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Original Article

Dosimetric comparison of different treatment planning techniques with International Commission on Radiation Units and Measurements Report-83 recommendations in adjuvant pelvic radiotherapy of gynecological malignancies

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ABSTRACT

Aim: The study evaluates the different treatment planning techniques according to three recommendation levels of the International Commission on Radiation Units and Measurements Report-83 in gynecologic cancer patients treated with adjuvant pelvic radiotherapy (APR).

Materials and Methods: Computerized tomography images of ten endometrial and cervical cancer patients who were treated with APR were assessed. For each patient, five different treatment plans were created. One homogeneity index and four different conformity indexes (CIs) were calculated for three-dimensional conformal radiotherapy (3D-CRT), field-in-field (FIF), seven-field intensity modulated radiotherapy (7-IMRT) with two different degrees beginning (7A-IMRT, 7B-IMRT) and 9-IMRT treatment plans. Dose volume histogram parameters and normal tissue complication probability (NTCP) were compared for organs at risk (OAR).

Results: The CI values of the IMRT were closer to 1 with respect to other plans ($P < 0.05$). The rectum and the bladder volumes which received more than 40 Gy were decreased with IMRT compared to 3D-CRT ($P < 0.05$). Doses received by the 195 cc volume of the small intestine and NTCP values were significantly decreased with IMRT ($P < 0.05$).

Conclusion: IMRT provided more protection than FIF plans at high dose volumes of the OAR; however, it did not show any superiority at low-dose volumes. The NTCP results supported IMRT for only small intestine protection. Because IMRT is increasingly used clinically, the comparison of NTCP will become more common in the near future. Therefore, new prospective studies with sufficient number of patients and appropriate NTCP models are needed for this treatment modality.

KEY WORDS: Conformity index, gynecological cancers, intensity modulated radiotherapy, normal tissue complication probability

INTRODUCTION

Endometrial cancers are the fourth most common female cancer worldwide, and cervical cancers are in the third place among gynecological malignancies.[1] Surgery is the curative treatment modality for endometrial cancers and in the presence of risk factors, adjuvant pelvic radiotherapy (APR) is indicated to decrease pelvic and vaginal relapses.[2,3] The treatment results of early stage cervical cancers with radical surgery or definitive radiotherapy are similar.[4] APR decreases local failure in the presence of high-risk factors after radical hysterectomy for early stage cervical cancers.[5,6]

The addition of APR to surgery increases the frequency and severity of treatment side effects. Gastrointestinal system complications are common due to the large irradiated volumes of intestine and rectum. Although the four-field box

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technique reduces the complication risk when compared to anterior-posterior/posterior-anterior treatment technique, a substantial part of the rectum and bladder still remains in the treatment field.[7] An irregularly shaped isodose line covering the tumor volume can be obtained with intensity modulated radiotherapy (IMRT) while the adjacent organs at risk (OAR) is maintained. However, there have been no prospective randomized phase III clinical trials comparing IMRT and three-dimensional conformal radiotherapy (3D-CRT) in adjuvant treatment of gynecological cancer patients. When retrospective studies and prospective phase II trial of the Radiotherapy Oncology Group (RTOG) 0418 were evaluated, the reduction in chronic complications with IMRT was found to be statistically significant, especially regarding gastrointestinal and hematological toxicities, without a loss of disease control and survival.[8]

The most important and essential steps in IMRT planning are identifying and contouring the target volume and OAR beyond reproach. Target volume and OAR descriptions were described in the International Commission on Radiation Units and Measurements Report-83 (ICRU-83) in detail.[9] The clinical target volume (CTV) should be defined at the beginning of the course because of the lack of gross tumor volume in operated gynecological tumors. A consensus guideline about CTV definitions in the adjuvant treatment of operated endometrial and cervical cancer patients was published by Small *et al*.[10]

