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Postoperative radio-chemotherapy for rectal cancer: A retrospective analysis from a tertiary referral hospital

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ABSTRACT

Aim: To report results of postoperative radio-chemotherapy (RT-CHT) for rectal cancer (RC).
Background: Total mesorectal excision (TME) is an essential treatment method in rectal cancer (RC). Perioperative radiotherapy in locally advanced RC improves loco-regional free survival (LRFS). Preoperative radiotherapy is a preferred option; however, some patients are not referred for it. In case of the risk of loco-regional failure postoperative radio-chemotherapy (RT-CHT) is indicated.
Material and methods: Between 2004 and 2010, 182 patients with pathological stage II-III RC (TME performed — 41%, resection R0 — 88%, circumferential resection margin evaluated — 55.5% and was above 2 mm in 66% of them) received postoperative RT-CHT in our institution. Overall survival (OS) and LRFS were estimated with the Kaplan–Meier method. Univariate and multivariate analysis were performed to compare the impact of prognostic factors on survival.
Results: Five-year OS and LRFS rates were 63% and 85%, respectively. Loco-regional recurrence and isolated distant metastases rates were 11.5% and 19%, respectively. Multivariate analysis showed stage (III *vs.* II), HR: 2.3 (95% confidence interval [CI]: 1.4–3.8), p = 0.0001; extent of resection (R1–2 *vs.* R0), HR: 2.14 (95%CI: 1.14–3.99), p = 0.017, and age (>65 *vs.* ≤65 years), HR: 1.66 (95%CI: 1.06–2.61), p = 0.027 as prognostic factors for OS. Extent of resection (R1–2 *vs.* R0), HR: 3.65 (95%CI: 1.41–9.43), p = 0.008 had significant impact on LRFS.
Conclusion: Despite a suboptimal quality of surgery and pathological reports, the outcome in our series is close to that reported in the literature. We confirm a strong impact of the extent of resection on patient's outcome, which confirms the pivotal role of surgery in the management of RC.

1. Background

Colorectal cancer is one of the leading cancers in terms of incidence as well as mortality rate worldwide. The most common cancer localization in large bowel is the rectum. In the report from 2014 for Poland, rectal cancer (RC) accounted for 4.57% in men and 2.90% in women of all reported cancer cases and was the cause of 3.5% of cancer deaths; relation of mortality to incidence was estimated at 0.55.[1]

The standards in the treatment of RC have been introduced over the last two decades.[2–4] The most important were improvement of surgical techniques and implementation of the total mesorectal excision (TME) technique to routine practice. The main visible result of TME was a reduction of the risk of local recurrence to about 10% from 30%, previously reported in stage II and III RC.[5,6] The local recurrence rate is strongly related to the quality of surgical treatment.[6–8] New pathological standard consists of macroscopic assessment of the quality of mesorectal excision and microscopic assessment of circumferential resection margin (CRM).[7,9,10] The use of preoperative radiotherapy (RT) with TME is related to further

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reduction of local recurrence rate to 5% without significant overall survival benefit.[6] The preoperative magnetic resonance imaging (MRI) assessment of the relationship between tumor and mesorectal fascia is highly accurate in the prediction of the status of CRM and is crucial in the decision-making process. The ability of MRI to identify with high probability malignant lymph nodes also underlines its importance in the proper referral for preoperative RT or radio-chemotherapy (RT-CHT).[11],[12]

Administration of postoperative RT has been significantly declining due to the evidence that preoperative concurrent RT-CHT or short-course RT have better outcome in terms of local control and toxicity.[13],[14] Patients with MRI-based staging have a risk-adapted strategy established before surgery and those who need RT are referred for preoperative treatment. However, if preoperative RT has not been given and despite a good quality of surgery, some unexpected adverse histopathological features are found — *e.g.* CRM ≤ 1 mm, pT4b, pN2 extracapsular spread close to mesorectal fascia, extranodal deposits (N1c), postoperative RT-CHT is recommended.[3] The reasons for the use of postoperative RT-CHT are complex, not only caused by unexpected pathological findings in properly staged and treated patients. These are most often related to the treatment of patients outside reference centers where experts' recommendations for various reasons are not respected: referral of patient to immediate surgery without multidisciplinary decision making due to long distance from surgical centers to radiotherapy departments and/or the absence of a radiation oncologist in the treating team, emergency operations due to bowel obstruction, inadequate surgery and/or pathological reports, underestimation of the loco-regional extent of the disease due to an inadequate staging procedure, mainly lack of preoperative pelvic MRI. Postoperative RT with concomitant fluoropirimidine-based CHT has always been used in patients with pT4, extensive lymph nodes metastases, positive resection margins in CRM, perforation in the tumor area, defects of the mesorectum in macroscopic assessment, but also in other cases with suspected high risk of local recurrence caused by an uncertain extent of surgery and/or incomplete pathological report, if preoperative RT has not been given.[2],[15]

