue tolerance doses, no further biological conversion was performed, because to the similarity of doses reached in BT.

In another 7 patients in whom the size of the cervical cancer exceeded 5 cm in longest diameter and the parametrium was invaded on both sides, a higher final dose and expanded target volume were used based on the local protocol. A further 10-Gy dose of parametrial boost was added to the pelvic RT after performing a new simulation CT for replanning procedure, while the treatment of the primary tumor was continued with doses of 2.4 Gy per fraction (the total dose to PTV-SIB was 79.2 Gy). The dose of 2.4 Gy delivered to 33 fractions corresponds to a BED of 98.21 Gy, with an α/β value of 10. The dose limits for the normal tissue were taken into account as detailed above.

Treatment delivery:

During the treatments and prior to the planning CTs, the patients were provided with strict dietary recommendations. Under the increased control of the volume and position of the bladder and the rectum, SIB-PTV was minimized by decreasing the displacement of the cervix. Using the ITV concept, we were able to compensate for the motion of the target area, thereby keeping the final PTV as small as possible. The irradiation treatment was on line controlled using 3D cone beam CT five times during the first week of the treatment and then once a week according

to an offline treatment protocol. The dietary protocol was in place that eliminates foods that cause bloating. Simultaneous weekly cisplatin was administered to all patients at a dosage of 40 mg/m^2. All patients were treated with 5 cycles of chemotherapy. In only 4 cases, we observed Gr I-II neutropenia when granulocyte stimulating factor needed to be administered for secondary prevention, according to institutional protocol.

Quality of Life and Follow up:

The primary endpoint of the study was acute toxicity and quality of life (QoL), for which the EORTC-QLQ 30 and CX-24 questionnaires were used. The patient completed the questionnaire on the first treatment day and on the third and fifth weeks of treatment. Weekly physician visits were performed to adjust adverse events with CTCAE grading and indicate supportive treatment if needed. After treatment completion monthly physician visits were performed in the first 6 months, then every 3 months. Primarily the main side effects, like diarrhea, vomiting, vaginal bleeding or discomfort were collected. No QoL questionnaires were performed during the follow-up period. The tumor regression rate was determined based on the first 3-4 months of follow-up MRI scan by measuring the primary tumor and lymph node metastasis reduction in the size of the longest diameter in accordance with the RECIST 1.1 (Response Evaluation in Solid Tumors) criteria. RECIST 1.1 radiological evaluation was performed on the same MRI machine with the same pelvis protocol. The percentage of tumor shrinkage for the whole population was calculated. The secondary endpoint was to collect the patients' survival data during the follow-up period exceeding the median value of 24 months. If 2 consecutive MRI scans confirmed residual mass, a PET/CT scan was performed to confirm residual tumor activity.

Results

The tumor stage was IVA in 78%, IIIB in 7%, and IIB in 14%, respectively. The average tumor diameter was 48.7 mm (22-83 mm) at the start of treatment, as measured on axial MRI. During our study, grade 3 to 4 toxicity was not observed, which provided a kind of a positive answer in terms of the feasibility and tolerability of the treatment. Longer than 3 days treatment interruption was not needed. The two SIB dosage schemes could be safely implemented. The doses regarding the organs at risk were maintained as originally planned.

Dose exposure for Organs at Risk:

The dose exposure of the bladder could be maintained at the mean and maximum doses as well as at the D2cc values in accordance with the literature data. The V50 values were on average higher than the standard, but the V70 values were markedly lower than expected (Table II/2.).

Table II/2. Bladder doses for all patients.

Bladder	*Mean (Gy)*	*MAX (Gy)*	*D2cc(Gy)*	*V50(%)*	*V70 (%)*
All Cases	48.09	72.00	67.30	46.20	10.84
67.2 Gy	44.08	68.34	64.39	27.87	0.00
79.2 Gy	52.11	75.66	70.21	64.53	10.84

Table II/3. Rectum doses for all patients.

Rectum	*Mean (Gy)*	*MAX (Gy)*	*D2cc(Gy)*	*V50 (%)*	*V70 (%)*
All Cases	49.77	72.89	68.25	42.29	10.34
67.2 Gy	46.09	68.99	64.17	32.17	0.00
79.2Gy	53.44	76.78	72.33	52.41	10.34

Table II/4. Sigma doses for all patients.