Throughout the history of radiotherapy, the aim has always been to provide maximal coverage of the target volume with more homogeneous dose distribution and maximal healthy tissue sparing.[11] ICRU-83 has grouped the recommendations about prescribing and reporting into three levels. Level-I is the minimum standard radiotherapy requirements for two-dimensional (2D) dose distribution on the central axis. Level-II involves 3D imaging to create a plan. Absorbed dose distributions and dose volume histograms (DVHs) are obtained with treatment planning algorithms that include inhomogeneity corrections. A quality assurance program is essential. Level-III includes newly developed techniques and approaches such as tumor control probability and normal tissue (NT) complication probability (NTCP), which are not used in the clinical standard.[9]

The aim of this study was to evaluate different treatment planning techniques (3D-CRT, field-in-field [FIF], IMRT) according to the three recommendation levels of ICRU-83 for planning target volume (PTV), OAR and NT remaining in the radiation field and with four different calculations of conformity index (CI) in gynecological cancer patients treated with APR.

MATERIALS AND METHODS

Computerized radiotherapy planning data of ten patients (five endometrial cancers and five cervical cancers) who were treated with APR in the Radiation Oncology Department, were retrospectively assessed.

Simulation and contouring

Patients were scanned in the supine position with the arms on the chest and computerized tomography (CT) (GE-LightSpeed 64, GE, US) images were obtained with adjacent axial slice spacing of 2.5 mm with intravenous contrast, covering the entire pelvis from the upper abdomen to the bottom of the perineum with a full bladder. CTV-tumor bed included the preoperative tumor bed with the vagina and paravaginal soft tissue ending at the lower limit of the obturator fossa. CTV-lymph nodes covered the common, external, and internal iliac nodal groups from the L5 vertebral level at the top and the presacral lymph node group up to the S3 vertebral level. The PTV was generated by adding a 7 mm axial margin to CTV-lymph nodes, 7 mm posterior, and 10 mm in the other directions of the CTV-tumor bed. The OAR outlined were the bladder, the rectum from the anal canal to the sigmoid curve, the bilateral femoral heads, and the small intestine surrounding the PTV. All tissue except the PTV in the treatment field was defined as NT.

Treatment planning

Five different treatment techniques were assessed with fixed parameters of 50.4 Gy total dose given in 28 fractions at 1.8 Gy/day. For each patient, one 3D-CRT, one FIF, and three different IMRT plans were designed with the CMS XiO (Elekta®, UK) treatment planning system (TPS). 3D-CRT and FIF plans were performed using 18 MV and IMRTs were planned with 6 MV photons. Four-field box technique was used for both 3D-CRT and FIF plans. Seven-field IMRT plans were designed with different angles between 51° with a gantry onset of 0° (7A-IMRT) or 26° (7B-IMRT). Equal 40° of gantry angle was used for the 9-IMRT plans. The goal was to provide 98% of the prescribed dose by 95% PTV coverage.

Treatment plan evaluation

Level-I

The simple 2D absorbed dose distributions over the transverse section in the center of the PTV were checked.

Level-II

The appropriateness of the dose distribution was checked visually on the transverse, coronal, and axial planes. DVHs were evaluated for the PTV, OAR, and NT. The quantitative analysis of NT Effects in the Clinic (QUANTEC) recommendations was used as a guide for OAR evaluation.[11] Homogeneity index (HI) was calculated according to ICRU-83, and four different CI values were calculated for the PTV according to the RTOG (CI_A), Saint-Anne-Lariboisiere-Tenon (SALT) (CI_B), Lomax and Scheib (CI_C), and Van't Riet *et al*. (CI_D) criteria [Table 1].[12]

Level-III

The NTCP calculation is an effective volume method proposed by Lyman and developed by Kutcher and Burman.[13] In this model, NTCP for uniform dose D of an organ is given by

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$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{u} e^{-t^2/2}\, dt \quad (1)$$

Where,

$$u = \frac{D - TD_{50}(V)}{m \times TD_{50}(V)} \quad (2)$$

m is a dimensionless parameter and TD_{50} is the whole organ tolerance dose for 50% complication probability after 5 years.[14]

$$TD_{50}(V) = \frac{TD_{50}(1)}{V^n} \quad (3)$$

The n, m, and TD_{50} values of the corresponding OAR as defined by Emami *et al*. were used for the calculation of NTCP in the TPS.[15] The primary endpoints of these values were contracture or volume loss of the bladder, obstruction or perforation of the small intestine, severe proctitis, necrosis, stenosis, or fistula of the rectum and necrosis of the femoral heads.