2. Aim

In our institution, with advances in RC management (MRI as a preoperative standard, multidisciplinary decision-making) we have also observed a declining referral for postoperative RT-CHT in favor of preoperative RT or RT-CHT. However, as a tertiary center, covering needs for RT for most hospitals of the Warmian-Masurian Voivodeship, at long distance from our institution, we have still RC patients referred for adjuvant RT-CHT. Thus, we aimed in this retrospective study to evaluate the efficacy of postoperative RT-CHT for locally advanced RC and to seek patient's, tumor's and treatment related factors associated with to survival and loco-regional control. We focused on the relation of the quality of surgery and patients' outcome.

3. Material and methods

3.1. Patients and treatment

One hundred and eighty-two consecutive patients with locally advanced rectal adenocarcinoma treated with surgery and qualified for postoperative RT-CHT between 2004 and 2010 in our institution were included into this study. Patients were operated in 25 different hospitals. RT with concomitant CHT was given in the Independent Public Health Care Facility of the Ministry of the Interior and Warmian & Masurian Oncology Center in Olsztyn. The list of included patients was generated from the institutional database. The medical records of all patients were available for the purpose of the study.

Patients without preoperative RT having pathological stage II–III (T3−4N0M0 or T1-4N1-M0) according to the TNM/AJCC 2002 classification[16] were referred for adjuvant RT-CHT. Patient and treatment characteristics are presented in Table 1. We have no details on the use of pelvic MRI for baseline staging in these patients; however, taking into account the limited availability of the MRI machines in Poland during the studied period, there were certainly very few patients with such examination performed.

Types of operations were anterior resection or abdominoperineal resection. Radical resection (R0) meant that all microscopic margins of the resection were negative. Three-dimensional conformal 3D-CRT with 6 or 15 MV photons consisted of 50.4 Gy or 45 Gy in 28 or 25 fractions, respectively. In 3 patients with macroscopically non radical operation the total dose was increased to 54 Gy (boost of 3.6 Gy in 2 fractions). Clinical target volume included tumor bed with mesorectal space and regional lymph nodes. In most cases, RT of the pelvis was given concurrently with the 2nd and 3rd or 3rd and 4th cycle of CHT, consisting of 5-FU-L (5-Fluorouracil–Leucovorin: 5FU:325 mg/m^2, L: 20 mg/m^2, both drugs in i.v. infusion days 1–5) in the first and fourth week of RT. CHT was continued then up to 6 cycles given every 28 days.

3.2. Statistics

The efficacy of postoperative RT-CHT was estimated by survival analysis with the Kaplan–Meier method. Overall survival (OS) was measured from the date of surgery to the last follow-up/death. Loco-regional recurrence-free survival (LRFS) was measured from the date of surgery to the date of first loco-regional recurrence or last follow-up visit/death without recurrence. The variables that could impact patient OS and LRFS (sex, age, tumor localization: ≤12 cm *vs.* >12 cm from anal verge, stage, tumor size, lymph node involvement, grade, extent of resection: R0 *vs.* R1–R2, number of lymph nodes removed, performance of TME as specified in pathological and/or surgical report, volume of surgical unit meant as performing radical RC surgery frequently — *high volume* [the average ≥16 operations of RC per year] *vs.* rarely — *low volume* [the average <16 operations of RC per year]) were analyzed in univariate analysis (log-rank test). Numbers of RC surgery performed between 2007 and 2010 in the Warmian-Masurian Voivodeship were based on the reports from the regional department of National Health Fund (NFZ).

The variables related to OS and LRFS in univariate analysis with $p \leq 0.1$ were included into the multivariate analysis using the Cox's regression model. A $p < 0.05$ was considered as statistically significant. Statistical analysis was performed using STATISTICA software (version 12.5) (StatSoft, Poland).