Sigma	*Mean (Gy)*	*MAX (Gy)*	*D2cc(Gy)*
All Cases	52.57	70.29	62.90
67.2 Gy	47.30	63.03	54.52
79.2 Gy	55.73	74.65	67.92

In the case of the rectum, the maximum and D2cc values were higher than the accepted dose limits of the HDR-AL technique, but the V50 and V70 percentages were well within the acceptable limits (Table II/3).

In the case of the sigmoid colon, a dose which may be associated with an increased risk of adverse reactions was not observed, and the average D2cc was between 62 and 67 Gy (Table II/4.).

Toxicity and Quality of life:

During the treatment, adverse reactions were assessed by EORTC questionnaires and weekly physician visits. The results of these studies confirmed the usual complaints, such as diarrhea, bladder inflammation, and nausea, associated with intensive combined therapy. During the evaluation of the well-being scales, in the case of the EORTC QLQ-C30 questionnaire,

worsening social life could be observed, which can be explained by the symptoms related to the treatment (Figure 1., 2.). The complaints of diarrhea, fatigue, insomnia and pain as measured on the symptom scale of the questionnaire became aggravated. However, similar adverse reactions also occur during conventional treatments. No acute adverse reactions above Grade 2 occurred. Currently, at the two-year follow-up, severe proctitis or bladder stricture have not developed. DFS was calculated from the percentage of patients without determined cancer. No further statistical statement could be done due to the small cohort size of our patients.

In the disease-specific EORTC QLQ CX 24 questionnaires, the aggravation of menopause-like complaints was considered normal since it is a common adverse reaction in the case of pelvic radiotherapy (Figure 3., 4.). Unfortunately, a very low percentage of the patients provided meaningful responses to questions about body image and sexuality possibly due to reasons associated with pudency.

