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HDR brachytherapy and supervoltage external beam therapy of cervical cancer: Protection of the intestinal tract during the treatment

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BACKGROUND: *During radiotherapy in most of the irradiated patients occur the symptoms of acute radiation enteritis, less frequently cystitis or proctitis. The aim of this work was to apply non-invasive exclusion methods to reduce the small bowel volume within the pelvic high dose volume and indirectly to reduce the number and severity of acute radiation enteritis.*

METHODS: *A total number of 183 patients were enrolled in our prospective randomised investigation we performed at the Clinic of Oncology in Knez Selo during one year. Ninety patients from E-group were irradiated with the standard technique - two opposite parallel fields on the Mevatron-7445 linear accelerator (SIEMENS) patient-table, while 93 from C-group were irradiated under special conditions on our unique patient-table (PT) manufactured at our special demands by the Jugorendgen Ei-Niš factory. Brachytherapy was administered with RALT technique in both groups with isotope machine BUCHLER.*

RESULTS: *Individual application of exclusion techniques led to protection of over 50% of the small bowel (118-1065 cm^3) in 30/43 (70%) patients, and even in 10/43 (23%) more than 90% of the small bowel was protected (118-835 cm^3), which would otherwise be irradiated with conventional techniques. None of the patients from E-group (out of 90) had more than 8 stools a day (G3), while in C-group there were 20 such cases. Seventy-seven percent of the patients from E-group had formed stool, while the percent in C-group was 29. In C-group 40% of the patients had so called "watery stools"; in E-group the percent was 4. Out of 53 patients from K-group with mobile small bowel, 21 (40%) had "watery diarrhoea".*

CONCLUSION: *Measures to prevent radiation enteritis should be taken before (surgical) or during (non-invasive) radiotherapy. At the Clinic of Oncology in Knez Selo, individual application of small bowel exclusion techniques using the unique patient-table (JUGORENDGEN Ei-Niš) led to protection of the small bowel during radiotherapy of uterine malignancies, which was reflected in a significantly reduced number and severity of acute enteritis symptoms.*

KEY WORDS: *Cervix Neoplasms; Radiotherapy; Radiation Injuries; Enteritis*

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INTRODUCTION

Radiotherapy of malignant uterine tumours inevitably leads to damage of adjacent normal tissues and organs in pelvis. Though most sensitive to ionising radiation, the small bowel is less frequently permanently damaged (due to its movability), except at the level of terminal ileum compared to the bladder or rectum. However, if any damage occurs it is so severe and life threatening (obstruction, perforation) that the whole oncologic treatment is compromised. During radiotherapy, in most of the irradiated patients occur the symptoms of acute radiation enteritis, less frequently cystitis or proctitis. The complaints are usually transient and respond to symptomatic medical therapy or temporary break in radiotherapy course. The symptoms of radiation

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enteritis are directly associated with the irradiated small bowel volume, while late digestive consequences correlate with the previous pelvic surgery and small bowel volume receiving >45 Gy. It may well be said that acute complications are volume-dependent, while chronic sequelae are dose-dependent. Reduction of transcutaneous pelvic dose would result in reduction of number and severity of radiation enteritis symptoms, but local tumour control would be compromised. Therefore, efforts should be directed to the reduction of the small bowel volume within the pelvic high dose volume (1-3).

Application of non-invasive exclusion methods to reduce the small bowel volume within the pelvic high dose volume and indirectly to reduce the number and severity of acute radiation enteritis symptoms during transcutaneous radiotherapy of malignant uterine tumours.