4. Results

One hundred sixty-one patients (88%) had complete, radical resection of the tumor. Microscopically and macroscopically non radical resection was performed in 10% and 2% of the patients, respectively. In 55% of the cases, the surgery was performed in the *high volume* centers. According to the surgical/pathological reports, TME was done in 75 cases (41%). The quality of TME was not routinely pathologically evaluated. CRM was evaluated and described in millimeters in pathological reports in 55.5% of cases. In 34.6% cases CRM was >2 mm. The time interval between surgery and the first course of CHT ranged from 20 to 147 days (median: 46 days). One hundred and seventy-three patients (95%) got the prescribed RT dose. In nine patients (5%), RT was terminated at the

Table 1
Patients and treatment characteristic.

Characteristics		No.	(%)
No. of patients		**182**	**(100)**
Sex			
	Males	106	(58)
	Females	76	(42)
Age, years	Median: 63; Range: 39–83		
	≤65	99	(54)
	>65	83	(46)
Distance from the anal verge [cm]			
	≤12	123	(67.6)
	>12	50	(27.5)
	Unknown	9	(4.9)
Clinical stage (TNM-UICC/AJCC; 2002)			
	II	75	(41)
	III	104	(57)
	Unknown	3	(2)
T stage			
	T1	3	(2)
	T2	15	(8)
	T3	148	(81)
	T4	16	(9)
N stage			
	Nx	3	(2)
	N0	75	(41)
	N1	73	(40)
	N2	31	(17)
Grade (G)			
	G1	3	(2)
	G2	164	(90)
	G3	13	(7)
	Unknown	2	(1)
Extent of resection			
	R0	161	(88)
	R1	18	(10)
	R2	3	(2)
Number of lymph nodes removed			
	<12	116	(64)
	≥12	66	(36)
Circumferential resection margin			
	>2 mm	63	(34.5)
	≤2 mm	38	(21)
	Unknown	81	(44.5)
Performance of TME as specified in pathological/surgical reports			
	Yes	75	(41)
	No	72	(40)
	Unknown	35	(19)
Operating Centers (NFZ data) as per number of operations performed annually			
	Ḧigh volume(̈≥16 operations of RC per year)	101	(55.5)
	“Low volume(̈<16 operations of RC per year)	81	(44.5)
Planned dose of radiotherapy (Gy)			
	45	54	(29.7)
	50.4	125	(68.7)
	54	3	(1.6)
Total number of chemotherapy cycles			
	6	126	(69.5)
	5	3	(1.5)
	4	4	(2)
	3	5	(3)
	2	10	(5.5)
	1	3	(1.5)
	Unknown	31	(17)
Number of chemotherapy cycles given concomitantly with radiotherapy			
	2	140	(77)
	1	30	(16.5)
	0	12	(6.5)

total dose lower than 30 Gy: poor tolerance and deterioration of performance status (8), liver metastases diagnosed during RT (1). One hundred and forty patients (77%) received 2 courses and 30 patients (16.5%) one course of concurrent CHT. One hundred and twenty-six patients (69.3%) received all six planned cycles of CHT. Twenty-five patients (13.7%) terminated CHT prematurely for various reasons (deterioration of performance status, recurrence in the pelvis, liver metastases, unacceptable toxicity of the treatment, and patient refusal).

Twenty-one patients were excluded from the survival analysis due to incompleteness of the follow-up data. At the time of analysis, 77 patients (42%) died. Follow-up after surgery ranged from 0.4 to 9.1 years (median: 4.9 years) for all analyzed patients and from 3.5 to 9.1 years (median: 5.8 years) for survivors. Loco-regional

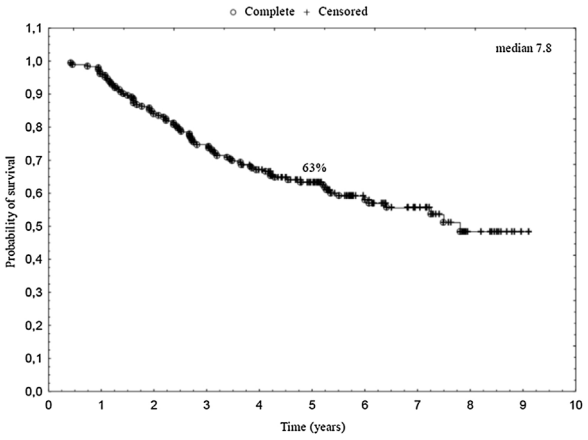

Fig. 1. Overall survival of all patients.