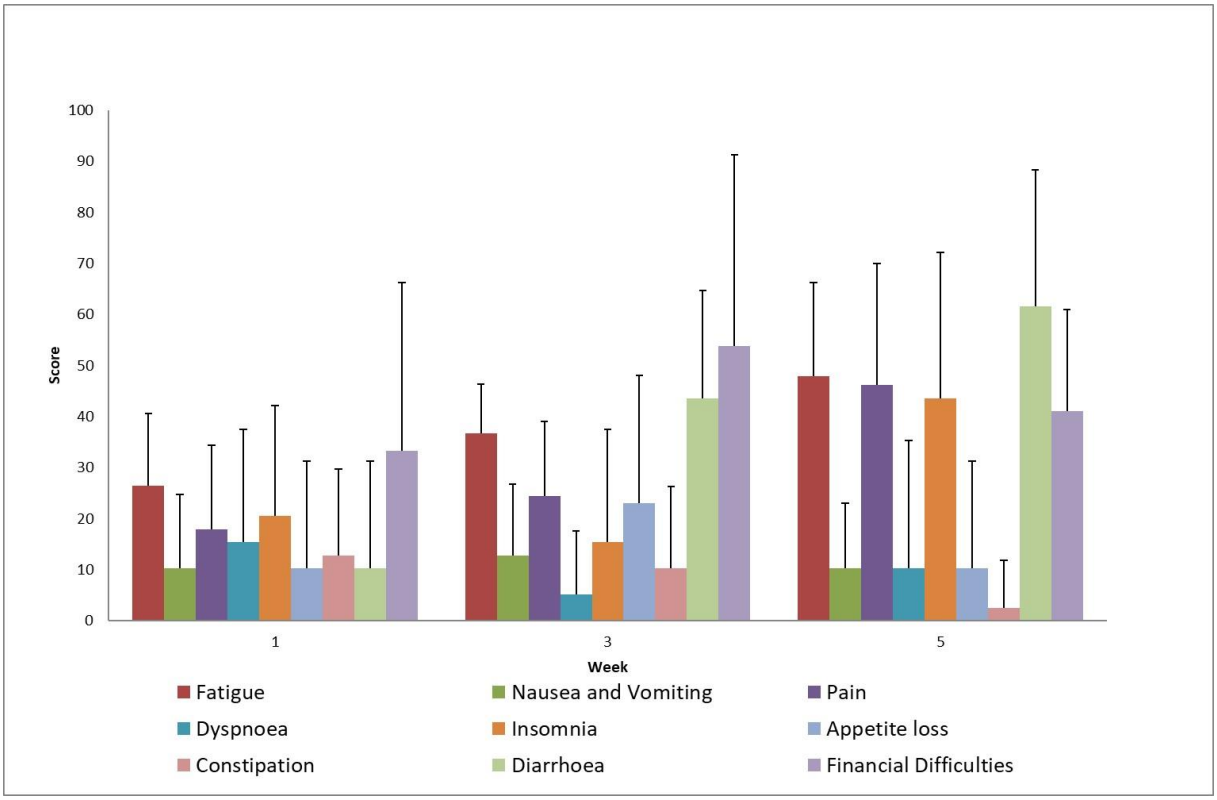

Figure 1. Evaluation of EORTC QLQ-C30 Symptoms questionnaires score mean value and SD (+), during treatment for all patients.

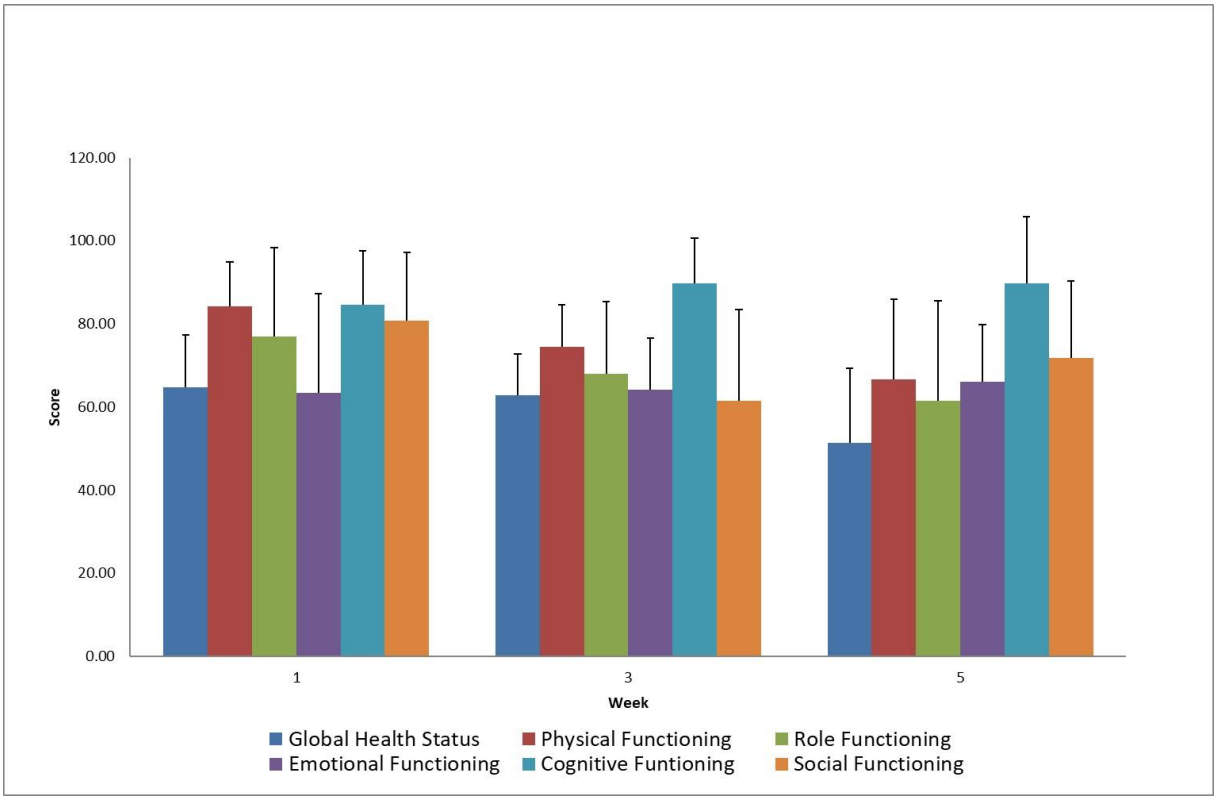

Figure 2. Evaluation of EORTC QLQ-C30 Functional Scale questionnaires score mean value and SD (+), during treatment for all patients.

