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MAGNETIC RESONANCE IMAGING IN RECTAL AND ANAL CANAL NEOPLASMS

ABSTRACT

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The numbering of the tables and figures in the abstract does not correspond to that in the dissertation.

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Abbreviations:

ADC – Apparent diffusion coefficient

AJCC – American Joint Committee on Cancer

AX – axial

COR – coronal

CRT – chemoradiotherapy

CRT – chemoradiotherapy

CT - computed tomography

DWI – diffusion-weighted imaging

EMVI – extramural vascular invasion

ERUS – endorectal ultrasound

ESGAR – European Society of Gastrointestinal and abdominal radiology

ESMO – European Society of Medical Oncology

FOV – field of view

FS – fat saturation

MRI - magnetic resonance imaging

mrTRG – MRI tumor regression grade

RECIST – Response Evaluation Criteria in Solid Tumors

SAG – sagittal

SD – standard deviation

TA – acquisition time

TE – echo time

TME – total mesorectal excision

TR – repetition time

I. Introduction

Colorectal carcinoma, and rectal carcinoma in particular, is one of the most common cancers worldwide. Along with the rare carcinoma of the anal canal, they are one of the socially significant diseases. The localization of these tumors in the pelvis significantly complicates their diagnosis with most imaging methods.

Magnetic resonance imaging has a number of advantages over other imaging methods, which make it the method of choice for the diagnosis of neoplasms of the rectum and anal canal. The high soft-tissue sensitivity and high resolution of magnetic resonance imaging combined with the availability of diverse sequences allow for the accurate and precise assessment of structures in the pelvis. Correct staging of neoplasms of the rectum and anal canal is extremely important for choosing the time and type of surgical intervention.

Magnetic resonance imaging has a key role in the preoperative evaluation in order to determine the most appropriate therapeutic behavior. Accurate evaluation of the response to neoadjuvant chemoradiotherapy is important for the optimization of the operative approach. The early determination of some prognostic factors is crutial for the planning of a therapeutic strategy and improving the outcome of patients with neoplasms of the rectum and anal canal.

II. Aim and objective

The aim of this dissertation is to study the possibilities of magnetic resonance imaging for the diagnosis of neoplasms of the rectum and anal canal.

To achieve this goal, we set the following tasks:

1. To explore the possibilities and demonstrate the advantages of 3 Tesla magnetic resonance for the study of patients with neoplasms of the rectum and anal canal;

2. To establish the frequency and localization of findings in the rectum and anal canal;

3. To study the role and necessity of conducting an MRI examination in restaging and determining the response of tumors to neoadjuvant radiochemotherapy;

4. To explore the additional possibilities of diffusion weighted imaging techniques, in particular the calculation of ADC values in the determination of important tumor characteristics and their potential role as a prognostic factor for treatment response and optimization of therapeutic strategy.

III. Materials and methods

1. Materials

For the period January 2017 - June 2023, in the Imaging Diagnostics Clinic of the University Multiprofile Hospital for Active Treatment Aleksandrovska, magnetic resonance examinations of the pelvis of a total of 103 patients with a focus on the rectum and/or anal canal were performed.

Hospitalized patients and outpatients sent with suspicion of presence of rectal and/or anal neoplasm, as well as patients sent for follow-up with an already known histologically verified tumor, were examined.

A total of 55 men (53%) and 48 women (47%) were examined. The percentage distribution by gender is presented on Figure 1.

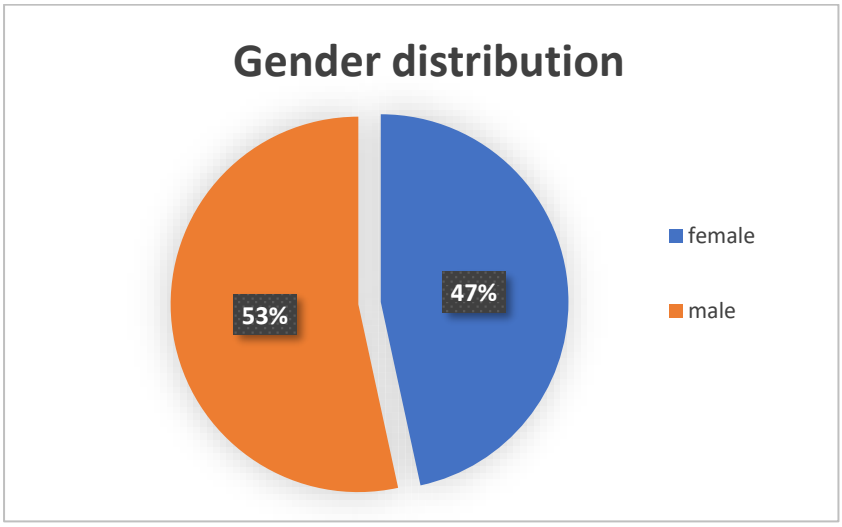


Figure 1 Gender distribution of all patients included in the study

The age of the patients at the time of the initial MRI examination was between 32 and 85. The mean age of all patients participating in the study was 65.8 (SD = 10.52). The mean age for women was 63.9 (SD: 11.34) and for men 67.4 (SD: 9.56) (Table 1).

Table 1 Gender and age distribution of patients participating in the study

gender	n	percentage	mean age	SD
female	48	47 %	63,9	11,34
male	55	53 %	67,4	9,56
all	103	100 %	65,8	10,52

The patients were divided into six age groups with an interval of 10 years, with 1% of them being between 30 and 39 years old; 7.8% are between 40 and 49 years old; 15.5% - between 50 and 59; 30.1% - between 60 and 69; 38.8% - between 70 and 79 and 6.8% are over 80. Table 2 and Figure 2 represents the distribution of patients by age.

Table 2 Percentage distribution of patients in different age groups

Frequency distribution		
age	n	%
30 - 39	1	1
40 - 49	8	7.8
50 - 59	16	15.5
60 - 69	31	30.1
70 - 79	40	38.8
80 - 89	7	6.8
all	103	100

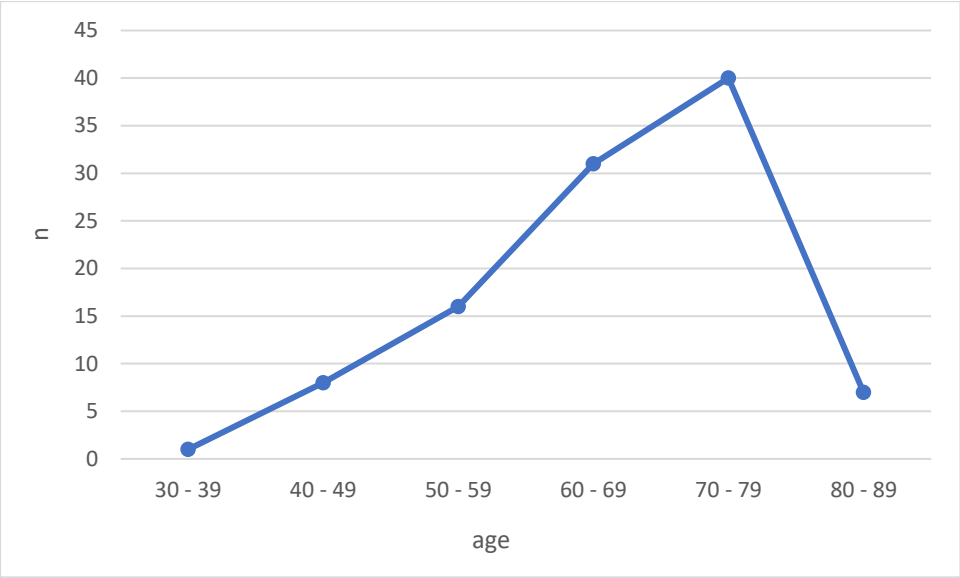


Figure 2 Number of patients in different age groups

The rectum was infiltrated by a tumor in all 103 patients, and in 6 of them it was secondarily infiltrated by a primary tumor in an adjacent organ. The anal canal was infiltrated in a total of 14 patients, 4 of whom had a proven primary tumor of the anal canal and 10 had secondary infiltration from a primary rectal neoplasm (Table 3).

Table 3 Distribution of patients based on the infiltrated organ

	primary	secondary	all
rectum	97	6	103
anal canal	4	10	14

Some of the patient information was collected retrospectively and some prospectively. Histologic verification was obtained in 84 of 103 patients with an MRI finding. 40 of the patients in the study were sent for follow-up with an MRI scan.

Patients meeting the following criteria were included in the study:

Inclusion criteria:

• Patients with clinical, endoscopic, CT or PET/CT finding for a tumor mass in the region of the rectum or anal canal;
• Patients with histologically verified carcinoma of the rectum or anal canal;
• Patients with a discovered tumor in the rectum or anal canal during an MRI examination performed for other clinical purposes;
• Patients with elevated values of tumor markers CA 19-9 and/or CEA;
• Patients with previous surgical intervention due to tumor in the rectum or the anal canal.

Exclusion criteria:

• Patients with MRI images that have significant motion artifacts;
• Patients with an MRI examination that was not performed in full extend;
• Patients with an MRI scan in which essential sequences needed for image interpretation are missing.

2. Methods

All patients were examined on a Magnetom Verio, A Tim+ Dot System, Siemens, Germany with a magnetic field strength of 3 Tesla. A large body matrix coil was used.

Images were processed on a Syngo workstation. All MRI examinations were interpreted by two radiologists, one with 6 years of experience and the second one with over 20 years of experience in abdominal imaging.

2.1 Patient preparation

Some of the patients were given antispasmodics and cleansing enemas to prevent motion artifacts from intestinal peristalsis as a preparation before conducting an MRI examination.

In all patients, prior to conducting the study, a laboratory test of serum creatinine was carried out in case of the need to apply contrast material.

2.2 MRI protocol and used sequences

Multiplanar T2 sequences without fat suppression were used in the three main planes – sagittal, oblique axial and oblique coronal planes. Oblique axial T2 sequences were planned perpendicular to the tumor mass to accurately assess the relationship of the tumor to surrounding structures. Oblique coronal T2 sequences were planned parallel to the long axis of the anal canal for accurate evaluation of the anal sphincter. During the sequence planning, saturation bands were used to suppress patient breathing artifacts.

Additional fat-suppressed T2 sequences were used in only a subset of patients with suspected perianal and perirectal fistulas.

Diffusion-weighted imaging techniques were used - axial DWI with high b values (50-400-800 s/mm2), from which a corresponding ADC map was calculated.

In some patients, contrast material was applied for a better assessment of the local status or in case of suspicion of presence of residual or recurrent lesions. A gadolinium contrast media was used - Gadovist 1.0 mmol/ml, Bayer Healthcare, Berlin, Germany in a dose of 0.1 ml/kg.

Table 4 presents the main sequences used in the rectal/anal canal protocol with their respective technical parameters.

Table 4 Technical parameters of the main sequences used in the MRI protocol for a pelvis with focus on the rectum/anal canal (FoV: field of view; TR: repetition time; TE: echo time; TA: acquisition time; SAG: sagittal plane; AX: axial plane; COR: coronal plane; FS: fat saturation)

sequence	FoV (mm)	Slice thickness (mm)	TR (ms)	TE (ms)	TA (min)
T2 SAG	250	4.0	3500.0	144.0	2:38
T2 AX	250	4.0	4600.0	153.0	3:13
T2 AX FS	250	4.0	4600.0	153.0	3:13
T2 COR	280	0.90	1300	180.0	3:54
T1 VIBE DIXON SAG	300	3.00	5.95	2.46	0:18

T1 VIBE DIXON AX	300	3.50	5.95	2.46	0:24
DWI AX (b50-400-800)	380	5.0	5900	59.0	3:32
POST CONTRAST					
T1 VIBE DIXON AX	180	3.50	5.95	2.46	1:15
T1 VIBE DIXON SAG	300	3.00	5.95	2.46	0:18
T1 VIBE DIXON COR	300	3.50	5.95	2.46	0:23
T1 SAG	250	4.0	600.0	23.0	4:14

2.3 Measuring ADC values

Mean ADC values were measured in 75 patients. Data were obtained using an oval-shaped region of interest (ROI) with a volume of 15-20 mm2 placed in a selected area of the tumor on the ADC map corresponding to the area of the most prominent diffusion restriction on the DWI sequence. The average of three foci demonstrating the lowest signal intensity from the tumor was calculated.

Figure 3 shows the technique used to measure the mean tumor ADC value.



Figure 3 Method of measuring ADC values using ROI placed in a selected region of the tumor with the lowest signal intensity

2.4 Statistical methods

The following statistical methods were used in the study:

- *Descriptive analysis* – quantitative summarization of the sample data in tabular and graphic form with presentation of the central tendency and the distribution of variables, use of indicators such as average value, standard deviation, etc.;

- *Graphical analysis* – presentation of results in tables, histograms, pie charts, bar charts, box-plot graphs, etc.

- *Kolmogorov-Smirnov test* – a test to determine the type or shape of the frequency distribution, checking whether the data from the studied population follows the normal distribution;

- *One-way ANOVA test* – variance analysis, comparing the mean values of two or more groups of independent variables;

- *Student's t-test* – a parametric method for testing a hypothesis by comparing the mean values of two samples with a normal distribution;

- *Mann-Whitney U test* – a non-parametric method for testing a hypothesis by comparing two samples of independent variables that do not follow a normal distribution;

- *Fisher Exact test* – a test to detect a significant relationship between two categorical variables;

- *Pearson's correlation coefficient* - a test to measure the linear relationship between two quantitative variables.