Statistical analysis

The Statistical Package for Social Sciences version 15.0 (SPSS Inc., LEAD Technologies, 1991/US) was used for the statistical analysis. The Friedman test and Wilcoxon signed-rank test were used for comparisons. $P < 0.05$ was considered to be significant.

RESULTS

The minimum, maximum, and mean values of HI and four different CI are shown in Table 2. All HI values were in the range of 0.09 ± 0.01. There was no statistical difference between the CI_B calculations of the plans. According to other calculations, the CI values were significantly closer to 1 for FIF when compared to 3D-CRT plans and also for IMRT when compared to FIF plans ($P < 0.05$).

Rectum

The V_{45} and V_{50} values were decreased with the FIF and IMRT plans compared to 3D-CRT ($P = 0.005$). Between FIF and IMRT, significant differences were found in favor of IMRT ($P = 0.005$) [Figure 1].

Bladder

A statistically significant decrease was observed in V_{40} and higher dose volumes with all IMRT plans when compared to FIF ($P = 0.005$) [Figure 2].

Small intestine

Doses received by the 195 cc volume were significantly higher in 3D-CRT with respect to other plans ($P < 0.05$) [Figure 3]. The dose was decreased with FIF and decreased even further with IMRT, with a statistically significant difference ($P < 0.05$). V_{30} and higher dose volumes were decreased with all plans when compared to 3D-CRT ($P < 0.05$) [Figure 4].

Normal tissue

For tissues in the treatment volume but outside of the PTV, volumes receiving 50% and 90% of prescribed dose were significantly decreased with FIF compared to 3D-CRT and with IMRT compared to FIF ($P = 0.005$) [Figure 5].

Table 1: Four different conformity index criteria

RTOG* (CI_A)	CI=V_{RI}/TV	Target coverage based on isodose line
SALT* (CI_B)	Geometric CI=LUF + HTOF LUV=$LV_{<RI}$/LV	Target coverage based on volumes
Lomax and Scheib (CI_C)	Healthy tissue CI=TV_{RI}/TV	Adjacent normal tissue coverage with RI
Van't Riet *et al.* (CI_D)	Conformation number=TV_{RI}/TV × TV_{RI}/V_{RI}	Both target and normal tissue evaluation

*RTOG=Radiation Therapy Oncology Group, SALT=Saint-Anne-Lariboisiere-Tenon. V_{RI}=Volume of the reference isodose, TV=Target volume, LUF=Lesion under dosage factor, HTOF=Healthy tissue overdosage factor, $LV_{<RI}$=Lesion volume receiving isodoses < reference isodose, LV=Lesion volume, HTV_{RI}=Healthy tissue volume covered by their reference isodose, TV_{RI}=Target volume covered by the reference isodose, CI=Conformity index, RI=Reference isodose

Table 2: Four different conformity index and homogeneity index values for planning target volume

	CI_A	CI_B	CI_C	CI_D	HI
3D-CRT					
Minimum	1.80	0.96	0.48	0.46	0.10
Maximum	2	0.97	0.54	0.52	0.11
Mean	1.89	0.96	0.51	0.49	0.10
FIF					
Minimum	1.60	0.96	0.53	0.51	0.07
Maximum	1.8	0.97	0.59	0.57	0.10
Mean	1.69*	0.96	0.57*	0.54*	0.08
7A-IMRT					
Minimum	1.10	0.97	0.82	0.80	0.08
Maximum	1.2	0.98	0.91	0.88	0.12
Mean	1.13*	0.97	0.85*	0.83*	0.09
7B-IMRT					
Minimum	1	0.96	0.81	0.79	0.09
Maximum	1.2	0.98	0.92	0.86	0.13
Mean	1.13*	0.97	0.85*	0.82*	0.10
9-IMRT					
Minimum	1	0.96	0.76	0.74	0.08
Maximum	1.3	1.07	1.11	0.90	0.14
Mean	1.11*	0.98	0.88*	0.84*	0.10

