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ORIGINAL ARTICLE

Individual participant data pooled-analysis of risk factors for recurrence after neoadjuvant radiotherapy and transanal local excision of rectal cancer: the PARTTLE study

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Abstract

Background An organ-preserving strategy may be a valid alternative in the treatment of selected patients with rectal cancer after neoadjuvant radiotherapy. Preoperative assessment of the risk for tumor recurrence is a key component of surgical planning. The aim of the present study was to increase the current knowledge on the risk factors for tumor recurrence.

Methods The present study included individual participant data of published studies on rectal cancer surgery. The literature was reviewed according to according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data checklist (PRISMA-IPD) guidelines. Series of patients, whose data were collected prospectively, having neoadjuvant radiotherapy followed by transanal local excision for rectal cancer were reviewed. Three independent series of univariate/multivariate binary logistic regression models were estimated for the risk of local, systemic and overall recurrence, respectively.

Results We identified 15 studies, and 7 centers provided individual data on 517 patients. The multivariate analysis showed higher local and overall recurrences for ypT3 stage (OR 4.79; 95% CI 2.25–10.16 and OR 6.43 95% CI 3.33–12.42), tumor size after radiotherapy > 10 mm (OR 5.86 95% CI 2.33–14.74 and OR 3.14 95% CI 1.68–5.87), and lack of combined chemotherapy (OR 3.68 95% CI 1.78–7.62 and OR 2.09 95% CI 1.10–3.97), while ypT3 was the only factor correlated with systemic recurrence (OR 5.93). The analysis of survival curves shows that the overall survival is associated with ypT and not with cT.

Conclusions Local excision should be offered with caution after neoadjuvant chemoradiotherapy to selected patients with rectal cancers, who achieved a good response to neoadjuvant chemoradiotherapy.

Keywords Rectal cancer · Radiotherapy · Neoadjuvant treatment · Transanal endoscopic microsurgery · Local neoplasm recurrence

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Introduction

Total mesorectal excision (TME) is the cornerstone of curative therapy. However, proctectomy is burdened with consistent postoperative morbidity, including long-term urinary, sexual and fecal incontinence, even the need for temporary or definitive ostomy, all severely affecting quality of life [1]. Therefore, for years clinical research in this area searched for less invasive and "organ preserving" methods that are equally curative in selected patients. Surgical and even non-surgical approaches that spare the rectum have been proposed [2].

Neoadjuvant therapy is known to have, in a significant number of cases, the potential to cause significant regression of disease, with reduction of the size of the primitive tumor, the depth of its penetration into the intestinal wall and even with potential nodal neutralization (downstaging). Therefore, it could be a fundamental element for organ preserving strategies, including the association with local excision of small and superficial residual tumors [3].

Identifying and quantifying the risk factors for recurrence and overall survival after neoadjuvant therapy and local excision provides a better understanding of when these techniques may be applicable with curative intent as alternatives to radical surgery. The need for accurate assessment of risk factors for recurrence and the relative rarity of this event prompted us to undertake this pooled analysis based on individual participant data.

Materials and methods

The Pooled Analysis of risk factors for Radio Therapy and Transanal Local Excision for rectal cancer (PARTTLE) study included individual participant data of published studies on rectal cancer surgery. The study was registered with PROSPERO (CRD42017076072). The literature was reviewed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data checklist (PRISMA-IPD) guidelines [4]. According to the Italian law, no ethics committee approval was needed, because of the observational nature of this research [5].

Search strategy

We searched the electronic databases of Embase, PubMed, and Cochrane Library up to September 1st 2017 using the following syntax as for Embase ('transanal endoscopic microsurgery'/exp OR ('tem' AND 'microsurgery'/exp) OR (trans* NEXT/3 endosc* NEXT/3 microsurg*)) AND ('rectum'/exp OR 'rectum tumor'/exp OR ((rectum OR rectal OR colorect* OR 'colo rect*') NEXT/3 (neoplas* OR tumor OR tumors OR tumora* OR tumor OR tumors OR tumora* OR cancer OR cancers OR cancero* OR carcinoma* OR malignan* OR oncol*))) AND ('neoadjuvant chemoradiotherapy'/exp OR ('radiotherapy'/exp AND 'neoadjuvant therapy'/exp) OR ((neoadjuvant* OR 'neo adjuvant*') AND (radiother* OR chemorad* OR radiochem* OR chemo-rad* OR radio-chem* OR rt))). All titles were screened and appropriate abstracts reviewed.

Inclusion criteria

Series of patients, whose data were collected prospectively, undergoing neoadjuvant radiotherapy followed by transanal local excision for rectal cancer, reporting data about recurrence and/or survival were selected for inclusion.

Exclusion criteria

Articles not mentioning recurrence and/or survival after neoadjuvant radiotherapy followed by transanal local excision for rectal cancer, overlapping studies, case reports, case series with less than ten patients, reviews, consensus statements, and opinion articles were excluded.

Extraction process

Two reviewers (GLS, LE) performed the search independently; a third author (AA) arbitrated any disagreements on inclusion or exclusion of studies. Studies and results were entered into a standardized database and duplicates removed. The reference lists of the included studies were searched manually. A flow-chart of the extraction process is shown in Fig. 1.

Outcomes of interest

The two main outcomes were the identification of risk factors for (a) recurrence after transanal local excision procedure and (b) overall survival (OS).