The software package IBM SPSS Statistics v.19.0 and Microsoft Office Excel 2016 were used for the statistical analysis of the data and the graphical presentation of the results. A value of $p<0.05$ was accepted as a statistically significant result.

IV. Results and discussion

1. Distribution by gender and age

Out of a total of 103 patients participating in the study, 97 (94%) had primary rectal carcinoma. 44 of them were women (45%), 53 were men (55%). The percentage distribution by gender is presented on Figure 4. The results show that rectal carcinoma in our study occurs more frequently in the male group, which is confirmed by the worldwide statistics.

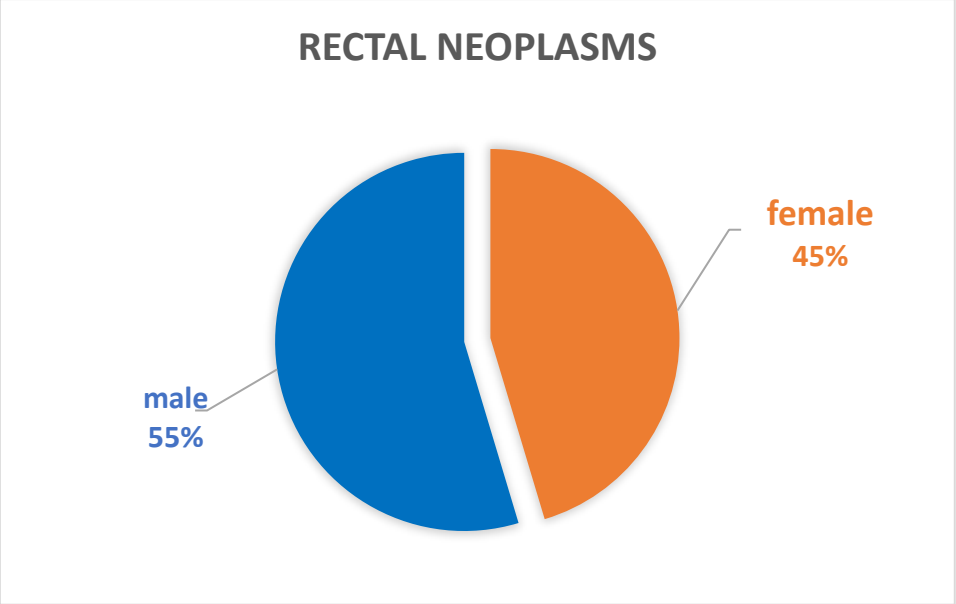


Figure 4 Gender distribution of patients with a primary rectal process

The mean age of all participants in this study was 65.8 (SD: 10.52). The mean age of patients with a primary rectal neoplasm was 65.9 (SD: 10.50), for women - 64.4 (SD: 11.33), for men - 67.2 (SD: 9.69).

The age distribution of patients with a primary rectal neoplasm is presented on Table 5.

Table 5 Mean age of patients with primary rectal neoplasm

gender	n	percentage	mean age	SD
female	44	45,36 %	64,4	11,33
male	53	54,64 %	67,2	9,69
all	97	100 %	65,9	10,50

The Kolmogorov-Smirnov test was used to check the type of frequency distribution of the data from the studied population. The obtained results show a lack of statistical significance (p=0.17), which suggests that the data in the sample group does not deviate from the normal distribution. The mean age for women with rectal cancer was 2.8 years younger than the mean age for men.

Table 6 and Figure 5 represent the distribution of patients with primary rectal neoplasm by age.

Table 6 Frequency distribution of patients with primary neoplasm of the rectum in different age groups

Frequency distribution		
age group	n	%
30 - 39	1	1
40 - 49	7	7.2
50 - 59	15	15.5
60 - 69	30	30.9
70 - 79	37	38.1
80 - 89	7	7.2
all	97	99.9

Patients with a primary neoplasm of the rectum were divided into six age groups with an interval of 10 years, with 1% of them being between 30 and 39 years old; 7.2% are between 40 and 49 years old; 15.5% - between 50 and 59 years old; 30.9% - between 60 and 69 years old; 38.1% - between 70 and 79 and 7.2% are over 80.

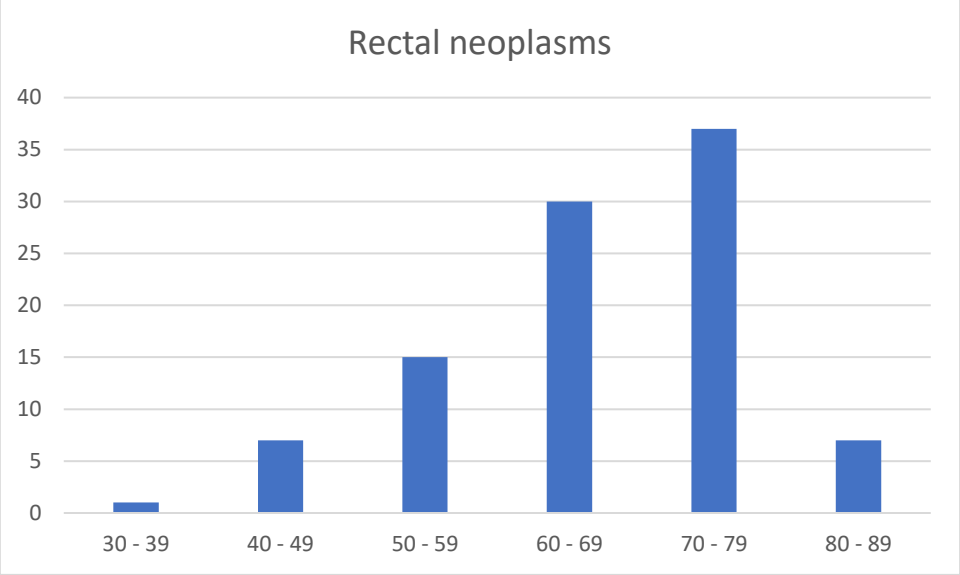


Figure 5 Age distribution of patients with primary rectal neoplasm

Rectal carcinoma was found most frequently in the age group of 70-79 years old (38.1%), and least frequently in the group <40 years old (1%). To verify the presence of a linear correlation between rectal carcinoma incidence and age, Pearson's correlation coefficient was calculated ($R=0.504$, $p<0.05$). The obtained results show a moderately strong and statistically significant positive correlation. As age increases, so does the incidence of rectal cancer in both women and men. Data from our study show that the incidence of rectal neoplasms begins to rise earlier in women than in men, with the rising curve being steeper in women, while a slower and plateau-like increase is observed in men (Figure 6).

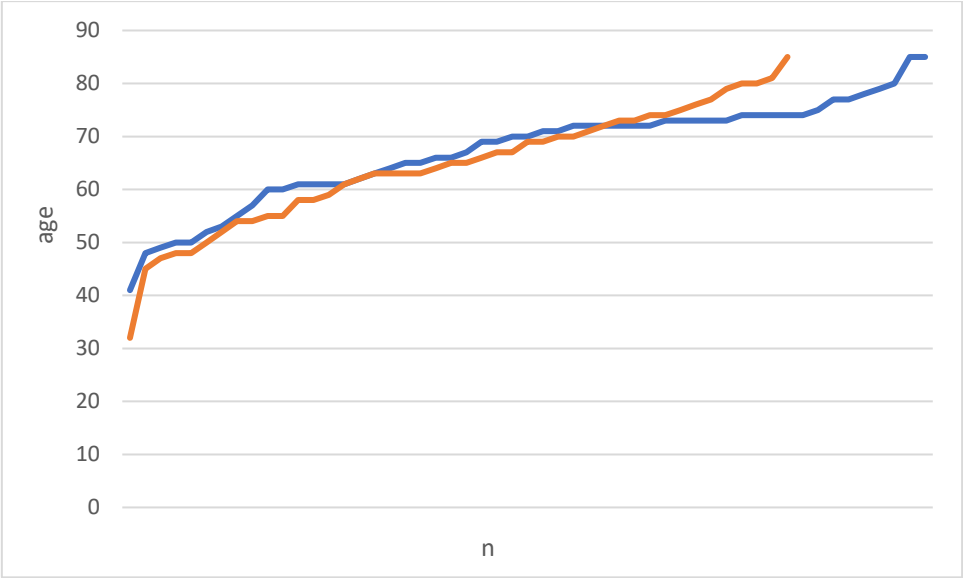


Figure 6 Correlation between age and frequency of rectal neoplasms in both sexes (blue - male; red - female)

There were 4 (3.9%) patients with a primary neoplasm of the anal canal in our study, 3 of which were women (75%) and 1 was a man. (25 %). The mean age was 67 (SD: 8.78) – for women it was 64.7 (SD: 9.07) and for men it was 74. The mean age for women is 9.3 lower.

In the studied population, the anal canal was more often involved secondary to a primary neoplasm of the rectum – in 10 patients (9.7%), 5 of which were women and 5 were men. The mean age in this group of patients was 67.9 (SD: 13.29) – in women it was 66 (SD: 15.13) and in men it was 69.8 (SD: 12.63) .The average age for women was 3.8 years lower in this group.

Primary neoplasms of the anal canal are very rare worldwide - less than 1% of all carcinomas. Despite the small number of patients in the study population, we found a tendency for a greater frequency in women than in men, as well as an earlier onset in women. In the group of patients with secondary anal canal infiltration, there was also a trend for an earlier onset in women.

2. Types of findings

Rectum was ifiltrated by a neoplasm in all 103 patients enrolled in the study. Patients were divided into the following groups:

- patients with infiltration of the rectum from a primary neoplasm – 91 patients, staged by MRI according to the TNM classification;

- patients with a primary tumoral mass in the rectum with a follow-up MRI examination, where a recurrence in a different site other than the rectum was found - 4 patients, 3 of which with a recurrence in the presacral space, 1 with a recurrence in the small intestine;

- patients with a primary tumoral neoplasm in the rectum with a follow-up MRI examination, where post-radiation proctitis was detected - 2 patients;

- patients with the rectum being infiltrated secondarily by a primary neoplasm in another organ – 6 patients, 4 of which had infiltration from carcinoma of the anal canal, 1 from carcinoma of the vagina and 1 from carcinoma of the bladder.

The distribution of patients in different groups is presented on Table 7 and Figure 7.

Table 7 Distribution of patients in different groups according to the MRI findings

	primary rectal neoplasm				recurrence elsewhere	post-radiation proctitis	secondary rectal infiltration	total
	T1	T2	T3	T4				
n	5	20	47	19	4	2	6	103
%	4,9 %	19,4 %	45,7 %	18,4 %	3,9 %	1,9 %	5,8 %	100 %

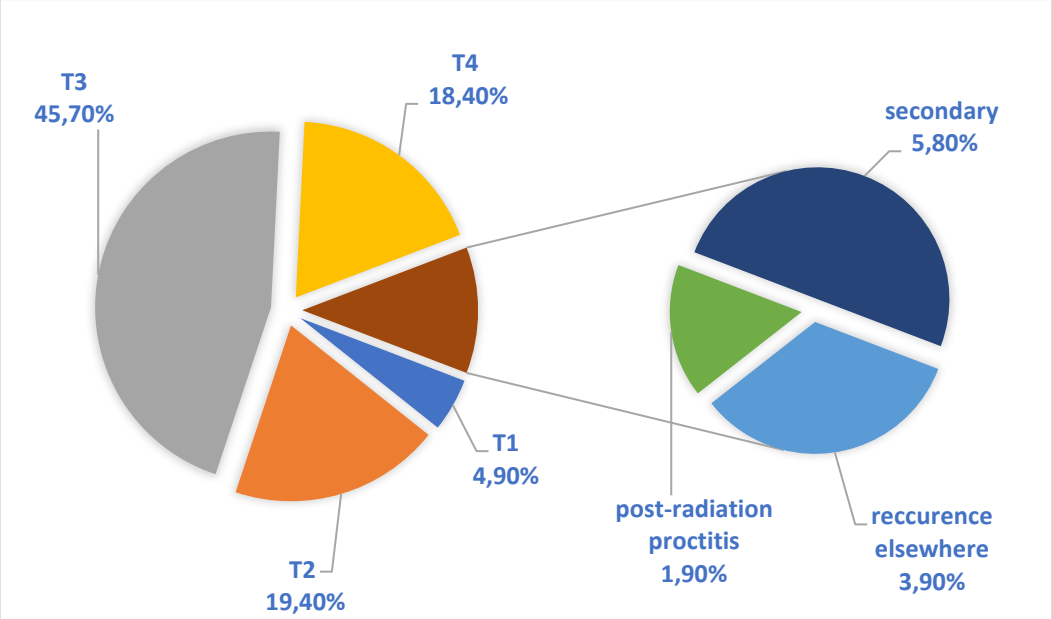


Figure 7 Distribution of patients in different groups according to the MRI findings

3. Localization of the neoplasms

In the study population, the lower third of the rectum was most often infiltrated by a tumoral process - in 45 of all 103 patients (43.6%). A tumor limited only to the lower third was found in 20 patients, and tumor in the lower third with infiltration of the anal canal – in 13 patients. The middle third was infiltrated in a total of 38 patients, and the upper third was infiltrated in 28. In 3 patients, rectal carcinoma infiltrated all parts of the rectum. Table 8 presents the frequency distribution of tumor findings according to localization.