MATERIALS AND METHODS

A total number of 183 patients were enrolled in our prospective randomised investigation we performed at the Clinic of Oncology in Knez Selo during one year. They were divided into two groups - experimental (E) and control (C), statistically not different from one another. We monitored 38 parameters for the patients in group C and 58 parameters for the patients in group E. All the parameters we monitored may be divided into three categories. The first category of parameters included patient's general data, anamnesis and factors predisposing to radiation enteritis. Those factors were: age, clinical diagnosis (FIGO), histopathology, surgery, type of radiotherapy, period from operation to radiotherapy (for those with surgical intervention) or the period from the consultative decision to the beginning of radiotherapy (for those without surgery), body weight, height, circumference of the abdomen, glycemia, blood pressure, previous abdominal and/or pelvic surgery, number of stools per day, previous inflammations of gynaecologic or other pelvic organs, in/out-patient status. The second group comprised mathematical/physical parameters associated with radiotherapy planning, which differed according to the methods applied. We observed the following in both groups: the length and width of radiation field (for pelvis and paraaortic space if possible), AP diameter, transcutaneous and intracavitary dose (in Gy), movability of the small bowel (mobile, relatively immobile, fixed), high dose volume, small bowel volume within the high dose volume and its proportional involvement in patients with lateral radiographs, i.e. whether the small pelvis radiological opening was observed as "free" from small bowel loops, more or less than a half, and whether the pronation was superior (regarding small bowel exclusion) to supination. For the patients from E-group, we additionally monitored parameters related to individualised radiotherapy planning and the use of radiation table. They were: absolute and proportional reduction of AP diameter, high dose volume and involvement of small bowel within that volume at irradiation under special circumstances, as well as the absolute and proportional value of the small bowel thus protected. The third group of parameters was collected during morning visits and graded according to severity (EORTC/RTOG recommendations - SOMA/LENT scale). Ninety patients (E-group) were irradiated with the standard technique - two opposite parallel fields on the Mevatron-7445 linear accelerator (SIEMENS) patient-table (PT), while 93 patients from C-group were irradiated under special conditions on our unique patient-table manufactured on our special demands by the JUGORENDGEN Ei-Niš factory. This table has dual purpose. In the phase of radiotherapy planning, (after barium application, with the "belly board", Trendelenbourg position, and after bladder filling, compression of the anterior abdominal wall etc.) we tried on this table to determine the patient position in which the largest volume of his small bowel is situated outside the high dose volume and so maximally radioprotected. In the phase of radiotherapy application the table offers simple patient positioning and reproducibility.

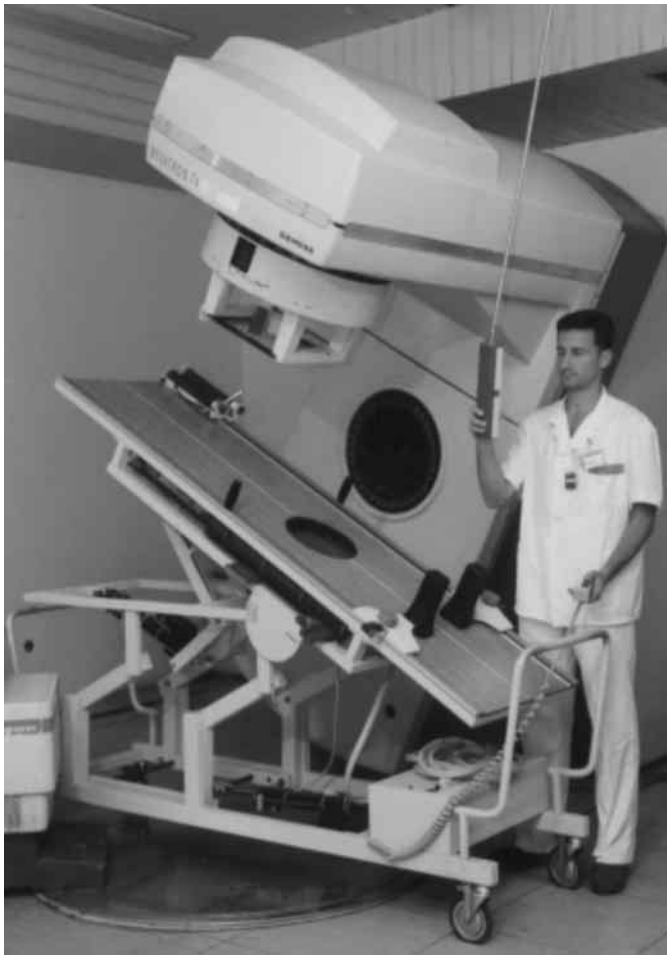

Figure 1. Radiotherapeutic table with which non-invasive small bowel exclusion from the high dose pelvic volume was obtained

Brachytherapy was administered with RALT technique in both groups with isotope machine BUCHLER and three Cs-137 sources (one intracervical and two in lateral vaginal fornices), which with coupling system were brought into the intracavitary placed leaders. The machine was adjusted to the MDR/HDR border according to the dose rate.