During the evaluation of the EORTC QLQ-C30 questionnaire regarding general symptoms, we noted an increase in the general adverse reactions experienced during the treatment. Minimal loss of appetite and the decrease in nausea suggest the use of appropriate supportive therapy. A decreased degree of participation in social activities while battling the disease is acceptable during therapy.

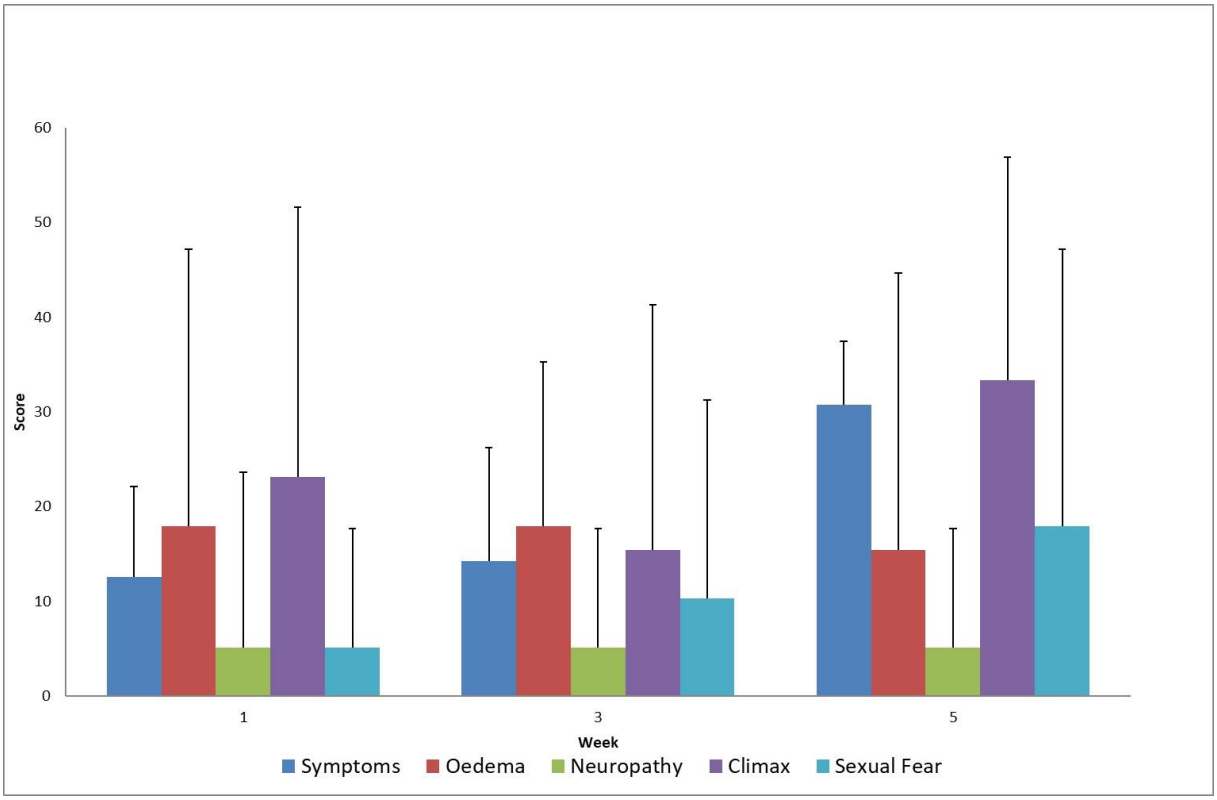

Figure 3. Evaluation of EORTC QLQ-CX24 Symptoms questionnaires score mean value and SD (+), during treatment for all patients.