Table 8 Frequency distribution according to the localization of the tumor

	infiltrated		limited	
	n	%	n	%
high	28	27,1 %	22	21,3 %
middle	38	36,8 %	25	24,2 %
low	45	43,6 %	20	19,4 %
all parts	3	2,9 %		
low + anal canal	13	12,6 %		

4. T-stage

A total of 91 patients with primary rectal carcinoma were staged by MRI. This group did not include patients with secondary involvement of the rectum from a primary neoplasm in another organ (6) and patients sent for MRI follow-up (6) where recurrence elsewhere or postradiation proctitis was detected. All patients were staged according to the TNM classification. The distribution by T-stage is presented on Figure 8.

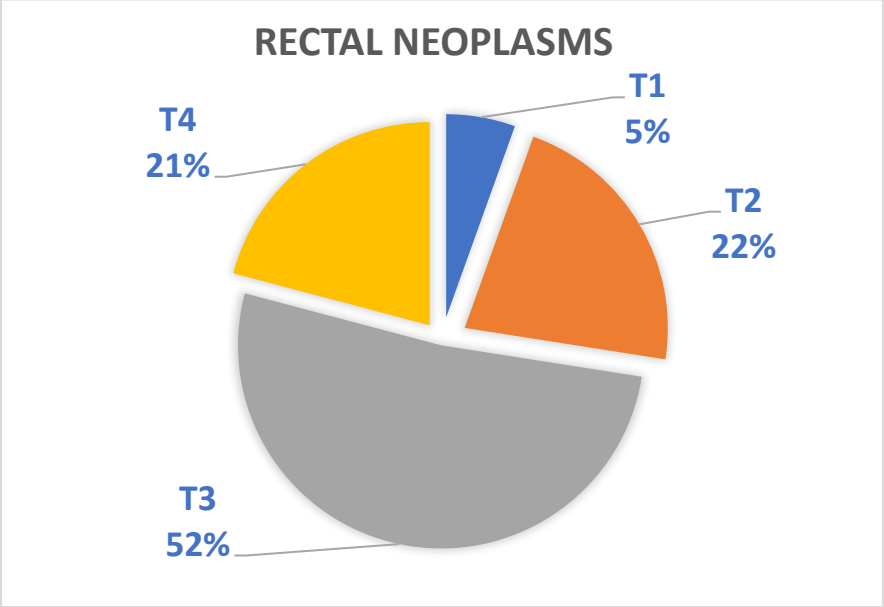


Figure 8 Distribution of rectal neoplasms according to T stage

The highest percentage of rectal tumors detected by MRI is in the T3-stage (Figure 9) – in 47 patients (51.6%). The lowest percentage is in T1-stage - 5 patients (5.5%). There were 20 (22%) patients with T2-stage tumors and 19 (20.9%) T4-staged tumors.

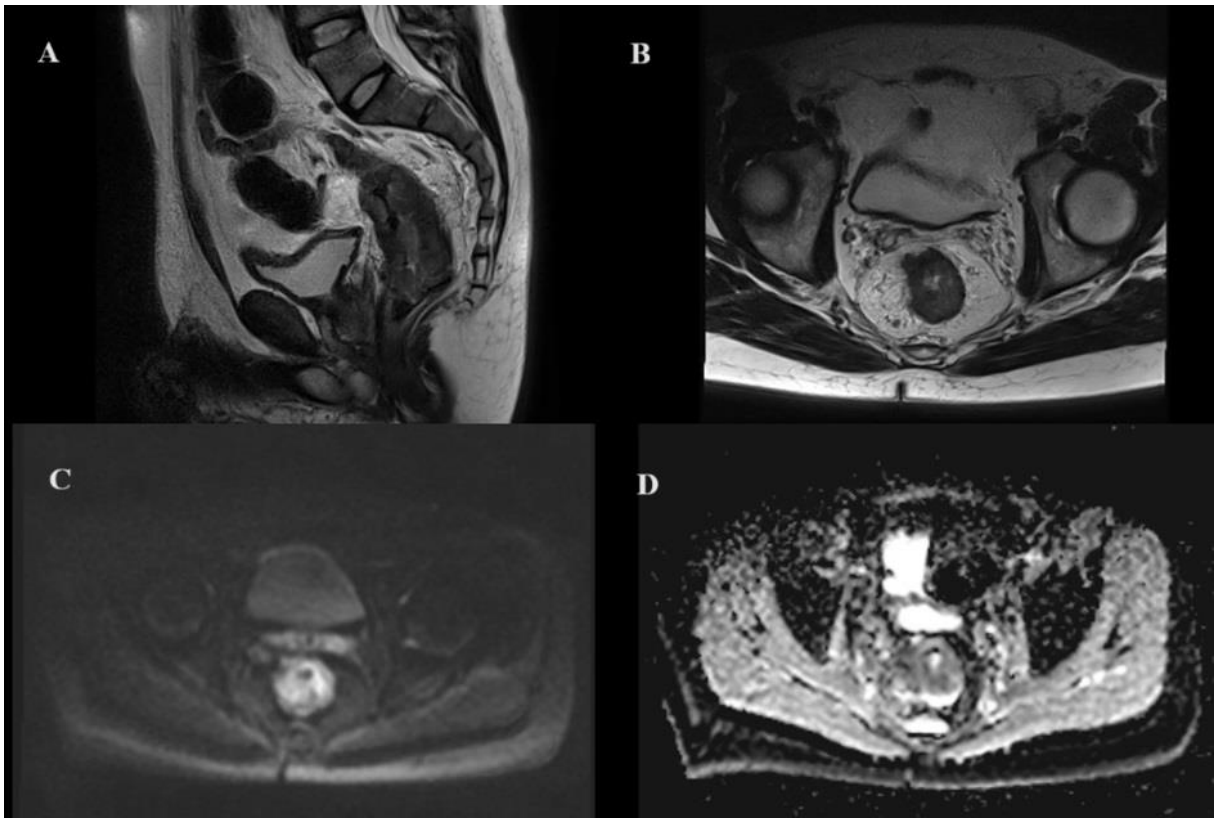


Figure 9 T3--staged rectal carcinoma - A: sagittal T2 sequence and B: axial T2 sequence show a circumferential thickening of the rectal wall from a tumor mass with infiltration of the perirectal fat; C: DWI and D: corresponding ADC map show prominent diffusion restriction in the area of the primary tumor

A statistically significant difference ($p<0.05$) was found when comparing the craniocaudal size of the tumor in the different T stages. The results are presented on Table 9. The largest mean tumor length was measured in the locally advanced tumors in stage T4– 64, 5 mm, followed by T3 tumors with a mean length of 55.4 mm.

Table 9 Comparison between the mean length of the tumors in different T stages

T-stage	mean length (mm)	SD	n	%	p-value
T1	41,2	15,3	5	5,5	0,002
T2	39,6	19,3	20	22	
T3	55,4	19,8	47	51,6	
T4	64,5	26,4	19	20,9	
all	50,2	11,9	91	100	

When comparing mean tumor wall thickness, no statistically significant difference was found between tumors in different T stages (p=0.065), although the greatest thickness was again measured in locally advanced T4 stage tumors - 22.1 mm. (Table 10).

Table 10 Comparison between the mean wall thickness of the tumors in different T stages

T-stage	mean wall thickness (mm)	SD	n	%	p-value
T1	15,8	2,2	5	5,5	0,065
T2	16,4	11,5	20	22	
T3	15,9	4,4	47	51,6	
T4	22,1	13	19	20,9	
all	18,1	3,4	91	100	

The results show that larger tumor size is associated with more advanced tumors. Unlike most solid tumors, rectal carcinoma staging by the TNM classification does not include a size criterion. However, there are studies that

show correlation between tumor size and patient prognosis – larger sizes are associated with poorer prognosis and poorer response to radiochemotherapy (Alese, Zhou et al. 2021).

In 75 of 91 patients, ADC values of the primary tumor were measured. Patients with mucinous adenocarcinoma, which due to its low cellularity leads to higher ADC values, were excluded from this group. Patients who did not have a DWI sequence performed on the initial MRI examination were also excluded.

The results showed a statistically significant difference (p=0.039) between the ADC values of tumors of different T stages (Table 11) - the higher the T stage, the lower the ADC values (Figure 10). The highest values were measured in tumors confined only to the rectal wall - T1 and T2 staged tumors - 886 and 881, and the lowest values were measured in locally advanced T3 and T4 staged tumors - 819 and 776. No statistically significant difference was found between ADC values in T3 and T4 stage tumors (p=0.36), but T3 and T4 stage tumors showed significantly lower values when compared to T1 and T2-staged tumors (p<0.05).

Table 11 Comparison between ADC values in tumors of different T stages

T-stage	mean ADC	SD	n	%	p-value
T1	886,8	49,7	5	6,7	0,039
T2	881,4	114,8	14	18,7	
T3	819,4	101,1	38	50,7	
T4	776,3	135,6	18	24	
all	841	100,3	75	100	

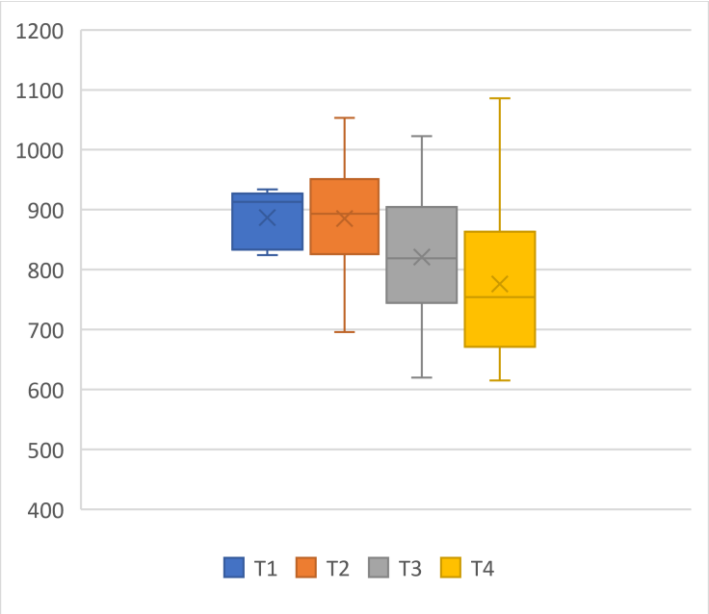


Figure 10 Comparison between ADC values of tumors in different T stages

Diffusion-weighted imaging is a non-invasive functional imaging technique based on the free Brownian motion of water molecules and is routinely used in MRI examination of rectal carcinoma. DWI with high b-values are particularly useful in restaging to differentiate between partial and complete response to CRT. However, some difficulties may arise in the interpretation of the images such as the "T2 shine through" effect and the high sensitivity of these sequences to artifacts. ADC is a quantitative parameter derived from DWI that can be used to assess tissue cellularity and distinguish benign from malignant masses, although it has not yet been adopted in daily practice due to lack of standardized protocols and validated thresholds (Beets- Tan, Lambregts et al. 2018). Some authors accept ADC values around 1.1-1.2×10-3 mm2/s as a cut-off value for distinguishing benign from malignant colorectal tumor (Soyer, Lagadec et al. 2010, Barral, Eveno et al. 2016, EMAN A AHMAD and ABO EL-HASSAN H. MOHAMED 2019). The measured ADC values from tumors in all T-stages in our study confirm this by demonstrating lower values than these. A correlation was also found - lower ADC values were associated with a higher T-stage and a correspondingly worse prognosis. This may be due to the fact that ADC values

are derived from the free movement of water molecules, which may be affected by tissue hypercellularity and heterogeneity (Sun, Tong et al. 2014). Our results complement those of other studies (Sun, Tong et al. 2014, Chen, Shen et al. 2018, Yildirim 2020, El Sayed, Nassef et al. 2022) and demonstrate that initial tumor ADC values before undergoing CRT could potentially reflect the degree of aggressiveness of tumors.

Out of 14 patients with anal neoplasms (Figure 11), 4 had primary cancer disease and 10 patients were secondary infiltrated by a low rectal carcinoma.

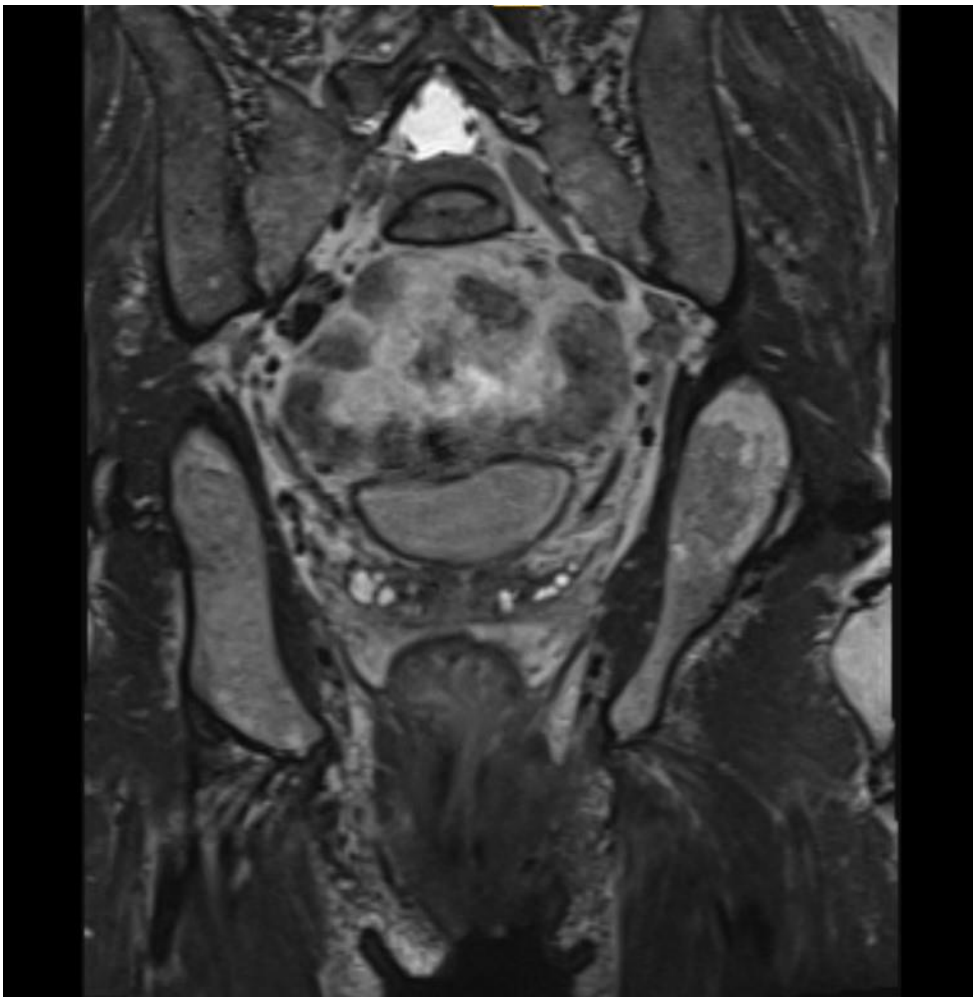


Figure 11 Neoplasm of the anal canal - coronary T2 sequence

The mean ADC values in primary neoplasms of the anal canal was 651, and in those with secondary infiltration - 843 (Table 12). A statistically significant difference was found between the two groups (p=0.03), indicating that ADC values could be used to differentiate primary anal from low rectal carcinoma. No statistically significant difference was found between ADC values in different T-stages of anal canal neoplasms due to the small number of patients in this group.