RESULTS

High dose volume was defined with the radiation field width, length and AP diameter. Average high dose volume in 183 enrolled patients was 5752 ± 1047 cm^3: 3360-8721 cm^3 for group E and 4080-8874 cm^3 for C-group. Average reduction of AP diameter (achieved with non-invasive exclusion technique) for patients in E-group was 2.91 ± 1.36 cm, which produced reduction of high dose volume by 738.00 ± 343.15 cm^3 (13.05 ± 5.25%). Small bowel volume within the high dose volume was calculated for 89/183 patients (49%). Average small bowel volume within the radiation field was 828.73 ± 388.53 cm^3. However, this was not the irradiated volume for the patients in E-group. Due to individual small bowel exclusion, 0-1431 cm^3 was irradiated and 14-1065 cm^3 was protected. Average small bowel volume reduction within the high dose volume with patients from E-group was 487.84 ± 249.52 cm^3 (63.23 ± 26.23%). Individual application of exclusion techniques led to the protection of over 50% of the small bowel (118-1065 cm^3) in 30/43 (70%) patients, and in 10/43 (23%) even more than 90% of the small bowel was protected (118-835 cm^3), which would otherwise be irradiated with conventional techniques. Two patients from E-group had 100% small bowel exclusion, thus 100% small bowel protection. Before radiotherapy, we established anamnestically that 73 (81%) patients from E-group and 77 (83%) patients from C-group did not have problems with their stool regarding consistency or frequency (Table 1).

Table 1. Anamnestic status of the patients relating to stool consistency

	E-group		C-group		Total	
	Nº	%	Nº	%	Nº	%
Diarrhoea	1	1.1	1	1.1	2	1.
Obstip./diarrhoea			1	1.1	1	0.
Obstipatio	16	17.8	14	15.1	30	16.
No problem	73	81.1	77	82.7	150	82.
Total	90		93		183	100.

Anamnestic status of the patients in the groups was not statistically different in relation to stool consistency immediately before radiotherapy (χ^2 = 1.19; p > 0.05)

During radiological preparation for transcutaneous radiotherapy, small bowel mobility was established with small bowel passage in all patients. Complete mobility was established in 105 (57%) patients, relative mobility in 25%, and total fixation in 18% (Table 2). Almost two-thirds of patients from E-group still have normal number of stools daily, while that percent is 24 in C-group. None of

Table 2. Small bowel mobility

Small bowel mobility	E-group		C-group		Total	
	Nº	%	Nº	%	Nº	%
R-immobile	22	24.4	23	24.7	45	24.
Fixated	16	17.8	17	18.3	33	18.
Mobile	52	57.8	53	57.0	105	57.
Total	90		93		183	100.

The structure of the groups in view of the small bowel mobility was similar (χ^2 = 0.013; p > 0.05)

90 patients from E-group had more than 8 stools a day (G3), while in C-group there were 20 of such cases (Table 3).

Table 3. Stool frequency

Stool frequency	E-group		C-group		Total	
	Nº	%	Nº	%	Nº	%
G1	24	26.7	36	38.6	60	32.8
G2	7	7.8	14	15.1	21	11.5
G3	0	0	20	21.5	20	10.9
Const G2	1	1.1			1	0.5
Const G3			1	1.1	1	0.5
Normal	58	64.4	22	23.7	80	43.8
Total	90		93		183	100.0

Const. G2 - 2 stools a week
Const. G3 – only 1 stool a week
The number of stools, as an index of radiation enteritis seriousness, is significantly higher in the C - vs. E - group (χ^2 = 42.896; p < 0.001)

This means that one-third of the E-group patients had slight (G1 - 2-4 stools daily) or moderate diarrhoeas (G2 - 5-8 stools daily). In both groups none of the patients had refractory diarrhoea (categorised as G4). Frequency of bowel emptying a day was reversely proportional to bowel mobility. More mobile small bowel would produce a smaller number of stools in case of radiation enteritis in E-group. Seventy-seven patients from E-group had formed stool, while the percent in C-group was 29. Most illustrative is the information that in group C 40% of the subjects had so called "watery stool"; in E-group the percent was 4. Stool consistency was significantly worse in control than in experimental group ($\chi 2 = 48.17$; $p < 0.001$) (Table 4).