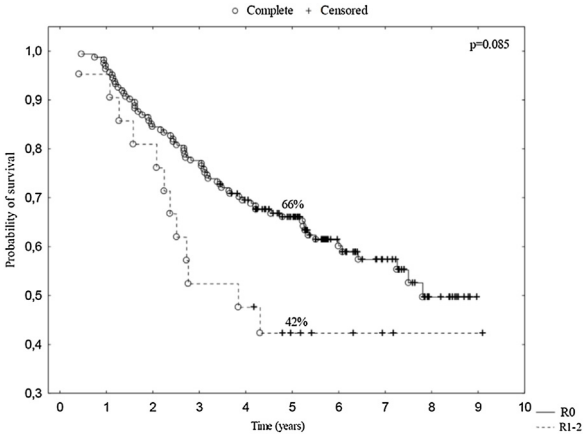

Fig. 2. Overall survival according to the extent of resection.

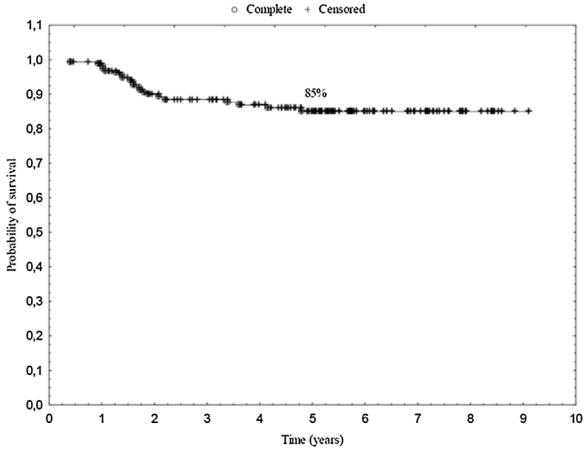

Fig. 3. Local recurrence-free survival for all patients with complete follow-up data (n=161).

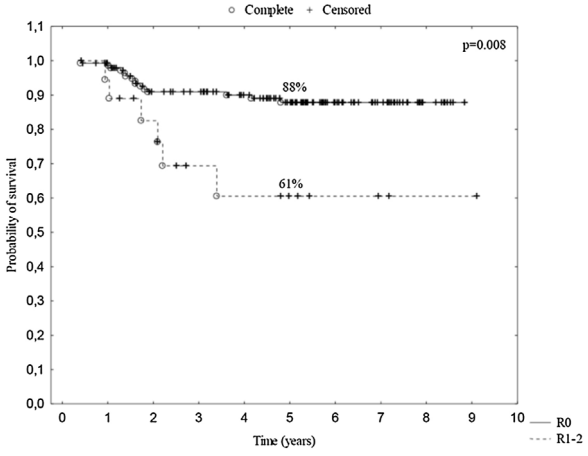

Fig. 4. Local recurrence-free survival according to the extent of resection.

recurrence was diagnosed in 21 patients (11.5%). Seven patients with loco-regional recurrence had also distant metastases. Distant metastases without loco-regional recurrence were diagnosed in 35 patients (19%). Toxic deaths were noted in 4 cases: two had small bowel obstruction during RT (1) and 5 days after termination of RT (1), two had toxicity of adjuvant CHT after termination of RT. A second cancer was diagnosed in four cases.

Five-year OS was 63% with a median of 7.8 years (Fig. 1). In univariate analysis the statistically significant impact on OS was demonstrated for stage of the disease ($p = 0.0015$), lymph node involvement ($p = 0.002$) and age ($p = 0.03$) (Table 2). Extent of resection had no statistically significant impact on OS (Fig. 2). Multivariate analysis showed stage of the disease (CS III *vs.* II), HR: 2.3 (95% confidence interval [CI]: 1.4–3.8), $p = 0.0001$; extent of resection (R1–2 *vs.* R0), HR: 2.14 (95%CI: 1.14–3.99), $p = 0.017$, and age (>65 *vs.* ≤65 years), HR: 1.66 (95%CI: 1.06–2.61), $p = 0.027$ as independent factors for OS. Five-year LRFS was 85% (Fig. 3). The significant impact on LRFS was demonstrated for the extent of resection ($p = 0.008$) (Fig. 4) and tumor size ($p = 0.012$) in univariate analysis (Table 2). In the multivariate analysis, the extent of resection (R1–2 *vs.* R0), HR: 3.65 (95%CI: 1.41–9.43), $p = 0.008$ was the only factor with a significant impact on LRFS.