Table 12 Comparison of ADC values of primary neoplasms of the anal canal and those with secondary infiltration from low rectal carcinoma

	mean ADC	n	p-value
anal canal	651	4	0,03
low rectal + anal canal	843	10	

Regarding tumor size, no statistically significant difference was found between the length and thickness of primary neoplasms of the anal canal and those with secondary infiltration from primary low rectal carcinoma. The results are presented on Table 13.

Table 13 Comparison of sizes of primary neoplasms of the anal canal and those with secondary infiltration from primary low rectal carcinoma

	length (mm)	thickness (mm)
anal canal	49	21,5
low rectal + anal canal	58,9	18,6

5. Lymph nodes

Regional lymph nodes were found in 40 (36.4%) of 91 patients with a primary rectal neoplasm. The mean diameter of the involved regional lymph nodes was 11 mm. No statistically significant difference was found between the lymph node size in patients with tumors of different T-stage, although a larger lymph node size was measured in patients with higher T-stage (Table 14).

Table 14 Comparison of lymph node size in patients with tumors of different T-stages

T-stage	lymph node size (mm)	SD	n	%	p-value
T1	-	-	0	-	0,14
T2	9,5	3,53	2	5	
T3	10,3	3	28	70	
T4	13	5,5	10	25	
all	11	4,02	40	100	

In 38 of the patients with lymph node involvement, ADC values of the involved regional lymph nodes were measured (Figure 12). Patients were excluded from this group in cases when DWI sequence was not performed during the initial MRI examination. The mean ADC value was 801. No statistically significant difference was found when comparing the ADC values of lymph nodes in patients with tumors of different T-stages (Table 15).

Table 15 Comparison between lymph node ADC values in patients with tumors of different T-stage

T-stage	ADC (lymph nodes)	SD	n	%	p-value
T1	-	-	0	-	0,75
T2	770,5	20,5	2	5,3	
T3	830,4	143,7	27	71	
T4	802,9	122,1	9	23,7	
all	801,3	95,5	38	100	

The mean ADC value of tumors with regional lymph node involvement was 825 (SD: 142.3), which was lower than the mean ADC value of all tumors (841). No statistically significant difference was found when comparing the ADC values of tumors with lymph node involvement and those in N0 stage (p=0.5).

Out of a total of 40 patients with involved lymph nodes, 24 were men and 16 were women. Fisher Exact test was used - we found no statistically significant correlation between presence of metastatic lymph nodes and gender (p=0.32).

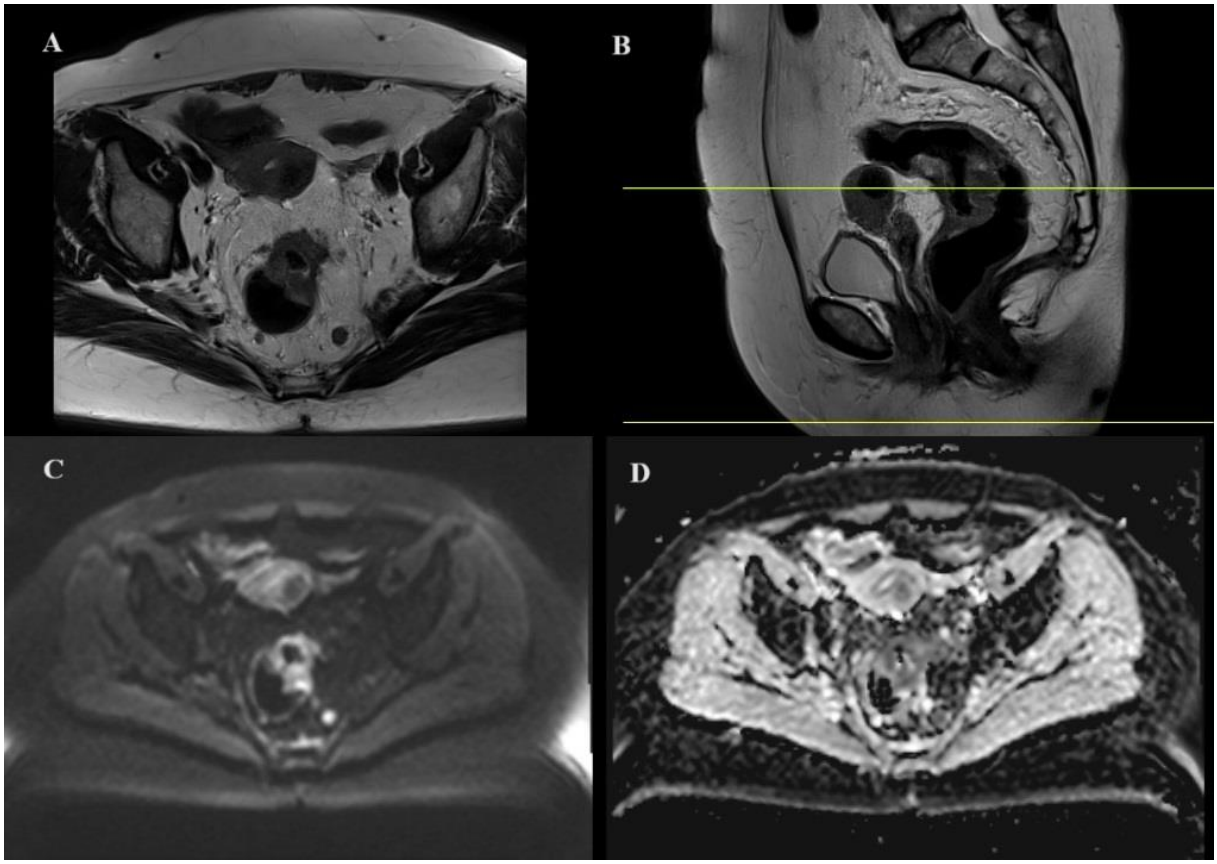


Figure 12 Rectal carcinoma in T3-stage with secondary pararectal lymph node involvement - A: axial T2; B - sagittal T2; C: DWI; D: ADC - diffusion restriction is present in the primary tumor as well as in the lymph node

6. Metastases

Distant metastases were found in 16 (14.56 %) of 91 patients with a primary rectal neoplasm. Liver metastases were the most common (Figure 13) – in 12 (75%) of the patients with distant metastases. Distribution of patients according to the location of distant metastases is shown on Table 16 and Figure 14.

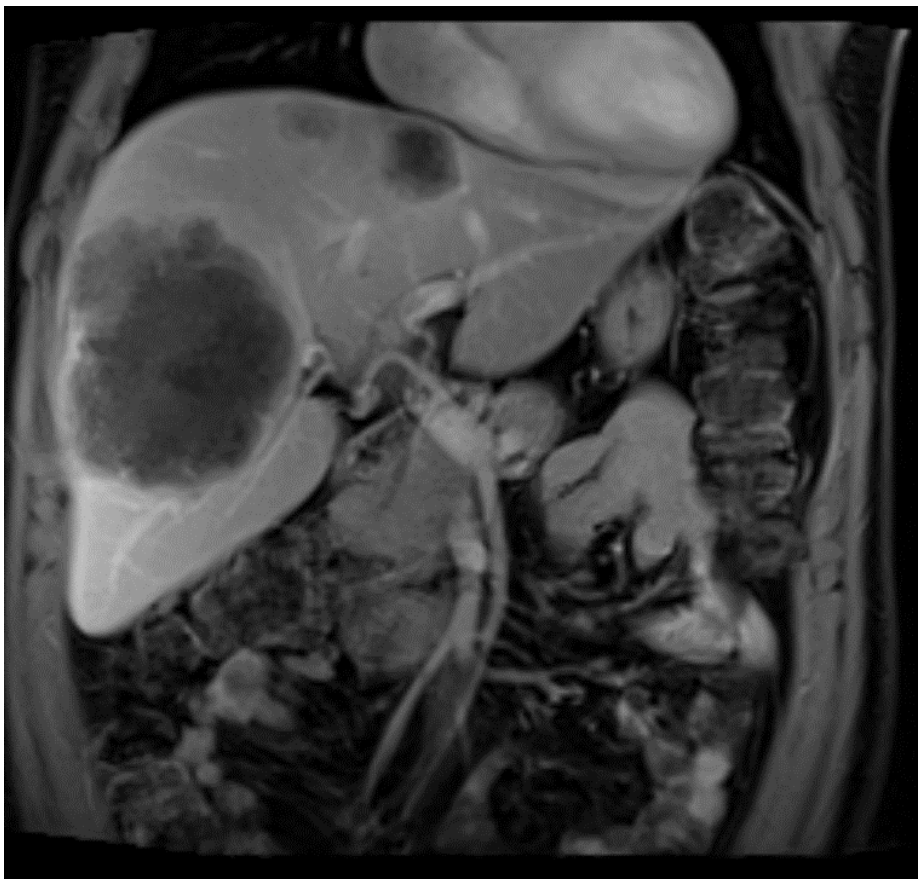


Figure 13 Coronary T1 after contrast enhancement - secondary hepatic spread from rectal carcinoma

Table 16 Frequency distribution of distant metastases

metastases	n	%
liver	12	75 %
lungs	3	18,75 %
visceral peritoneum	3	18,75 %
spleen	1	6,25 %
small intestine	1	6,25 %
adrenal glands	1	6,25 %
all	16	100 %

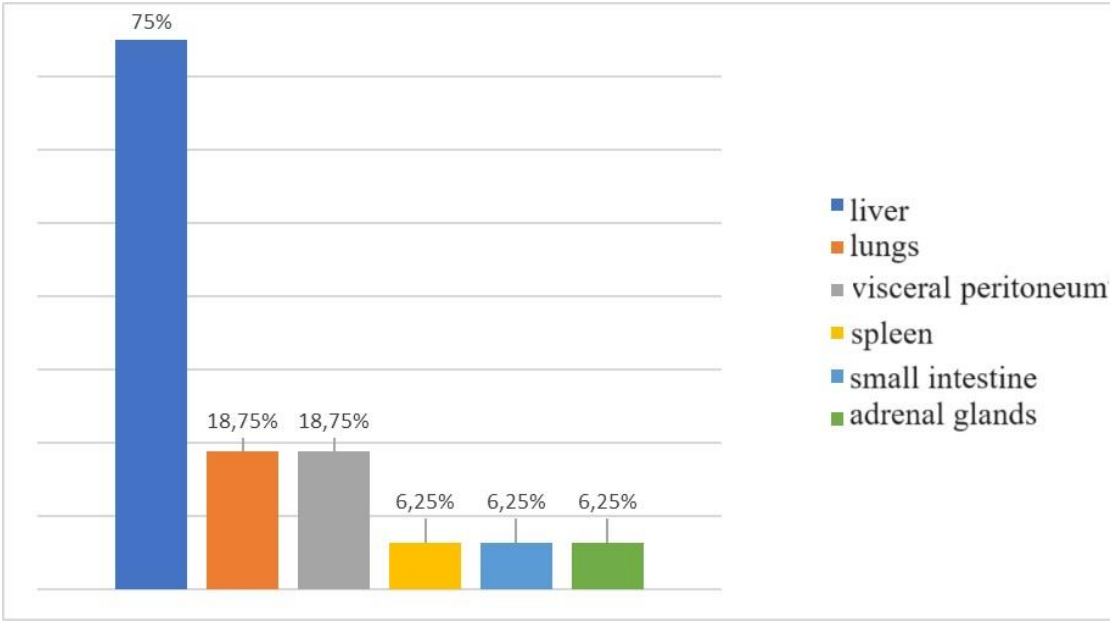


Figure 14 Frequency distribution of distant metastases

The mean length of the primary tumor in all 16 patients with distant metastases was 62.5 mm, which was greater than the mean length of all tumors (50.2 mm) and the mean length of tumors without metastases (51.8 mm). However, no statistically significant difference was found. The mean wall thickness of tumors with distant metastases was 16.5 mm. The results are presented on Tables 17 and 18.