*Statistically significant results when compared to 3D-CRT ($P<0.05$). CI_A=RTOG, CI_B=Saint-Anne-Lariboisiere-Tenon, CI_C=Lomax and Scheib, CI_D=Van't Riet *et al.*, HI=Homogenity index, 3D-CRT=Three-dimensional conformal radiotherapy, FIF=Field in field technique, 7A-IMRT=0°-51°-102°-153°-204°-255°-306°, 7B-IMRT=26°-77°-128°-179°-230°-281°-332°, 9-IMRT=0°-40°-80°-120°-160°-200°-240°-280°-320°, CI=Conformity index, IMRT=Intensity modulated radiotherapy

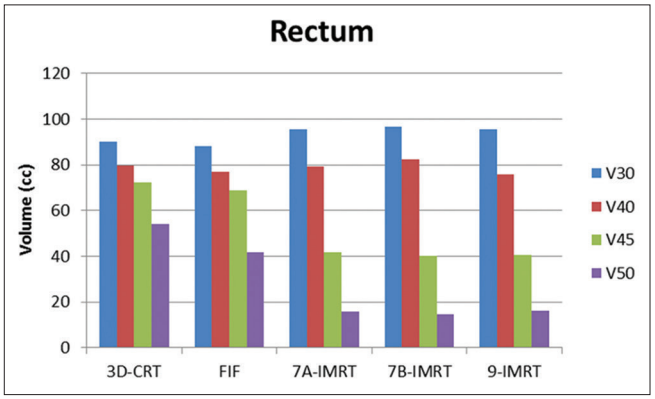


Figure 1: The mean V_{30}, V_{40}, V_{45}, V_{50} values of the rectum

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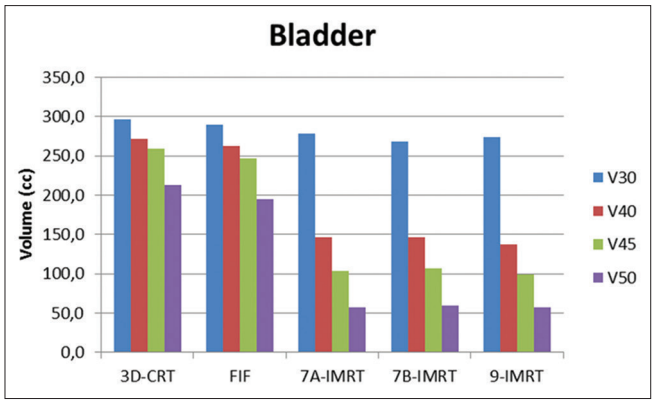