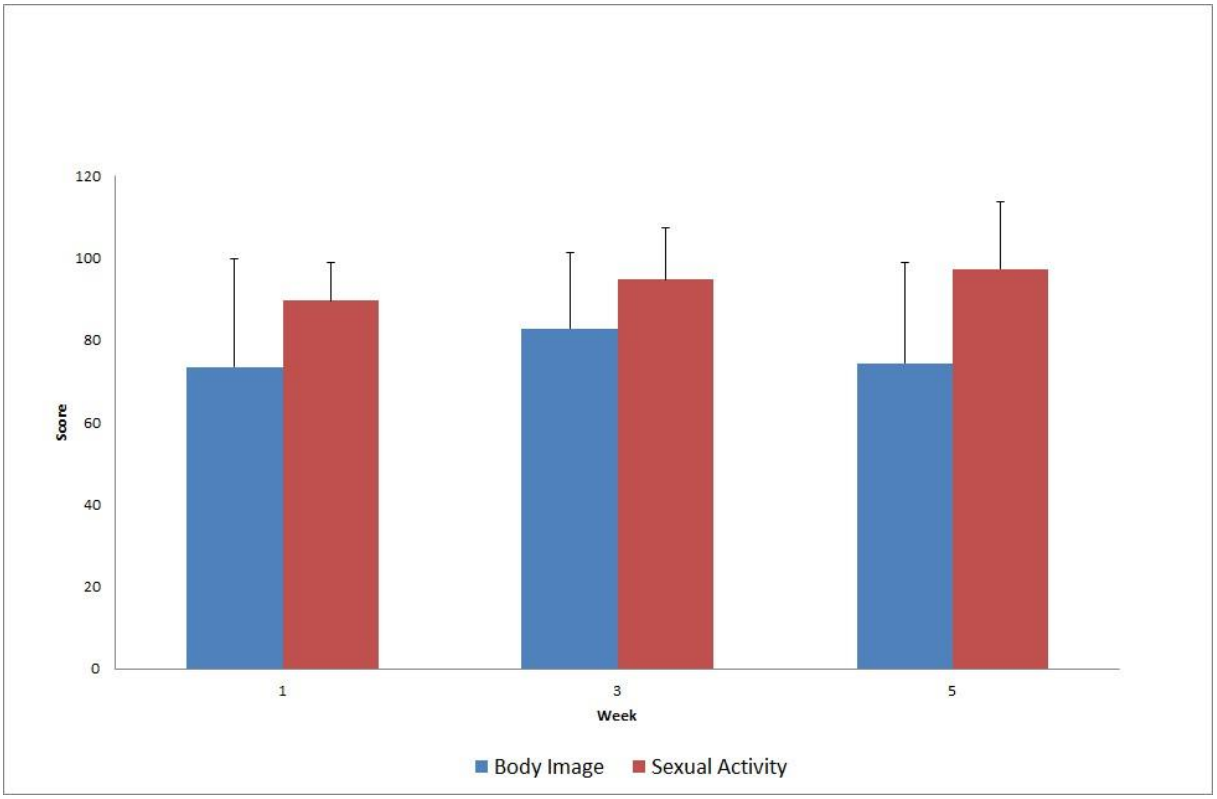

Figure 4. Evaluation of EORTC QLQ-CX24 Functional Scale questionnaires score mean value and SD (+), during treatment for all patients.

The results of EORTC QLQ-CX24 functional scale questionnaire are difficult to interpret because a low willingness to respond was noted during the evaluation of the questionnaire. Thus, the absence of actual changes in sexual activity and body image is questionable.

Supporting the QLQ-C30 questionnaire results, an increase in treatment related symptoms was also observed in the tumor-specific questionnaire. The increase in menopause-like symptoms as a result of iatrogenic infertility caused by radiotherapy is normal side effect and is not specifically associated with the delivery of the SIB dose.

Follow up data:

The data is presented at a median follow-up time of 24.5 months (in a range of 9 to 45 months).

Based on the 3-month follow-up MRI scans after the treatment, an average of 95.31% regression rate was measured in terms of tumor size reduction. Complete response was achieved in 10 patients, and partial response was achieved in 4 patients. (Table II/5.)

Table II/5. Evaluation of the treatment.