Table 17 Mean length of tumors with distant metastases

	mean length (mm)	SD	n	%	p-value
metastases	62,5	22,5	15	13,7	0,1
all	50,2	11,9	91	100	

Table 18 Mean thickness of tumors with distant metastases

	mean thickness (mm)	SD	n	%	p-value
metastases	16,5	5,3	15	13,7	0,6
all	18,1	3,4	91	100	

The mean ADC value of tumors with distant metastases was 818.8 (SD: 107.1), which was overall lower than the mean ADC value of all tumors (841). No statistically significant difference was found when comparing the ADC values of tumors with distant metastases and those of M0 stage (p=0.4).

Out of all 16 patients with distant metastases, 9 were men, 7 were women. Fisher Exact test was used, which found no statistically significant correlation between presence of metastases and gender (p=1).

7. Extramural vascular invasion

A total of 32 (33%) of all patients who participated in the study had both MRI and histologically proven presence of extramural vascular invasion - 22 men and 10 women. All patients with EMVI had locally advanced rectal carcinomas - 21 of the patients had T3-staged tumors and 9 were T4-staged. 28 of them had regional lymph node involvement and 14 had distant metastases. The most common localization of tumors with EMVI was the middle third of the rectum - 19 patients (59%).

When measuring the length and thickness of tumors with presence of EMVI, a statistically significant difference was found in terms of length - tumors with EMVI had a significantly larger craniocaudal size compared to tumors without EMVI (Table 19). Although no statistically significant difference was found, measured wall thickness was shown to be greater in tumors with EMVI compared to tumors without EMVI.

Table 19 Comparison between length and thickness of tumors with EMVI and tumors without EMVI

	EMVI (+)	EMVI (-)	p-value
length	69,3	46,2	<0,001
thickness	19,9	16,3	0,07

Larger primary tumor size as well as higher T-stage in patients with EMVI might be associated with a greater degree of aggressiveness in these tumors.

ADC values in primary rectal tumors were calculated in 28 of 32 patients with EMVI. Patients who did not have a DWI sequence on the initial MRI examination were excluded from this group, as well as those with mucinous

adenocarcinomas where ADC values were higher due to the mucinous component.

Student's t-test was used and a statistically significant difference (p=0.1) was found between the two groups (Table 20). ADC values in tumors with EMVI (782) were significantly lower than in those without EMVI (885). This also suggests that low ADC values might be associated with a more aggressive tumor behavior and could potentially predict a higher probability for the presence of extramural vascular invasion. Our results confirm and complement those of other studies where low ADC values were measured in tumors with EMVI (Gursoy Coruh, Peker et al. 2019, Ao, Zhang et al. 2022) and demonstrate that the addition of diffusion-weighted imaging techniques DWI/ ADC to standard T2 sequences can significantly contribute to the early detection of extramural vascular invasion. The results are shown on Table 20 and Figure 15.

Table 20 Comparison between ADC values in tumors with EMVI and those without EMVI

	ADC	SD	n	p-value
EMVI (+)	782	131	27	0,01
EMVI (-)	885	186	48	

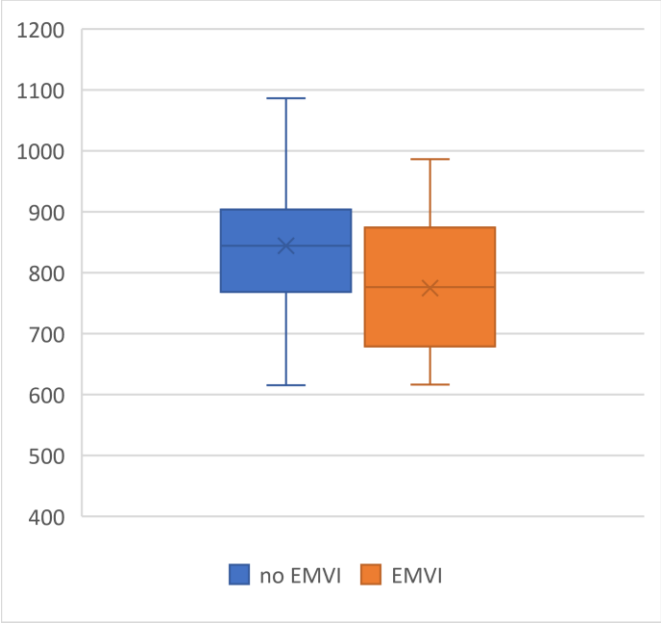


Figure 15 Comparison between ADC values in tumors with EMVI and tumors without EMVI

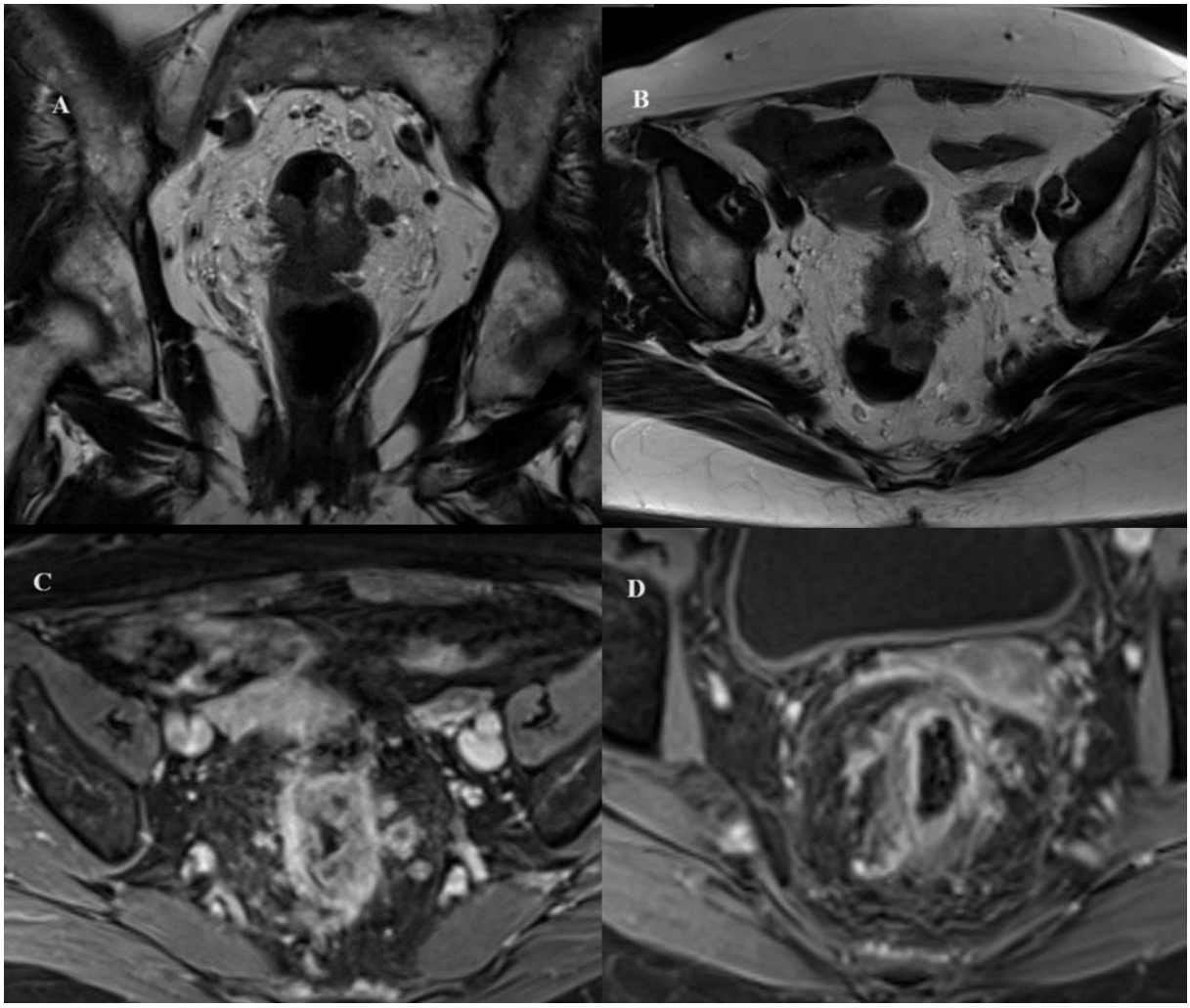


Figure 16 Examples of rectal carcinoma with extramural vascular invasion: A and B – non-contrast T2 sequences in the coronal (A) and axial (B) plane - irregular worm-like vascular structures arising from the primary tumor; C and D - postcontrast T1 sequence - EMVI is visualized as a filling defect - presence of low signal intensity from the tumor in the vessel

Various sources state that the presence of extramural vascular invasion (Figure 16) is associated with more frequent occurrence of distant metastases and local recurrences and it is considered an independent poor prognostic factor for overall patient survival (Smith, Barbachano et al. 2008). The role of EMVI detected by MRI has been proven to be an important factor in the planning and decision-making of subsequent therapy for patients with rectal carcinoma (Chand, Swift et al. 2014, Inoue, Sheedy et al. 2021). Venous invasion is the first step to hematogenous dissemination (van Zijl, Krupitza et al. 2011). There is evidence that direct venous invasion by a tumor draining through an inferior mesenteric vein, such as rectal carcinoma, facilitates hematogenous dissemination through the portal circulation, most commonly to the liver (Jin, Gao et al. 2012, Lord, Knijn et al. . 2020).

In our study, Fisher Exact test was used to detect a significant correlation between presence of EMVI and presence of distant metastases (Table 21). Our results demonstrated evidence of a statistically significant correlation - $p<0.001$. Out of all 16 patients with metastases, extramural vascular invasion was also detected in 14 of them (87.5 %). Our results complement those of other studies and prove higher risk for distant metastases in patients with rectal carcinomas with EMVI and therefore worse prognosis for overall patient survival (Siddiqui, Simillis et al. 2017, Schaap, Ogura et al. 2018, Leijssen, Dinaux et al. 2019, Tripathi, Guo et al. 2020).

Table 21 Correlation between presence of EMVI and presence of distant metastases

	M0	M1	total
EMVI (+)	2	14	16
EMVI (-)	85	2	87
total	87	16	103

Fisher's test was also conducted to detect a significant correlation between presence of EMVI and the gender of the patients (Table 22). The results showed a significantly higher rate of EMVI in men - 70% (22/32) compared to the rate in women - 30% (10/32), p=0.05.

Table 22 Correlation between EMVI and gender

	EMVI (+)	EMVI (-)	total
male	22	33	55
female	10	38	48
total	32	71	103

8. Histology

Histological verification was obtained in 80 (82%) of all patients with primary rectal carcinoma (97). The most common variant in our study population was moderately differentiated adenocarcinoma - in 56 (70%) of all rectal carcinomas, and the rarest type was squamous cell carcinoma - in 3 patients (3.75%).

The distribution of tumors of different histological subtypes is presented on Table 23 and Figure 17.

Table 23 Distribution of rectal tumors according to histological type

	adenocarcinoma			mucinous adenocarcinoma	squamous cell carcinoma
	well differentiated	moderately differentiated	poorly differentiated		
n	5	56	8	8	3
%	6,25 %	70 %	10 %	10 %	3,75 %

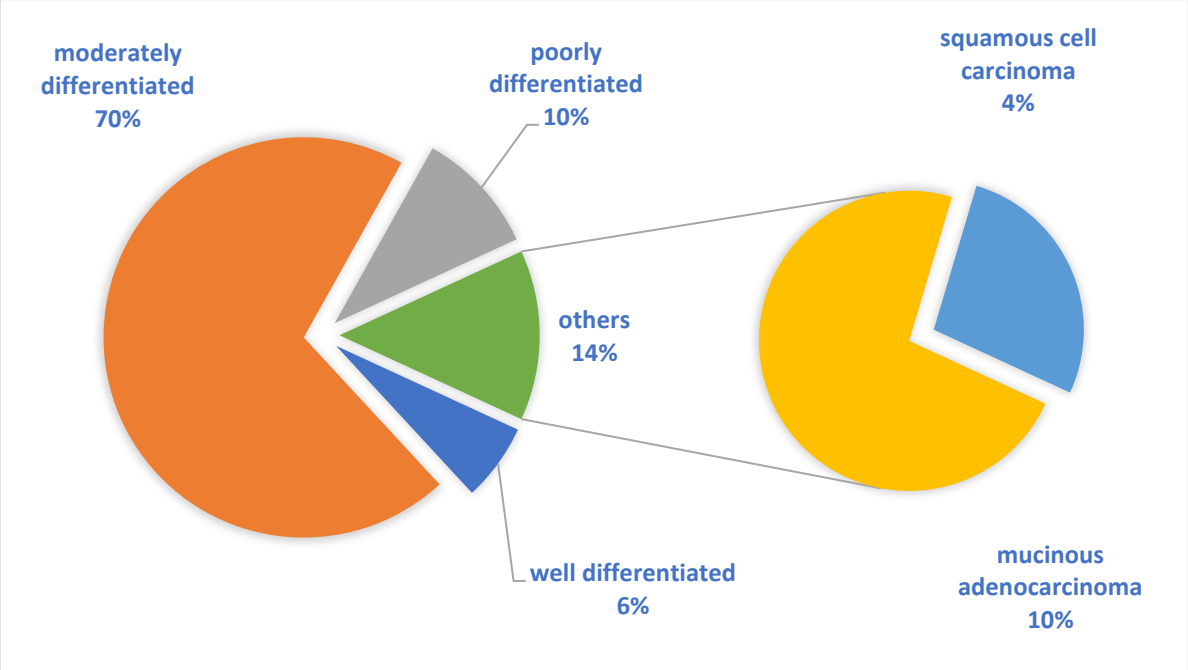


Figure 17 Percentage distribution of rectal cancer histological variants

When comparing the sizes of the tumors from different histological variants, no statistically significant difference was found in neither the length, nor the thickness of the tumors ($p>0.05$), although mucinous adenocarcinomas demonstrated the largest craniocaudal size and greatest tumor wall thickness, which could be associated with worse prognosis of this histological subtype. The results are presented on Tables 24 and 25.