5. Discussion

In our study five-year OS and LRFS rates were 63% and 85%, respectively. These results are close to published data on postoperative RT-CHT. Genovesi et al. [17] in group of 1338 patients with locally advanced RC treated with postoperative RT-CHT between 1985 and 2005 reported 63.5% and 87% of 5-year OS and LRFS rates, respectively. In retrospective Polish study, including 178 patients treated with postoperative RT-CHT, the 5-year OS and LRFS were 65% and 73%.[18] All these reports come from the era of broader indications for postoperative RT-CHT, related to the frequency of deficient quality of surgery and/or pathological reports, as well as poor preoperative imaging, *i.e.* lack of the pelvic MRI for staging. We have no results based on large series of postoperative RT-CHT used selectively in properly staged and operated patients. We expect that treatment outcome of such patients would be better than in the cohort of under-staged, often with low-quality surgery patients, as in older series, like ours. A question arises to what extent the use of postoperative RT-CHT may compensate some deficiencies in surgery and baseline staging. Obviously, we cannot have prospective data for that. Thus, such reports on the treatment of RC that come from the rural areas where the access to the reference centers is limited could indirectly answer this question.

Prognostic factors well recognized in the literature, such as clinical stage, extent of resection, and age had independent impact on OS in our study.[19] Extent of resection was also prognostic for LRFS. We did not demonstrate that some determinants of quality of surgery in RC other than the extent of resection, such as completeness of TME, number of lymph nodes removed, "volume" of surgical center (*i.e.* number of rectal surgeries performed annually), or CRM are related to survival and/or local control. The small number of patients in the analyzed group may be a reason for this result. It is also possible that this resulted from relatively poor quality of

Table 2
The results of univariate analysis of influence of patient and treatment related factors on overall survival and loco-regional recurrence-free survival.

		Overall survival (OS)			Loco-regional recurrence-free survival (LRFS)		
		5-year	Median (years)	*p*	5-year	Median (years)	*p*
Sex							
	Males	66%	7.8	*p = 0.63*	86%	–	*p = 0.51*
	Females	60%	–		83%	–	
Age (years)							
	≤65	69%	–	*p = 0.03*	86%	–	*p = 0.65*
	>65	56%	6		84%	–	
Tumor distance from the anal verge [cm]							
	≤12	60%	7.5	*p = 0.105*	85%	–	*p = 0.57*
	>12	72%	–		89%	–	
Clinical stage (TNM-UICC/AJCC; 2002)							
	II	77%	–	*p = 0.0015*	87%	–	*p = 0.49*
	III	53%	5.3		84%	–	
T stage							
	T1	100%	–	*p = 0.56*	100%	–	*p = 0.012*
	T2	50%	4.8		75%	–	
	T3	65%	7.8		88%	–	
	T4	54%	–		62%	–	
N stage							
	N0	77%	–	*p = 0.002*	87%	–	*p = 0.68*
	N1	52%	7.8		84%	–	
	N2	54%	5.2		84%	–	
Grade (G)							
	G1-2	64%	–	*p = 0.056*	84%	–	*p = 0.43*
	G3	46%	1.7		100%	–	
Extent of resection							
	R0	66%	7.8	*p = 0.085*	88%	–	*p = 0.008*
	R1-2	42%	3.8		61%	–	
Number of lymph nodes removed							
	<12	63%	7.8	*p = 0.83*	82%	–	*p = 0.26*
	≥12	65%	–		91%	–	
Circumferential resection margin							
	>2 mm	70%	–	*p = 0.76*	86%	–	*p = 0.68*
	≤2 mm	65%	–		90%	–	
Mesorectum							
	Removed	69%	–	*p = 0.26*	90%	–	*p = 0.09*
	Not removed	61%	7.3		79%	–	
Operating Centers (NFZ data) as per number of operations annually							
	Ḧigh volume ẗ(≥16 operations of RC per year)	64%	7.5	*p = 0.88*	83%	–	*p = 0.27*
	Low volume" (<16 operations of RC per year)	63%	7.5		88%		

non-standardized surgical and pathological reports in our series. However, we cannot exclude, that the use of postoperative RT-CHT compensated to some extent a deficient quality of surgery, but this is a very debatable issue.