	PreTreatment MR Size (mm)	PostTreatment MR Size (mm)	RECIST	Regression Rate (%)
PT-001	25	0	CR	100%
PT-002	22	0	CR	100%
PT-003	47	0	CR	100%
PT-004	42	0	CR	100%
PT-005	80	3	PR	96%
PT-006	59	4	PR	91%
PT-007	49	30	PR	67%
PT-008	85	0	CR	100%
PT-009	52	0	CR	100%
PT-010	60	0	CR	100%
PT-011	82	18	PR	65%
PT-012	67	0	CR	100%
PT-013	35	0	CR	100%
PT-014	38	0	CR	100%

CR: Complete Response, PR: Partial Response

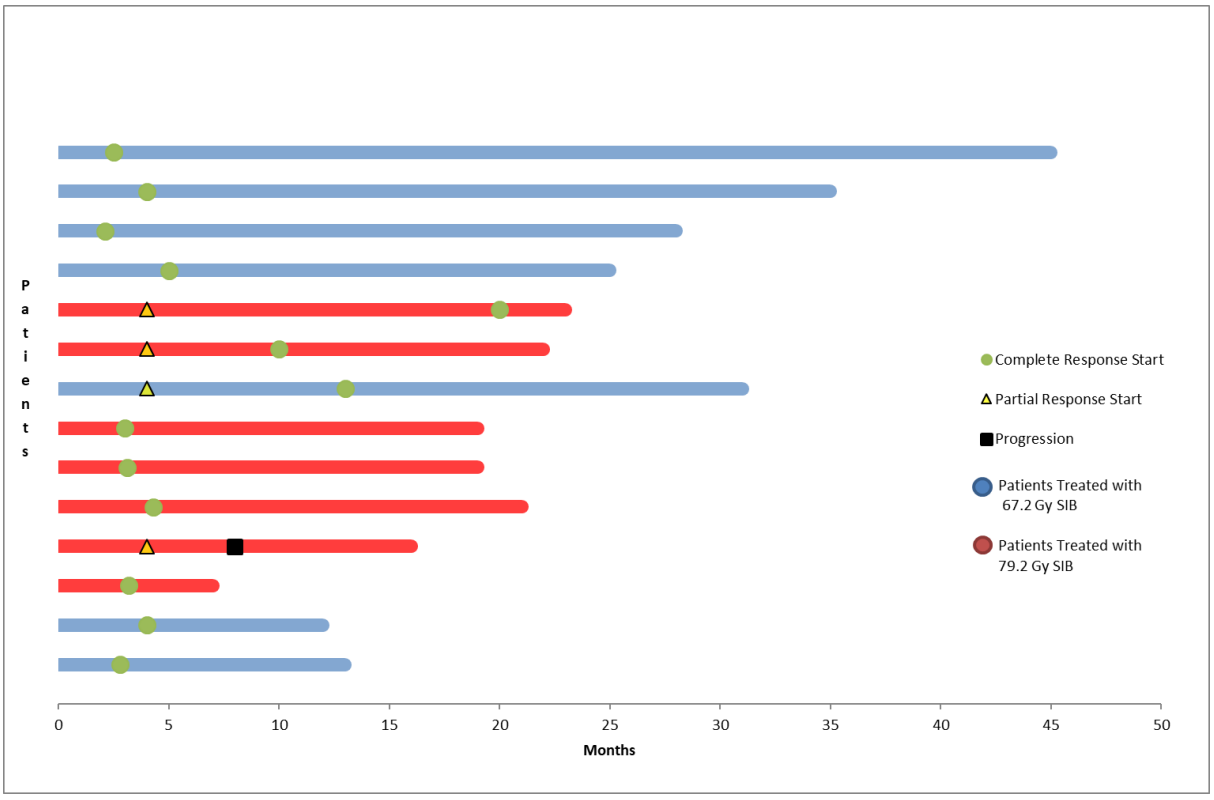

Figure 5. Evaluation of survival data at a median follow-up of 24 months.

After the median 24-month follow-up, the actuarial DFS value was 92,86%.

At the termination of the follow-up, all of the patients were alive and symptom free. Follow-up visit was performed at 3 to 4 months after treatment termination. (Figure 5.).

Complete remission was generally observed upon the first follow-up MRI at 3 to 4 months. In patients with higher tumor volumes receiving higher doses, complete remission occurred more slowly. In this population the first follow-up imaging showed only partial remission in 42% of patients. PET/CT, a diagnostic procedure complemented with biological information, was performed after 2 consecutively positive MRI results. It yielded to a negative result in 5 patients and only 1 patient had a positive result.