Table 24 Comparison between the length of rectal tumors in different histological subtypes

histological subtype		length (mm)	SD	n	%	p-value
adenocarcinoma	well differentiated	50,2	20,5	5	6,25	0,74
	moderately differentiated	52,1	22,2	56	70	
	poorly differentiated	50,5	28	8	10	
mucinous adenocarcinoma		62,1	22,5	8	10	
squamous cell carcinoma		44,7	21,6	3	3,75	

Table 25 Comparison between the wall thickness of rectal tumors in different histological subtypes

histological subtype		thickness (mm)	SD	n	%	p-value
adenocarcinoma	well differentiated	19,2	11,4	5	6,25	0,77
	moderately differentiated	18,1	10	56	70	
	poorly differentiated	15,8	4,7	8	10	
mucinous adenocarcinoma		20,4	16,4	8	10	
squamous cell carcinoma		12	1,7	3	3,75	

Mean ADC values of the tumors from different histological variants were measured. The results are presented on Table 26. A statistically significant difference was found when comparing the mean ADC values of mucinous versus non-mucinous carcinomas ($p<0.001$). Mucinous tumors (Figure 18) showed the highest ADC values, despite their worse prognosis. They are a rare histological subtype that is associated with more advanced tumors, a greater risk of distant

metastases, as well as a poorer response to CRT and, therefore worse patient outcome (McCawley, Clancy et al. 2016, Barbaro, Leccisotti et al. 2017). The high mucin content and low cellular density in these tumors results in high ADC values and lack of diffusion restriction (Wnorowski, Menias et al. 2019). Our results complement those of other studies (Nasu, Kuroki et al. 2012, Colakoglu Er and Erden 2017) and show that the measurement of ADC values can be used in daily practice to distinguish mucinous from non-mucinous rectal carcinomas, which is of significance for the patient's prognosis.

Table 26 Comparison between ADC values in tumors of different histological subtypes

histological subtype		mean ADC	SD	n
adenocarcinoma	well differentiated	838	204	5
	moderately differentiated	834	130,8	50
	poorly differentiated	779	142,8	6
mucinous adenocarcinoma		1083	325,6	7
squamous cell carcinoma		870	50,5	3

No statistically significant difference was found between mean ADC values and different grades of tumor differentiation of non-mucinous adenocarcinomas (p=0.69). However, the lowest values were measured in poorly differentiated adenocarcinomas (779), which might be associated with a worse prognosis for tumors of a lower grade of differentiation. The histological grade of tumor differentiation has been shown to be an important prognostic marker for patient prognosis. There are many studies that demonstrate a statistically significant

correlation between ADC values and different grades of tumor differentiation (Curvo-Semedo, Lambregts et al. 2012, Yildirim 2020). However, our results did not reach statistical significance, which may be due to the relatively small study population in the different subtypes, especially in the groups with low- and high-differentiated adenocarcinomas.

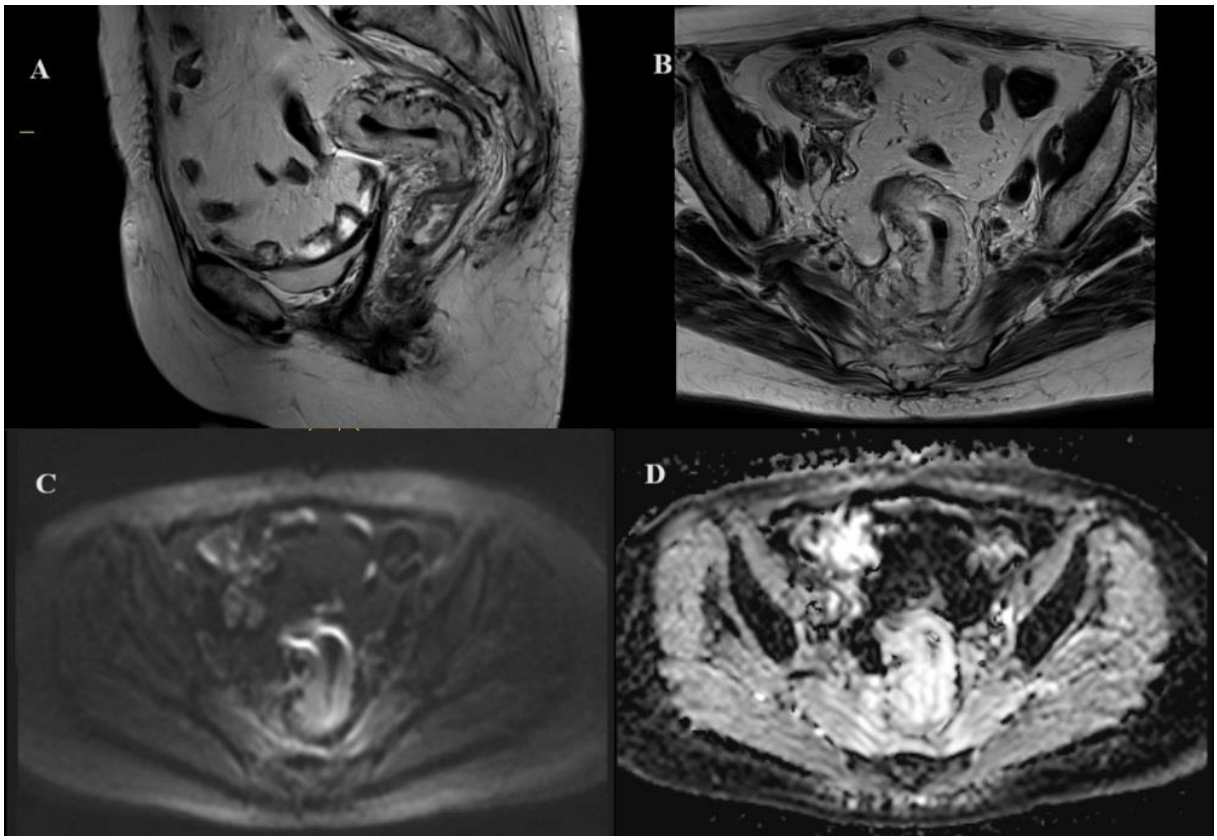


Figure 18 Mucinous adenocarcinoma of the rectum - A: sagittal T2; C: axial T2; C: DWI; D: ADC

9. Follow-up MRI

A total of 40 patients (38.8%) out of all 103 who participated in the study were referred for follow-up with an MRI examination. The results are presented on Table 27.

Table 27 Follow-up MRI results

	n	%
all followed-up patients	40	100 %
reduction	22	55 %
no dynamics	3	7,5 %
progress	1	2,5 %
local recurrence	14	35 %
complete therapeutic response	5	12,5 %
abscess	2	5 %
postradiation proctitis	2	5 %

In 26 patients, a comparison was made between the size of the rectal tumor before and after neoadjuvant radiochemotherapy. This group did not include 3 patients with carcinoma of the anal canal, 4 patients in whom recurrence outside the rectum was detected on the follow-up postoperative MRI examination, 5 postoperative MRI examinations of patients with a complete therapeutic response and no recurrence, and 2 patients with post-radiation proctitis.

According to the RECIST criteria for the assessment of solid tumors, partial response is defined as a > 30% reduction in the sum of the longest diameters of

the lesion (Figure 19), and progression is defined as a > 20% increase in the size (Eisenhauer, Therasse et al. 2009).

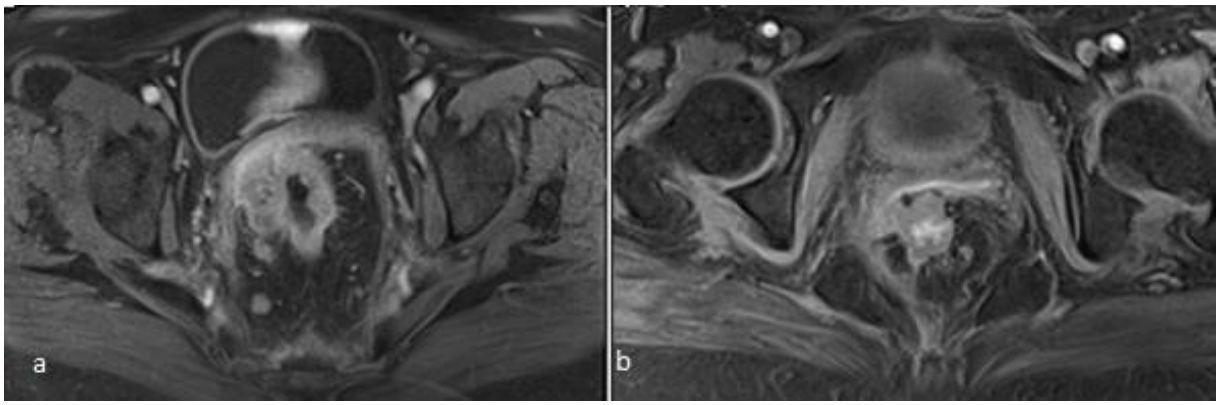


Figure 19 a. Locally advanced rectal carcinoma stage T4N2bM0; b. follow-up MRI examination after CRT – size reduction > 30% (partial response)

Out of 26 patients followed up after neoadjuvant chemoradiotherapy, 22 (85%) showed a reduction in the size of the primary tumor, 3 (11%) showed no significant change in size, and 1 (4%) showed progression in the size of the primary tumor (Figure 20).

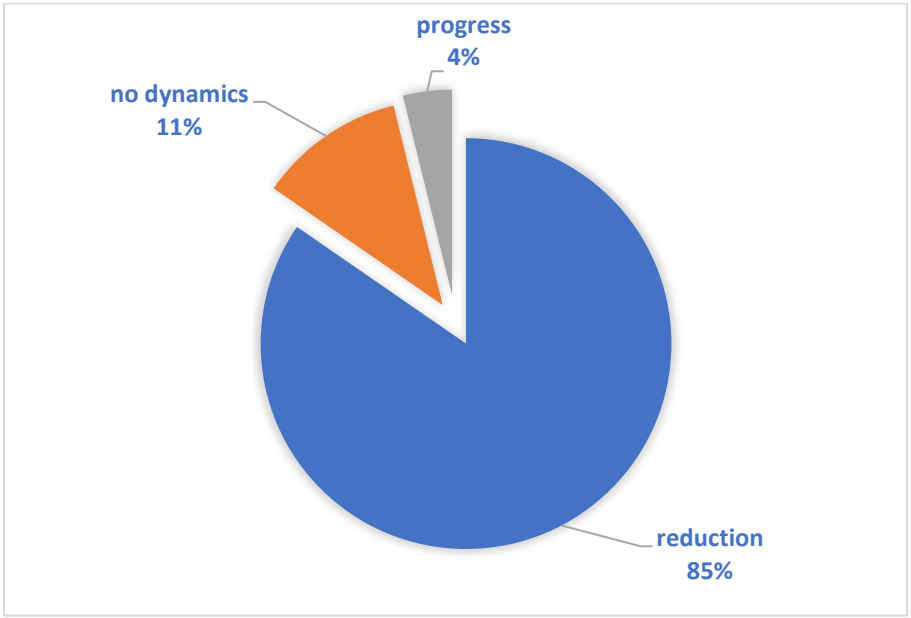


Figure 20 Follow-up after neoadjuvant chemoradiotherapy

Reduction in the craniocaudal size (length) and thickness of tumors were observed separately. No statistically significant difference was found regarding the length of tumors after CRT (p=0.4), but such was found when comparing the thickness of tumors before and after CRT (p=0.01). The results are presented on Table 28 and Figure 21.