Table 4. Stool consistency

Stool consistency	E-group		C-group		Total	
	Nº	%	Nº	%	Nº	%
G1	69	76.7	27	29.0	96	52.
G2	16	17.8	28	30.1	44	24.
G3	4	4.4	37	39.8	41	22.
Constipatio	1	1.1	1	1.1	2	1.
Total	90		93		183	100.

Stool consistency was significantly worse in the C - vs. E- group (χ^2 = 48.17; p < 0.001)

A direct relation between the small bowel mobility and faeces consistency was found: 87% of E-group patients with mobile bowel had formed stools, compared with only 44% in those with fixed bowel loops. Out of four E-group patients three had fixed loops, while just one had totally mobile small bowel. Out of 53 C-group patients with mobile small bowel, 21 (40%) had "watery diarrhoea" (Table 5).

Table 5. Stool consistency in relation to bowel mobility

Stool consistency	Small bowel mobility							
	Mobile		R-mobile		Fixated		Total	
C-group	Nº	%	Nº	%	Nº	%	Nº	%
G1	17	32.1	5	21.7	5	29.4	27	29
G2	14	26.4	7	30.4	7	41.2	28	30
G3	21	39.6	11	47.8	5	29.4	37	39
Constipatio	1	1.9					1	1
Total	53		23		17		93	100

Stool consistency in patients with mobile, relatively mobile or fixated small bowel, in the control group, was not significantly different ($\chi^2 = 3.11$; $p > 0.05$)

Even more illustrative is the information that these 21 patients comprised 57% out of 37 C-group patients with serious "watery diarrhoea". The visibility of small pelvis radiological opening in AP graphs is important in the evaluation is important in the evaluation of faeces consistency, for quick orientation purposes of a radiotherapist. Seventy-seven percent of the patients with visible whole radiological opening (free of barium filled loops) had formed stools. During and also between bowel emptying, clinical picture of radiation enteritis was characterised by pains and cramps in the abdomen, the intensity of which varied from minimal and occasional (G1) to refractory (G4). One third of C-group patients did not have pains, while 81% of E-group patients had the whole therapy course free from pains (Table 6).

Table 6. Pain frequency

Pain	E-group		C-group		Total	
	Nº	%	Nº	%	Nº	%
G1	12	13.4	28	30.1	40	21.9
G2	2	2.2	27	29.0	29	15.8
G3	2	2.2	5	5.4	7	3.8
Constipatio G2	1	1.1	1	1.1	2	1.1
Without pain	73	81.1	32	34.4	105	57.4
Total	90		93		183	100.0

Pain was significantly more frequent in the C - vs. E - group ($\chi^2 = 45.21$; $p < 0.001$)

Intensive and persistent pain (G3) occurred in two E-group and five C-group patients. Future detrimental consequences of the small bowel irradiation a radiotherapist may predict by reviewing the AP graphs. Filling up of the small pelvis radiological opening with the small bowel loops is proportional to the pain that occurs during radiotherapy of pelvic malignancy. For a clinician, predictive value of this quick orientation is very important. Loperamide (an antidiarrheal) use was monitored, and it was concluded that this medication was used in 47% of C-group patients, and in only 10% of E-group patients (Table 7), i.e. almost every other patient from C-group took Loperamide, compared to every tenth from E-group.