Figure 2: The mean V_{30}, V_{40}, V_{45}, V_{50} values of the bladder

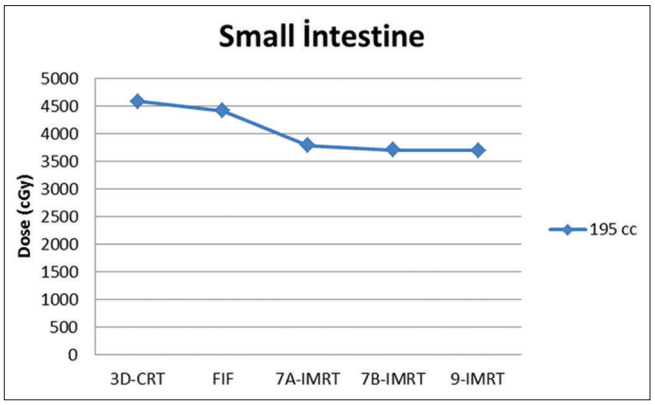


Figure 3: The mean doses received by the 195 cc volumes of the small intestine

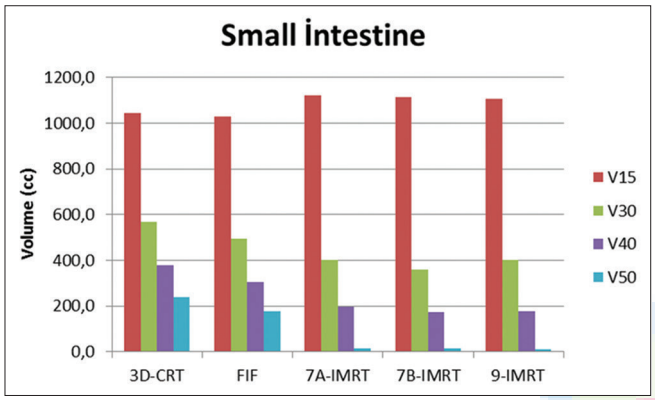
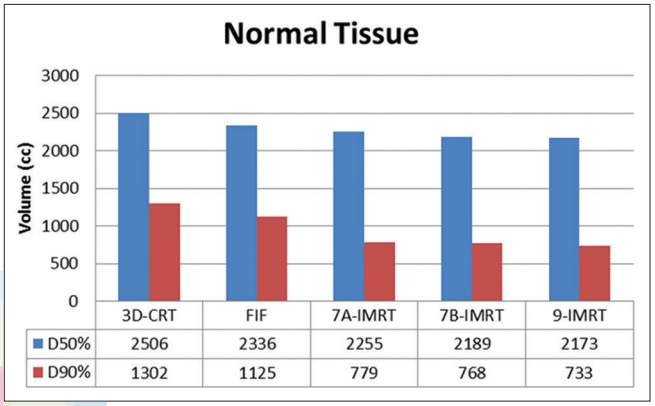
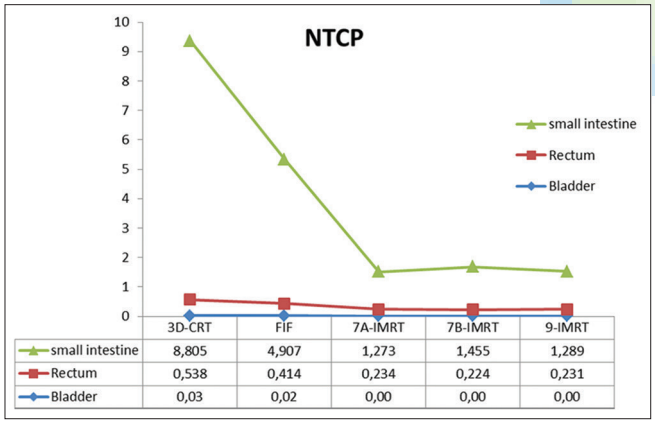


Figure 4: The mean V_{15}, V_{30}, V_{40}, V_{50} values of the small intestine



	3D-CRT	FIF	7A-IMRT	7B-IMRT	9-IMRT
D50%	2506	2336	2255	2189	2173
D90%	1302	1125	779	768	733

Figure 5: The mean volumes received 50% and 90% of the prescribed dose for the normal tissue



	3D-CRT	FIF	7A-IMRT	7B-IMRT	9-IMRT
small intestine	8,805	4,907	1,273	1,455	1,289
Rectum	0,538	0,414	0,234	0,224	0,231
Bladder	0,03	0,02	0,00	0,00	0,00

Figure 6: The mean normal tissue complication probability values of the small intestine, rectum, and bladder

Depending on the prescribed dose received by the PTV, the NTCP was found to be <1% for both the rectum and bladder. The NTCP of the small intestine was significantly decreased with FIF when compared to 3D-CRT and with all IMRT plans compared to FIF ($P = 0.005$) [Figure 6].