The results of colorectal cancer treatment strongly correlate with the technique of resection and quality of operation.[6–8] TME operation is an essential treatment method in RC, it provides a local control effect that is better than in other techniques.[14,20,21] In our study, the mesorectum was not removed in 40% of cases. Moreover, in our material the surgical reports were, unfortunately, in some proportion incomplete; in 19% of patients there was no data about completeness of mesorectal resection. Literature data indicated that using the TME technique is strongly recommended, but not strictly applied. Unsatisfactory quality of TME operations was demonstrated in 24% cases by pathologist's evaluation in a Dutch study, despite an introduction of special training for surgeons.[22] Polish audit of the Mazovia region showed an inadequate quality of operations; in 42% of analyzed surgical reports, authors found that some statements suggested no-TME resections performed.[23] Our data show similar results with regard to the quality of surgery and provided surgical and/or pathological reports. We demonstrated that the extent of resection (R1–2 *vs.* R0) was a factor with a significant impact both on OS and LRFS. Since publication of Quirke et al.,[24] it has been well known that local recurrence in RC strongly depends on the lateral spread of the tumor. CRM ≥ 2 mm, is associated with a local recurrence risk of 16% compared with 6% in patients with a greater distance of tumor from radial margin.[8] CRM should be well described in a pathological report,[8,24–26] but when routine pathological reports were analyzed, it was shown that a proper description of CRM was not provided in 21–75% of cases.[23,27] A pathology report should include such elements as the measurement of the free CRM and macroscopic assessment of the quality of mesorectal excision missed by a significant proportion of pathologic reports in our study. In our material, CRM was described in 55.5% of specimens and had no effect on OS and LRFS, which may be related to the small size of the group and a large proportion of lacking data. The number of invaded LN in pathological report was reported as an important prognostic factor with negative impact on OS.[28] In our study, the number of LN retrieved did not have any impact on OS and LRFS, but only 36% of our patients have an

appropriate number of LNs resected, indicating once again a complex problem of decision making in qualification for postoperative RT-CHT in the face of incomplete and poor surgical/ pathological reports.

In our study, a division of centers into frequently or rarely operating does not have any impact on patients outcome; however, some literature data are different. A relationship between recurrence rate, operating centers and number of RC operations performed by the surgeon himself annually was demonstrated.[29] One may argue that in the face of poor quality of staging/treatment, without multidisciplinary decision-making, a number of operated cases did not compensate for these limitations. There is a compelling body of evidence that patients with RC should be treated only in specialized centers by a multidisciplinary team.

The five randomized studies demonstrated that the use of adjuvant CHT +/− RT gives 20% of absolute survival benefit compared with observation or post-operative radiation alone.[30] TME combined with RT improves local control in locally advanced RC, but mainly when RT was used preoperatively.[4] Preoperative RT gives a better local control and lower acute and late toxicity, especially from the small bowel.[4,20] Sauer et al. reported 40% *vs*. 27% acute and 24% *vs*. 14% late complications for postoperative and preoperative RT, respectively.[13] In our study, two cases (1.5%) of toxic deaths due to small bowel obstruction were reported. Nevertheless, we are aware, that a retrospective nature of our study limits the accuracy of reporting toxicity. Preoperative RT is recommended routinely, because it is more effective and safer, however, frequently patients are directed to radiotherapy departments after surgery, especially in community centers. This may happen occasionally, however, multidisciplinary management with active participation of a radiation oncologist in decision making should replace the postoperative use of RT-CHT by a preoperative setting.

6. Conclusions

We confirm a strong impact of the extent of resection of RC on patient's outcome, which indicates that the quality of surgery is essential for further improvement of treatment results. Thus, the use of postoperative RT-CHT cannot compensate for the deficiencies in the quality of surgery and in the proper qualification of patients at risk of recurrence for preoperative treatment. An extremely important role of multidisciplinary boards for the best choice of sequence and proper qualification to different treatment methods of RC based on the pelvic MRI should be emphasized. Standardization of surgical procedure and pathological assessment is necessary for proper qualification for postoperative treatment in respect to the current guidelines. We expect that postoperative RT-CHT used in very selective cases according to these recommendations will give better results than demonstrated by reports like ours. Thus, such reports are awaited and case-series like ours will serve for comparison.

Conflict of interest

None declared.

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None declared.

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