As clearly noted, all of our patients are alive. However, disease progression occurred in one patient due to local progression. This patient received chemotherapy at the time of the termination of data collection.

Discussion

A prerequisite of performing state-of-the-art image-guided and ultra-precision, ultra-conformal RT-s is the precise determination of the target volume. This information is great importance for the use of definitive RT in cervical cancer and during a dose escalation study. The mandatory role of MRI and PET/CT scan for detecting the primary and lymph node or distant metastases is shown in several studies. Compared to MRI, the sensitivity of PET/CT in detecting lymph node metastases was 50% and 83%, respectively. The lymph nodes confirmed as abnormal by histology but negative by PET were less than 1 cm in size.

Definitive radiation therapy for cervical cancers is performed in accordance with the following guidelines. The standard treatment in the therapy of this tumor type is the BT boost, which method has been continually improved since the 1960s. In the generally accepted protocols, a total dose of 45 to 50 Gy is delivered to the pelvic region. External beam RT is followed by 3 to 4 sessions of BT at a dose of 7 Gy, which is delivered as a single dose to the residual lesion using the HDR technique. MRI-controlled BT is the most effective method to determinate residual tumor, as Pötter et al suggests. The delivery of the following doses is recommended to the designated target areas: 85 to 90 Gy EQD2 (D90) to CTV-T_{HR}, 60 Gy (D98) to CTV-T_{IR}, and 90 Gy (D98) to GTV_{RES}-T. The coverage of the anatomically defined point “A” should be

kept in mind at all times, which should be 75 Gy (EQD2). Maximum success can be achieved by following these dose requirements. Since the tumor is surrounded by normal tissues, the dose limitations of these tissues must be kept in mind to avoid late toxicity. In the case of HDR BT, the following dose limits relating not to an entire organ but to 2 cc are respected: rectal wall D2cc, 64 Gy; bladder wall D2cc, 85 Gy; and sigmoid colon wall D2cc, 63 Gy. The clinical outcome of MRI based image guided adaptive BT (IGABT) was observed by Pötter et al. Between 2001 – 2008 156 patients were treated with IGABT. In the early IB – IIB stages a 95-100 % local control (LC) could be achieved at 3 year follow up period. In the more advanced stages (IIB/III/IV) LC rates were 85-90 %. Moderate treatment related toxicity was observed in this single-institutional study.

Over 700 patients with cervical cancer were included for IGABT, in the RetroEMBRACE multicenter trial. The LC at 3/5 years for IB, IIB, IIIB was 98%/98%, 93%/91%, 79%/75%. Treatment related morbidity at 5 years was 5%, 7%, 5% for bladder, gastrointestinal tract, vagina. The important results of these studies were the QoL for BT treated patients. The early 24 months' report from the EMBRACE study for vaginal morbidity showed no severe increase. Less than 3.6 % of the patient reported > grade 3 vaginal complaints. Although grade I (89%) and grade II (29%) morbidity was present. The QoL data from the EMBRACE study was observed with the questionnaires of EORTC QLQ-30, and CX-24 from all 744 patients, it was presented in 2015. The questionnaires were completed at the baseline, then every 3 months in the first year, and every 6 months in the second and third year. At the baseline the general and functional QoL was impaired then got better during the follow up period. Tumor related symptoms resolved after treatment, but treatment related symptoms were developed or persisted after treatment ending.

Along with the development of external beam RT, other therapeutic options have also emerged. In addition to the application of the IMRT technique, several stereotactic treatment attempts were made to replace the known treatment algorithm of the tumor. Kilic et al. summarized the research by reviewing publications in the PubMed database. During the review, retrospective studies were found, but 3 prospective studies were also identified. These studies involved low numbers of patients and applied different techniques. Stereotactic boost or IMRT boost were generally performed instead of BT in those cases where either the patient refused the therapy or it was not feasible due to anatomical reasons. In these treatments, total doses of 16 to 36 Gy

were delivered at doses of 1.8 to 6 Gy per fraction. In the realm of intensity-modulated external beam RT, some authors dealt with the issue of replacement of BT in the treatment of cervical cancers. The advantageous features of the technique include better protection of organs at risk and homogenous coverage.