DISCUSSION

In radiotherapy, the objective of all planning techniques is to get the best plan that surrounds the prescribed isodose line of the tumor volume while healthy tissues are irradiated as little as possible. This requires an assessment by studying different techniques from different angles for each patient. Slice by slice isodose assessment and/or DVH assessment may be sufficient for target volume evaluation; however, it is useful to compare the different plans with a reliable and easy CI formula, which also considers the target volume with OAR doses. CI is not used routinely, but it is a very important tool for the comparison of different treatment plans and in the long-term evaluation of new modalities and treatment machines. Feuvret *et al.* reviewed different CI calculations. CI_A (RTOG criteria) calculated the quantitative evaluation as well as the required reference isodose that covers the target volume seen on CT scans. The requirement supplied by CI_B (SALT criteria) was based on the evaluation of the intersecting area between the target and the reference isodose volume. Both formulations could not provide a risk assessment for normal organs and tissues. CI_C (Lomax and Scheib) allowed for an evaluation of the critical organs and NT with the reference isodose volume remaining outside the target volume, but could not make an assessment of the target volume. CI_D (Van't Riet *et al.*) evaluated both the target volume and OAR.[12] In our study, the IMRT plans were shown to achieve significantly better coverage of the target volume with CI_A ($P < 0.05$). While the difference between treatment

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plans disappeared with the CI_B results, CI_C evaluations of the IMRT plans were shown found to be better for the protection of the OAR. IMRT CI_D results were significantly closer to 1 with respect to other plans ($P < 0.05$). Our CI results show that the isodose lines surrounding the target volume were covered less NT volume with IMRT, but did not provide information about how NTs were influenced by the dose outside the reference isodose. When NTs except PTV were evaluated, the 50% and 90% volumes of the prescribed dose were decreased statistically significantly with IMRT ($P < 0.05$).

Yavas *et al*. compared the 3D-CRT and FIF planning techniques in ten early stage endometrial cancer patients who were treated with adjuvant radiotherapy and found a statistically significant reduction in the maximum dose for PTV ($P < 0.001$) along with statistically better HI values ($P < 0.001$) using FIF. The volumes receiving more than 45 Gy of the bladder, rectum, small intestine, bilateral femoral heads, and OAR containing the bone marrow were decreased significantly by FIF ($P = 0.039$, 0.016, 0.01, 0.04, and 0.01, respectively).[16] In the current study, although the reduction in both the maximum dose to the PTV ($P = 0.005$) and the HI values ($P = 0.006$) were significantly in favor of FIF with respect to 3D-CRT, both of the results were in acceptable range. In the OAR assessments, the volume receiving more than 30 Gy in the bladder, rectum, and small intestine decreased significantly with FIF when compared to 3D-CRT ($P < 0.05$).

Heron *et al*. compared the four-field box technique and 7-IMRT in their study. The reduction in the volumes receiving 30 Gy or more of the bladder, rectum, and small intestine were 36%, 66%, and 52%, respectively. All DVH values of the IMRT plans were reported to be superior to 3D-CRT.[17] In our study, the V_{30} and V_{15} values of the rectum and the small intestine were increased by 6% for both of the 7-IMRT planning techniques; on the other hand, the rectum V_{45}, the bladder V_{30}, and the small intestine V_{40} values decreased by 79%, 85%, and 58%, respectively.

Roeske *et al*. compared the four-field box and 9-IMRT plans in ten patients with cervical or endometrial cancer undergoing whole pelvic radiotherapy. In their study, rectum, bladder, and small intestine volumes receiving the treatment dose were decreased significantly ($P = 0.0005$, $P = 0.0002$, and $P = 0.0005$, respectively). Both the rectum and the bladder irradiated volumes were reduced with IMRT at 25 Gy and higher doses. Small intestine irradiated volumes were larger when compared to 3D-CRT up to 30 Gy.[18] In our study, the small intestine and the bladder volumes receiving more than 30 Gy decreased significantly with 9-IMRT when compared to 3D-CRT ($P < 0.005$). For the rectum, V_{30} increased significantly ($P = 0.005$). Volume reduction started at higher doses and became statistically significant after 45 Gy ($P = 0.005$). 3D-CRT plans yielded better results with respect to FIF and IMRT for doses below 30 Gy, however this might have been solely due to technique since no dose constraints were applied in FIF and IMRT plans for low-doses in this study.