Table 7. Diarrhoea treatment

Loperamide use	E-group		C-group		Total	
	Nº	%	Nº	%	Nº	%
Without	76	84.4	49	52.7	125	68.3
With	8	8.9	39	41.9	47	25.7
Loperamid+inf.	1	1.1	5	5.4	6	3.3
Infusio	1	1.1			1	0.5
Wrong diet	4	4.4			4	2.2
Total	90		93		183	100.0

In the C - group there was a significantly greater need for Loperamide with or without infusion in the E - group ($\chi^2 = 33.91$; $p < 0.001$)

DISCUSSION

Diarrhoea, with or without abdominal cramps (acute radiation enteritis) is almost inevitable event during radiotherapy of pelvic tumours. The period from radiotherapy completion to the appearance of chronic radiation enteritis symptoms is individual and varies from persistent diarrhoea, occurring during therapy, to the disease symptoms appearing even 25 years after irradiation, with median of 1-2 years (4). Intracavitary administered dose contributes insignificantly regarding total dose to the small bowel so it is not discussed in this context. Pelvic dose is defined as the dose received by the whole pelvis by external therapy, while total dose is defined as pelvic dose plus any dose given to the reduced field. With retrospective analyses it was found that higher dose rate (HDR-Selectron) produces complications of degree 2 and 3 in 32% cases, compared to just 12% with manual filling LDR, and that volumes larger than 300 cm3 should be treated with special attention (5-8). Acute radiation enteritis symptoms (nausea, emesis, abdominal cramps, tenesmus, often bloody and mucous diarrhoea) depend on the total administered dose, dose fractionation schedule, radiation volume and treated portion of the small bowel. Patients are usually informed about the symptoms and expect them 2-3 weeks after they have started with their therapy (after received 20-30 Gy). Late radiation changes may be life-threatening (adhesions, fistulae, bowel obstruction). Some of the factors predisposing to radiation enteritis cannot be influenced upon, since they were in existed before treatment (younger patients, gracile constitution, hypertension, cardiovascular diseases, diabetes, previous bowel diseases, pelvic inflammation, laparotomy, previous abdominal surgery, uterus dilatations and curettage, disease stage). The correction of others may have preventive effect since they are present during treatment (transcutaneous or intracavitary therapy, size and number of radiation fields, dose per fraction and integral dose, radiation beam energy, total radiation time, number of intracavitary applications of radiation sources, dose to the point A etc.) (9-11). Small bowel volume within the radiation field, and the dose it receives during radiotherapy course for malignant uterine tumour are two most important factors with negative impact in enteritis onset (1-3). Reduction of the volume dose to the small bowel cannot be achieved by reducing the given dose but by reducing the small bowel volume within the radiation field. If the volume is reduced by 25%, the number of serious complications (obstructions, perforations) will be reduced by 25-30%; if the volume is reduced by 55%, the number of complications will be reduced by 60-65% (12,13). Exclusion methods are

based upon these findings. With surgical exclusion methods, either aiming to occupy the pelvic space ("STEP"), or with synthetic nets made of resorptive material to sustain small bowel loops cranially from the sacral promontory (PGA, Vicryl, Dexon, 910-Polyglactin), the small bowel is no longer dose-limiting organ (40-45 Gy); dose-limiting organs are then the more resistant organs - bladder and rectum - with the opportunity to apply more radical dosage (to smaller fields even 55-70 Gy) (14,15). Shortcomings of invasive methods are the necessity of surgical application, high morbidity rate, limitation to operable tumours and impossibility of routine use. From the previously mentioned shortcomings, the advantages of individual irradiation on the PT arise. If the radiotherapy planning for E-group patients was based solely on small bowel mobility, it would be reasonable to irradiate under special conditions 52 patients with mobile and 22 with relatively immobile small bowel (82% out of the total number). However, irradiation of all of the patients (those with fixed small bowel too) produced reduction of AP diameter, thus the high dose volume too and small bowel within, above all owing to the nonretracility of fluids.

CONCLUSION

1. Number and severity of symptoms of acute radiation enteritis are directly dependent on the volume of irradiated small bowel. Measures to prevent radiation enteritis should be taken before (surgical) or during (non-invasive) radiotherapy.
2. At the Clinic of Oncology in Knez Selo, individual application of exclusion techniques using the unique patient-table (JUGOREND-GEN Ei-Niš) led to protection of the small bowel during radiotherapy of uterine malignancies, which was reflected in a significantly reduced number and severity of acute enteritis symptoms.

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