Table 28 Reduction in the size of rectal tumors in 22 patients after CRT

	preCRT	postCRT	reduction (mm)	reduction (%)	p-value
length	52	46,7	5,8	10 %	0,4
thickness	21	13,6	7,5	31 %	0,01

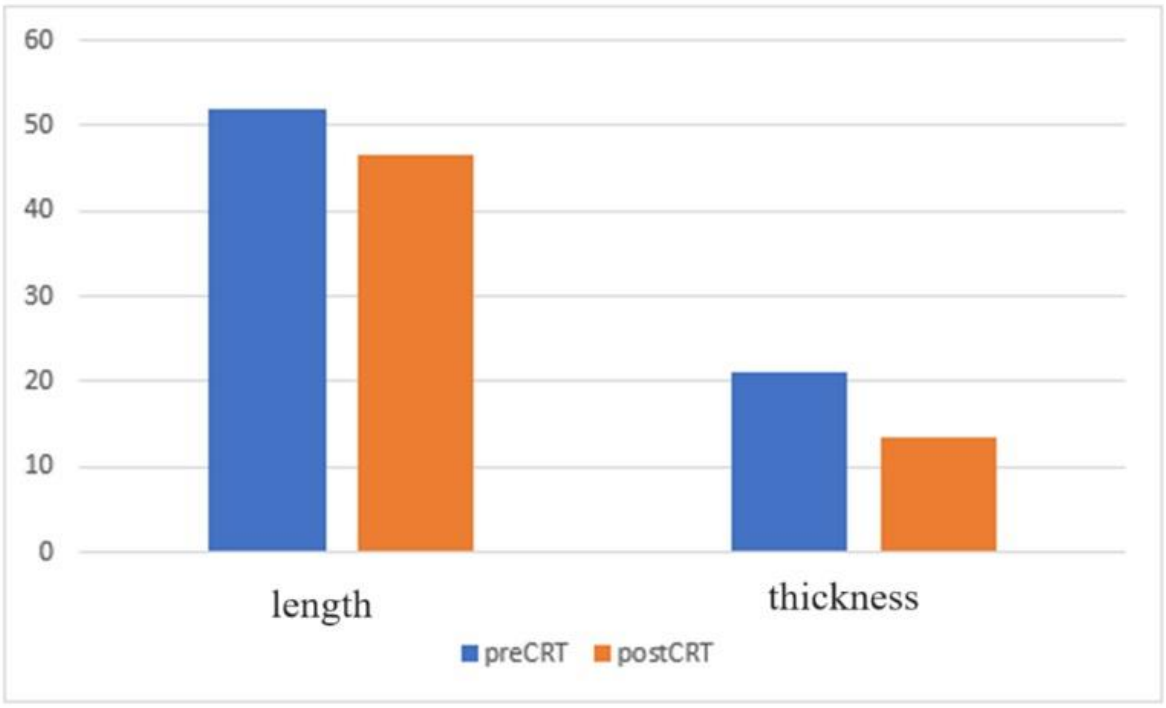


Figure 21 Comparison between the length and thickness of rectal tumors in 22 patients with reduction in the tumor size after CRT

In 18 of 26 patients that were followed-up, ADC values before and after radiochemotherapy were measured and compared (Figure 22). This group does not include patients who did not have a DWI sequence performed on the initial MRI examination.

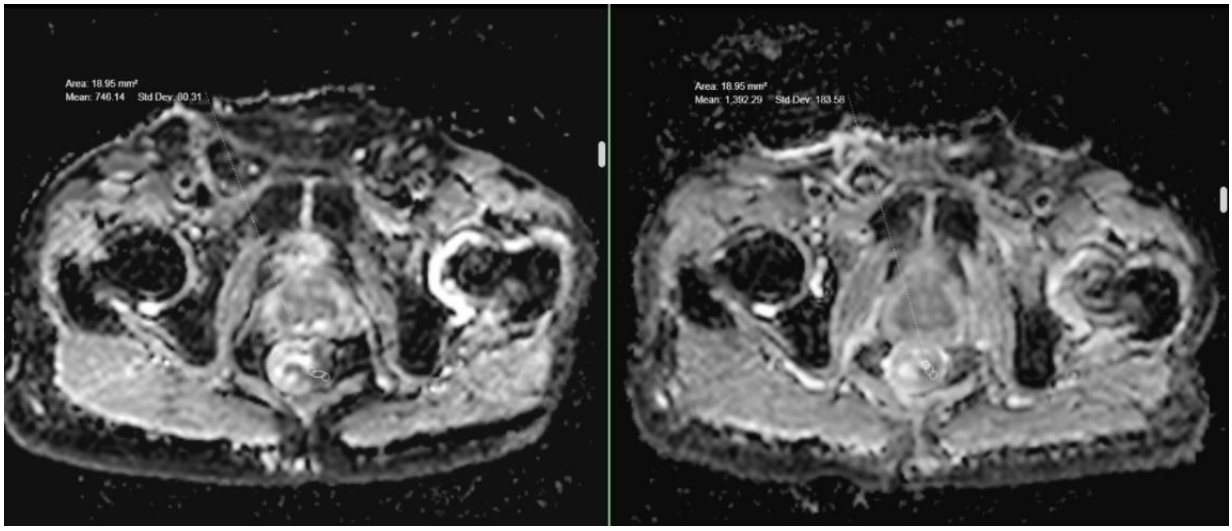


Figure 22 Rectal carcinoma stage T3 - ADC values before and after radiochemotherapy

All 18 patients had an increase in the ADC values after CRT (Figure 23). The mean ADC value in this group before CRT was 826 and after CRT was 1067 ($p<0.001$). In 14 of 18 patients, a partial response to therapy was observed with a > 30% reduction in tumor size and an increase in the ADC values, which correlates with a good therapeutic response. Decreased tissue cellularity and increased extracellular space after CRT leads to increased ADC values (Choi, Oh et al. 2016, Xu, Xu et al. 2021).

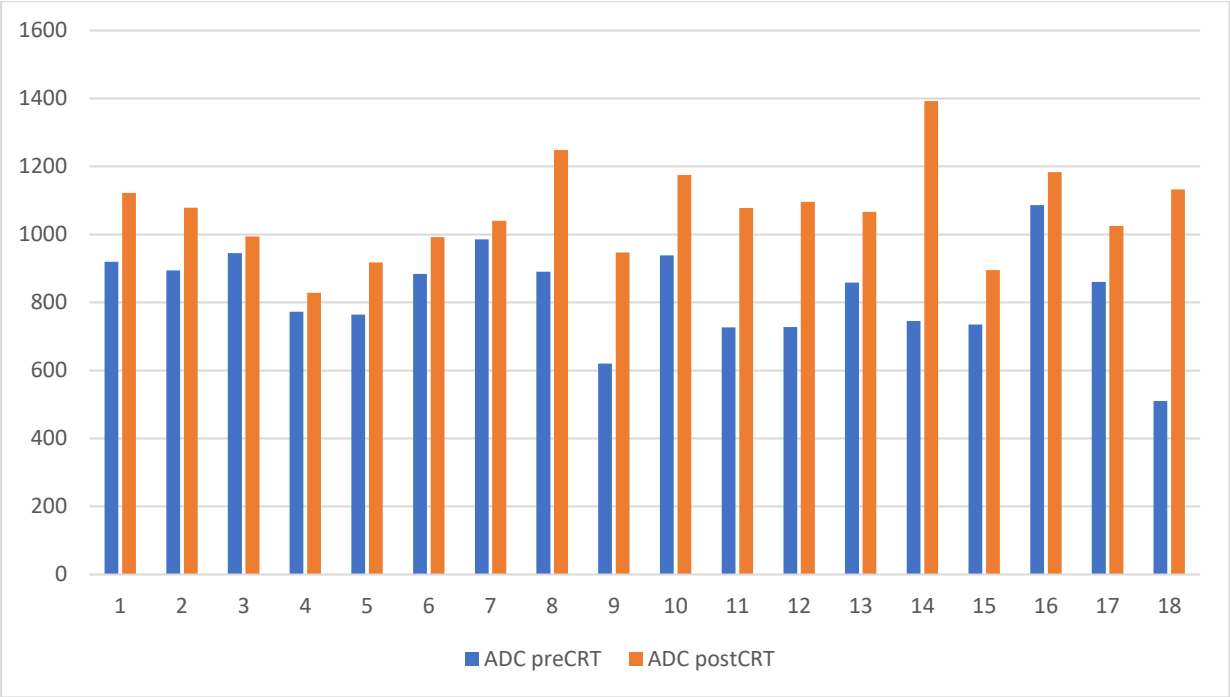


Figure 23 Comparison between the mean ADC values before and after CRT in all 18 patients

Although not all tumors showed size reduction - 14 (78%) showed size reduction, 3 (16%) showed no change in the size, 1 (5%) showed size progression, an increase in the mean ADC values was observed in all 18 patients (Figure 23). This indicates that an increase in the ADC values can be observed before a reduction in the size occurs. Therefore, DWI/ADC can be used as an early prognostic marker for tumor response to therapy. Similar observations have been described in various studies and demonstrate that the calculation of ADC values in the assessment of response to CRT can significantly influence patient management by allowing appropriate optimization of therapy and contributing to overall patient outcome (Afaq, Andreou et al. 2010).

The mean increase in ADC values after CRT compared to baseline values was 241, showing a statistically significant difference - $p<0.001$. Mann-Whitney U test was used to detect a statistically significant difference between mean ADC values in different groups. The mean increase in ADC values in T2 stage tumors was higher (257; $p<0.05$) compared to T1 stage (202; $p<0.05$) and T3 stage tumors

(205; p<0 ,05). Tumors in stage T4 showed the highest percentage of increase in ADC values (288; p<0.05). The results are presented on Table 29.

Table 29 Mean increase in ADC values after radiochemotherapy in tumors of different T stages

	mean increase in ADC values after CRT	% increase in ADC values	p-value
all	241	29 %	<0,05
T1	202	22 %	<0,05
T2	257	30 %	<0,05
T3	205	25 %	<0,05
T4	288	37 %	<0,05

The greatest difference in ADC values before and after CRT was observed in locally advanced T4 stage tumors (Figures 24 and 25).

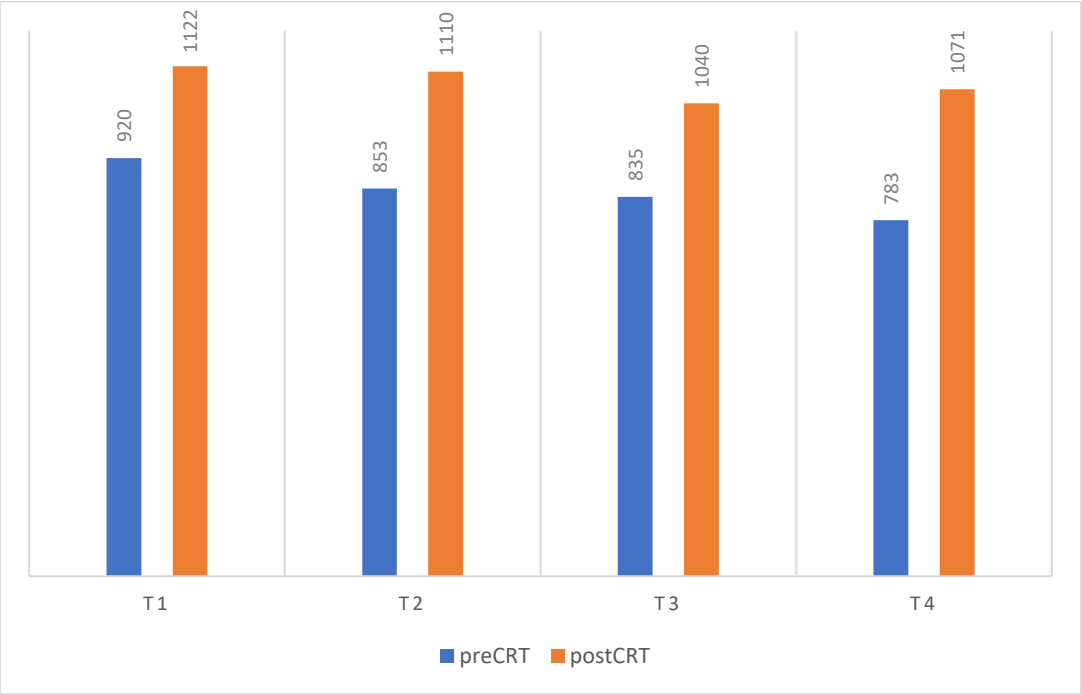


Figure 24 Comparison between the mean ADC values of tumors of different T stages before and after CRT

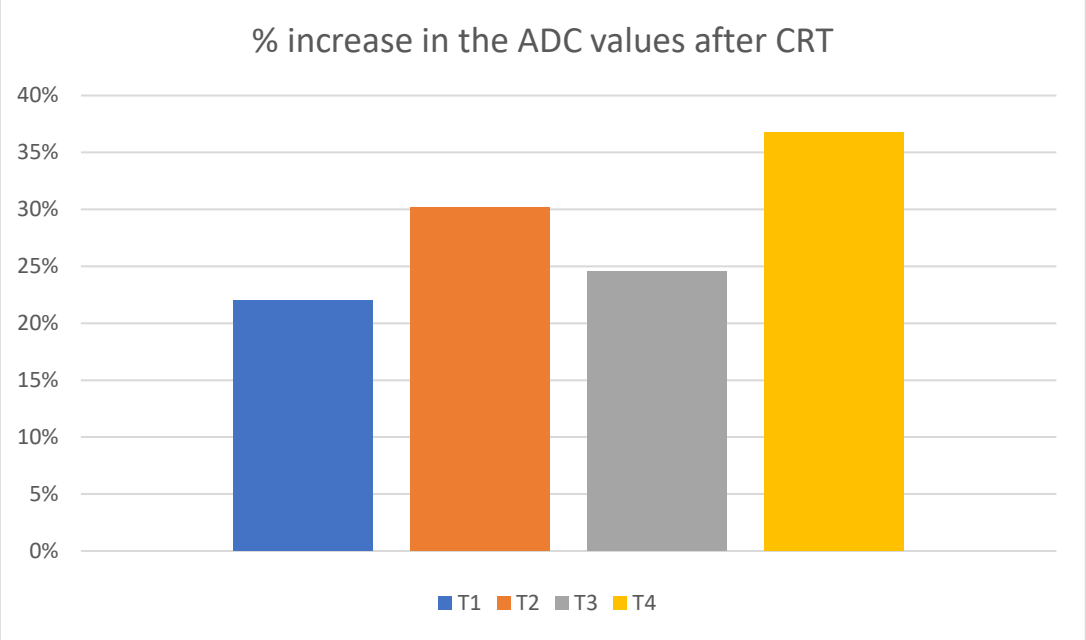


Figure 25 Percentage of increase in the ADC values after CRT in tumors of different T stages.