A meta-analysis by Yang *et al*. analyzed 13 studies to perform a dosimetric comparison of the 3D-CRT and IMRT plans in patients with gynecological malignancy. When compared to the volume of the rectum receiving <30 Gy, there was no statistically significant difference between IMRT and 3D-CRT. A statistically significant dose-response relationship was observed between decreasing volume (%) and increasing dose ($P = 0.003$). For the rectum, 26.40% ($P = 0.004$), 27.00% ($P = 0.040$), 37.30% ($P = 0.006$), and 39.50% ($P = 0.002$) decreases were obtained with IMRT at V_{30}, V_{35}, V_{40}, and V_{45}, respectively. The evaluation of the small intestine in the same study yielded a 17.80% decrease at V_{40} ($P = 0.043$) and %17.30 at V_{45} ($P = 0.012$) with IMRT. There was no significant difference between IMRT and 3D-CRT in the irradiated small intestine volume at 20 Gy and below. A nonsignificant decrease of more than 10% was observed with IMRT in the small intestine volume between 25 and 35 Gy. The bladder and the irradiated bone volume with IMRT did not show any statistically significant superiority to 3D-CRT.[19]

ICRU-83 stated that especially leading up to higher doses with advanced technology, the importance of a biological evaluation has increased.[9] Organ damage risk varies depending on cell type, response of the target volume to the total dose and/or the dose per fraction. At the same time, the risk also varies whether the OAR is parallel or serial. NTCP is the possibility of complications due to the damaged OAR volume. In our study, only the small intestine volume had an increased dose-specified risk of causing complications. The NTCP values for the small intestine were consistent with the DVH evaluation. The QUANTEC recommends that, to decrease the incidence of acute toxicity below 10%, 195 cc of the irradiated small intestine volume should receive < 45 Gy.[20] In our study, the V_{45} values for 3D-CRT, FIF, 7A-IMRT, 7B-IMRT, and 9-IMRT were 305, 254, 102, 92, and 92 cc, respectively. V_{45} was decreased significantly with IMRT ($P < 0.05$). Simpson *et al*. reported on fifty cervical cancer patients treated with definitive, postoperative, or extended field concurrent chemoradiotherapy. In this trial, 9-IMRT was used, and acute GI toxicity with dosimetric parameters was retrospectively evaluated by an appropriate NTCP model. Small intestine's V_{45} was significantly higher for Grade 2 and higher toxicity ($P = 0.043$). Furthermore, V_{15}, V_{20}, V_{35}, and V_{40} were found to be statistically significant for acute side effects ($P = 0.046$, $P = 0.043$, $P = 0.04$, and $P = 0.03$, respectively).[21] In our study, the low-dose small intestine volumes of the IMRT plans were similar to conformal planning, but at 30 Gy and higher, the doses decreased significantly. The statistically significant reduction in the small intestine NTCP values in favor of 7-IMRT and 9-IMRT could suggest that side effects are associated with higher doses rather than low-doses. However, as our knowledge, new prospective studies with sufficient number of patients and an appropriate NTCP model are needed.

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Radiotherapy is an important part of the therapy in gynecological cancers. IMRT provides better dose distribution than FIF plans for the higher dose volumes of the OAR. However, only small intestine protection had statistically significant advantage for IMRT in NTCP calculations. Since IMRT is increasingly used in the clinic, new prospective studies with sufficient number of patients and appropriate NTCP models are needed for this treatment modality.

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Conflicts of interest
There are no conflicts of interest.

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