The application of the SIB technique was also proposed by other authors as a possibility for external field dose escalation. Guerrero et al. studied cases of cervical cancer where a BT boost providing appropriate coverage could not be delivered due to the size of the tumor. Theoretically the simultaneous integrated boost (SIB) technique can provide an appropriate alternative. Based on the linear quadratic model used in RT and the calculation of the biologically effective dose, the dose of external beam RT of the pelvis with added BT may be equal to the dose of the SIB technique. In their practice, the following doses were delivered: 25 x 3.1 Gy, –2.8 Gy, –2.4 Gy. Bladder and colon exposure did not exceed average doses of 60 and 70 Gy, respectively. The treatment time could be shortened to 5 weeks. Due to the information above the SIB IMAT treatment technique offers a reassuring alternative to the conventional technique.

Vandecasteele et al. studied the feasibility of arc therapy in patients with inoperable cervical cancer. Based on PET/CT-based planning, the delivery of median doses (D50) of 62, 58, and 56 Gy to the primary tumor was recommended. The delivery of a 60 Gy (D98) dose to PET-positive lymph nodes was recommended. The IMAT technique made the delivery of the dose to the primary tumor and the positive lymph nodes by SIB possible in the 9 cases.

Several studies reporting on the successful application of the SIB technique have been published recently. Wang et al. integrated a dose of 60.2 Gy delivered in 28 fractions into the total pelvic irradiation at a total dose of 50.4 Gy. The integrated boost technique was compared with a regimen of a 3-Gy boost delivered on 3 occasions following conventional fraction delivery (25 x 2 Gy). Both treatment alternatives provided excellent local control values (98% vs. 100%), and no late-onset toxicity was observed.

During their neoadjuvant study involving 30 patients, Vandecasteele et al. integrated the boost dose of 2.48 Gy into 25 fractions, which was delivered in addition to the total pelvic dose of 45 Gy. At the end of the treatment, during the 2-year follow-up period, local control of 96% was achieved. Late-onset adverse reactions were considered acceptable, as grade 4 intestinal toxicity occurred in 4% of the participants, and grade 3 urinary side effects occurred in 14%. O'Donell et al used the National Cancer Database to study women with invasive cervical cancer

who were treated with radiation between 2004 and 2013 either with BT or IMRT or stereotactic body radiotherapy (SBRT) boost. Outcomes were evaluated among 15,905 cervical cancer patients with Kaplan-Meier and propensity score matching. The propensity score match results showed significant difference for patients treated with BT boost than to IMRT boost patients. There was no significant difference for SBRT boost patients. The authors suggest the SBRT boost could be a therapy option. Herrera et al found that SIB treatment for cervix cancer patient is promising but tumor motion should be taken in account to avoid target under-dosing and OAR over-dose. In the study of Morgenthaler et al SBRT boost was performed to 31 cervical cancer patients with IB – IVB stage tumor on Cyberknife. The results were presented at a median follow-up of 40 months. No severe acute toxicity was observed and LC was 92% at 3 and 5 years. The median PFS was 41 months.

The role of brachytherapy is well known in the treatment of cervical cancer. The new development in treatment suggest a population of patient how could benefit of either SBRT or SIB/IMRT. To summarize the findings of these papers further investigation in well-designed prospective clinical studies is requested to find the relevant dose for both techniques.

In this study, an excellent local control rate was achieved with completely tolerable adverse reactions and an acceptable quality of life. With respect to the totality of patients, disease-free survival is good; however, it is difficult to evaluate given the short follow-up period.

However, the limitations of this study are the small patient number and the two different treatment arms, which makes it difficult to interpret our data comparing to previous studies. Although, it strengthens the suggestion, as in other small case studies, for the use of a novel technical approach, SIB, in the treatment of cervical cancer patients with no option for BT.

Conclusion

Based on our results, in patients with advanced cervical cancer who cannot receive brachytherapy boost, definitive external beam radiotherapy with an integrated boost replacing brachytherapy is feasible and may represent an appropriate alternative. Though the routine use of this treatment cannot be recommended yet due to the lack of well-powered comparative studies, the results of this study and the favorable comparison with the standard treatment supports the further evaluation of this technique on a larger patient population.

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