Pearson's correlation coefficient test was used when comparing initial tumor ADC values and the mean increase in ADC values after administration of radiochemotherapy (Figure 26). A statistically significant and moderately strong negative correlation was observed (r=-0.6572; p=0.004) – tumors with the lowest initial ADC values showed the greatest increase in values after CRT, meaning a more pronounced response to therapy or in other words, lower cellular differentiation of tumors is associated with higher sensitivity to CRT.

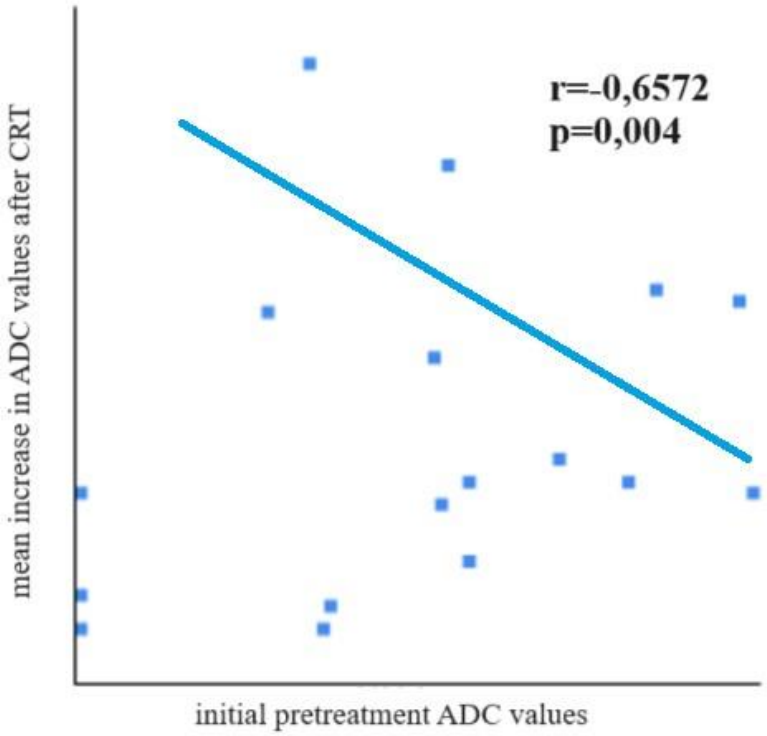


Figure 26 Pearson's correlation test shows a negative correlation between the initial ADC values of the tumors and the mean increase in ADC after CRT (r=-0.6572; p=0.004)

The results showed that locally advanced rectal carcinomas with lower initial ADC values showed greater increase in the ADC values after treatment, whereas those with high initial values did not increase that much after therapy. Our results complement those of other studies (Sun, Zhang et al. 2010, Zhao, Zhao et al. 2021), indicating that measuring ADC values during routine MRI exams

might be useful for predicting response to therapy since tumors with low baseline ADC values are more likely to respond better to radiochemotherapy (DeVries, Kremser et al. 2003, Birlik, Obuz et al. 2015). This may be due to the fact that tumors with higher initial ADC values are more prone to have necrotic areas, which is associated with low tissue perfusion and greater resistance to radiochemotherapy (Intven, Reerink et al. 2013) .

Our results suggest that measuring ADC values could be useful for the proper decision making of patients' treatment - in patients with tumors with high initial ADC values and expected poor response to therapy, the adverse effects of CRT can be avoided and earlier and on time surgical treatment can be applied.

Out of all of the patients with a primary neoplasm of the anal canal (4), three were followed-up with MRI. No significant changes in the tumor size were observed in two (<30% reduction in size), and in one, a recurrence was found in the rectum after surgery. Similar to the patients in the group with rectal carcinomas, a statistically significant difference in ADC values before and after CRT was also found ($p=0.01$). The mean ADC values before therapy were 519, after CRT – 1202.

Regarding the rectal carcinoma patients that were followed-up, recurrences were found in 14 patients. No gender difference was found - 7 male, 7 female. The mean age of patients in this group was 65. The mean ADC of these tumors was 759, significantly lower than the mean ADC of all tumors (841, $p<0.05$). These results again show the association of low ADC values with the degree of aggressiveness of the tumors and the corresponding worse prognosis.

10. Synchronous and metachronous tumors

Out of all 103 patients participating in the study, in 12 (11.7%) we found a synchronous or metachronous tumor in a different organ other than the primary neoplasm in the rectum or anal canal. Synchronous tumors are defined as tumors in which the second primary neoplasm was detected within 6 months of the first tumor, while metachronous are the second primary neoplasm was detected more than 6 months after the first (Lv, Zhang et al. 2017).

The mean age of the patients in this group was 65.9. 7 of the patients were men, 6 were women. Synchronous or metachronous tumors were found in the following organs, outside the primary tumor in the rectum - prostate (2, Figure 27), cervix (2), breast (2), bladder (1), kidney (1, Figure 28), duodenum (1), small intestine (1), skin (1), and Hodgkin lymphoma (1).



Figure 27 Carcinoma of the rectum and synchronous carcinoma of the prostate with bladder infilltration

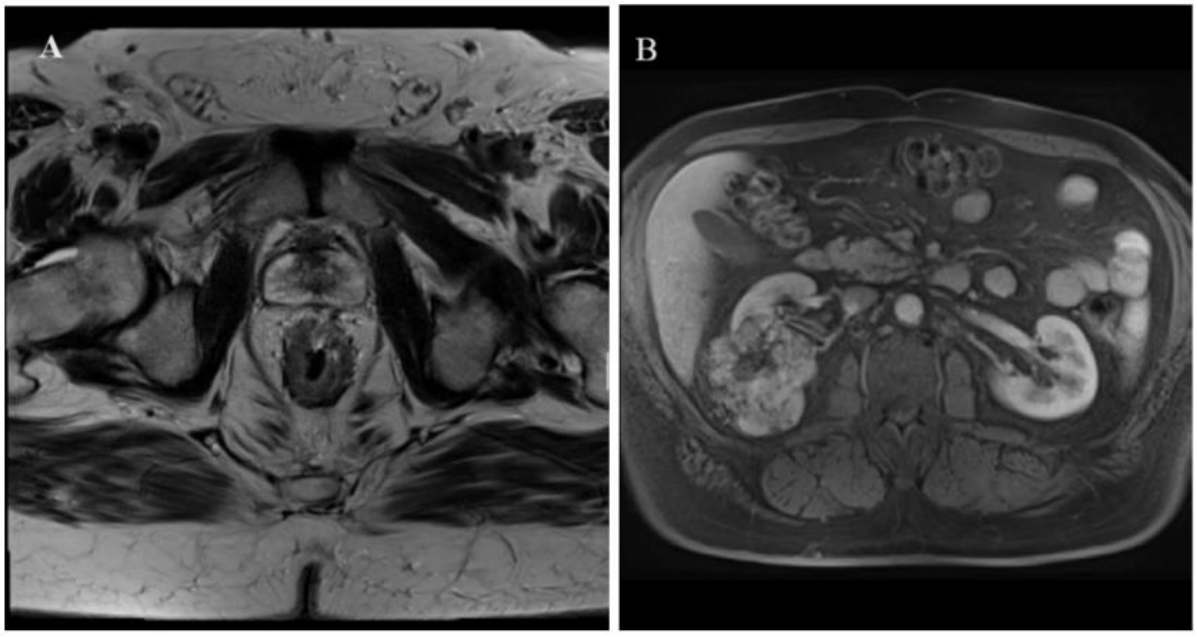


Figure 28 Rectal carcinoma (A) and synchronous renal carcinoma (B)

There are many risk factors for the occurrence of a second primary neoplasm such as genetic factors, infections, environmental factors, etc. Many cases have been described in patients who underwent pre- or postoperative combined chemoradiotherapy for the primary disease, who subsequently developed a second neoplasm in another organ (Pan, Huang et al. 2022). Our results complement those of other studies that observed a higher risk of a second neoplasm in patients treated with radiotherapy for rectal carcinoma (Birgisson, Pahlman et al. 2005, Halamkova, Kazda et al. 2021), the risk of such occurrence being particularly high in the irradiation area (Guan, Wei et al. 2021). In the routine primary staging or restaging of rectal carcinoma with MRI, it is of particular importance for the radiologist to be aware of the possibility of the presence of a second neoplasm in another organ, outside the primary focus. Early diagnosis of synchronous and metachronous tumors can significantly contribute to the therapeutic behavior and overall survival of patients with rectal carcinoma.

V. Summary

Magnetic resonance imaging is the method of choice for the diagnosis of neoplasms of the rectum and anal canal, especially in locally advanced tumors. It has a key role in the proper preoperative staging and determining the most appropriate therapeutic behavior.

Our study confirms that the magnetic resonance examination not only provides accurate information about the depth of tumor invasion and the relation to the surrounding structures, but can also be of use for the identification of important prognostic factors that can significantly influence the course of therapy.

Measuring ADC values of tumors can be an effective and convenient addition to the traditional imaging methods. It is a non-invasive technique that correlates well with important tumor characteristics. ADC values have an additional role in the evaluation of rectal and anal canal neoplasms and could be useful in predicting the expected response of tumors to neoadjuvant radiochemotherapy.

Their introduction into routine practice can significantly contribute to the optimization of the therapeutic strategy. Selecting patients who are more likely to respond well to radiochemotherapy based on the measured ADC values could avoid risks related to unnecessary toxicity and delayed operative intervention.

VI. Conclusions

1. MRI allows for the most accurate assessment of neoplasms of the rectum and anal canal;

2. A trend was found for earlier onset of rectal and anal canal neoplasms in women;

3. There is a statistically significant difference in the craniocaudal size of the tumor in the different T-stages – a higher T-stage is associated with a larger tumor size;

4. A statistically significant difference in the ADC values of the rectal tumors in the different T-stages has been proven – tumors of higher T-stage have lower mean ADC values;

5. The anal canal is more often infiltrated secondary from a primary low rectal carcinoma;

6. A statistically significant difference was found between ADC values in primary and secondary tumors of the anal canal - lower ADC values in primary anal canal tumors compared to secondary infiltrated anal canal from low rectal carcinoma;

7. There is a statistically significant difference in the length of tumors with EMVI compared to tumors without EMVI – greater length in tumors with EMVI;

8. There is a statistically significant difference between ADC values in tumors with EMVI and those without EMVI – lower ADC values in tumors with EMVI;

9. The correlation between extramural vascular invasion and the presence of distant metastases has been confirmed;

10. Higher incidence of EMVI was found in males;

11. During MRI follow-up after CRT we found:
    - a statistically significant reduction in the tumor thickness;
    - a statistically significant increase in the mean ADC values after CRT;
    - an earlier increase in the ADC values before reduction in the tumor size;
    - a statistically significant correlation between T-stage and percentage of increase in ADC values – greater increase in tumors of higher T-stage;
    - a statistically significant negative correlation – greater increase in ADC values in tumors with lower initial ADC values, correspondingly more pronounced response to therapy;

12. Some patients have a second synchronous or metachronous neoplasm in another organ

VII. Contributions according to the author

1. A statistically significant correlation was found between some magnetic resonance imaging characteristics and the degree of aggressiveness of the tumors;

2. The ability of MRI to identify some prognostic factors that can alter the course of therapy has been demonstrated;

3. The necessity of conducting an MRI examination during restaging and its role in evaluating the response to therapy has been confirmed;

4. The role of measuring ADC values for additional evaluation of the characteristics of neoplasms of the rectum and anal canal has been proven, as well as for the prediction of tumor response to treatment and the optimization of therapeutic strategy.

VIII. Publications related to the dissertation

Full text publications:

1. Yacheva, A.; Dardanov D.; Zlatareva, D.
   The multipurpose usage of diffusion-weighted MRI in rectal cancer
   Medicina, 2023; ISSN 1648-9144; doi: 10.3390/medicina59122162
   (Impact factor: 2,6)

2. Yacheva, A.; Zlatareva, D.
   Magnetic resonance imaging in rectal and anal canal neoplasms
   Roentgenologia and Radiologia, 2022, LXI: 189-198, ISSN 0486-400X

3. Yacheva, A.; Dardanov D.; Zlatareva, D.
   Follow-up MRI in the assessment of rectal cancer response to neoadjuvant chemoradiotherapy
   Roentgenologia and Radiologia, 2021, LX: 54-57; ISSN 0486-400X

Participation in international and national forums:

1. Milenov, G.; Fileva, N.; Kyumyurdzhiyski, Ya.; Yacheva, A.; Belyanova, M.; Dardanov, D.; Zlatareva, D.
   MRI evaluation of perianal fistulas – which MRI sequences and why we use them?
   ECR 2023, Vienna, Austria

2. Yacheva, A.; Zlatareva, D.
   The role of MRI for the detection of extramural vascular invasion in patients with rectal cancer
   XIX congress of BAR, 3-6 November 2022, Plovdiv, Bulgaria

3. Yacheva, A.; Zlatareva, D.
   Role of MRI for incidental detection of synchronous and metachronous tumors in patients with rectal cancer
   XIX congress of BAR, 3-6 November 2022, Plovdiv, Bulgaria

4. Mitkov, Y.; Dardanov, D.; Simonova, L.; Zhivkov, E.; Bashliev, I.; Shavalov, Zh.; Bonev, S.; Yonkov, A.; Zlatareva, D.; Yacheva, A.
   The importance of complex coloproctological examination in rectal cancer and methods for assessing the function of the anal sphincter complex - literature review
   XVIII National Congress of Surgery with international participation, October 8, 2022, Pleven

5. Yacheva, A.; Dardanov, D.; Mitkov, Y.; Zlatareva, D.
   MRI Pelvic Anatomy In Rectal Cancer Patients After Preoperative Radiotherapy