The authors of the studies deemed suitable were contacted up to four times via e-mail (or phone if no e-mail was available); they were sent an electronic spreadsheet and asked to complete it with their data, respecting the privacy of the single patients.

For both outcomes, the following risk factors (independent variables) were investigated, and divided into two groups using the median as threshold: age at transanal local excision (> 70 vs. ≤ 70 years), diabetes (any vs. none), ypT (3 vs. 1–2), ypN (positive vs. negative), grade (high grade: G1, G2 vs. low grade: G3, G4), lymph-node invasion (any vs. none), tumor size at diagnosis assessed via

magnetic resonance imaging (MRI), or computed tomography scan if MRI was not possible (> 40 vs. ≤ 40 mm), distance from anorectal junction (> 60 vs. ≤ 60 mm), previous pelvic radiotherapy (any vs. none), simultaneous chemotherapy(CT) and radiotherapy(RT) vs RT alone, RT regimen (long course vs. short course), tumor size after radiotherapy (> 10 vs. ≤ 10 cm), stoma because of complications and dehiscence occurrence (any vs. none), time from preoperative chemoradiotherapy(CRT) to transanal local excision (> 8 vs. ≤ 8 weeks). Long course RT was defined as any RT regimen entailing administration of ≤ 2 Gy per day for 5 days a week for 5 consecutive weeks, while short course RT was defined as any radiotherapy regimen entailing administration of > 2 and < 5 Gy per day for 5 consecutive days. Tumor size at diagnosis, distance from the anorectal junction and tumor size after radiotherapy were stratified at their median values.

Statistical analysis

For the rate of recurrence after transanal local excision procedure, three independent series of univariate/multivariate binary logistic regression models were estimated, having as outcome (dependent variable) the risk of local, systemic and overall (local + systemic) recurrence, respectively.

The whole cohort overall survival (OS) was estimated either by the Kaplan–Meier method or the Cox univariate/multivariate proportional hazard regression model, comparing the impact of any risk factor levels either by the log-rank test or Wald one, respectively. Due to the number of OS events and to respect the ideal events: covariate ratio ≥ 10:1, a second multivariate Cox proportional hazards model, independent from the above described one, was used to only assess the cTNM and ypTNM role in OS.

The association between categorical variables was analyzed by the Fisher's exact test, while the Mann–Whitney and the Kruskal–Wallis ones were used for continuous variables: their results were expressed as the median [interquartile range (IQR)]. All reported *p* values were obtained by the

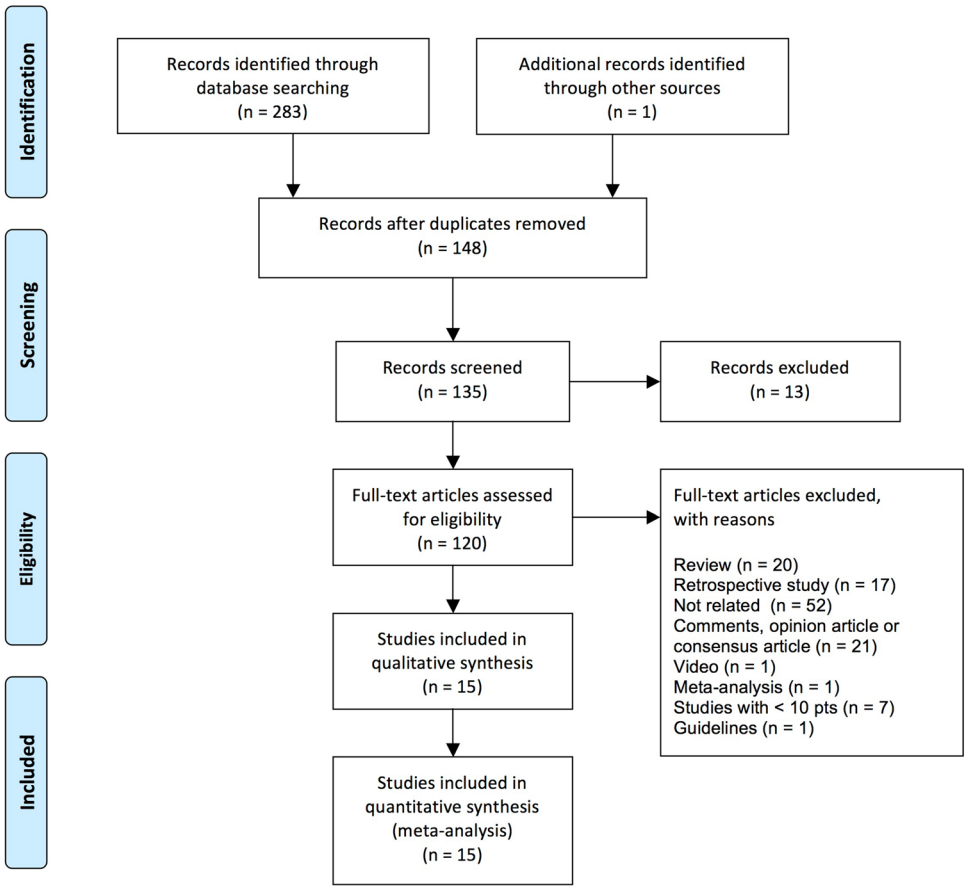

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Fig. 1 Flowchart diagram illustrating the systematic search and study selection strategy

Table 1 Characteristics of patients before surgery

Author	*n*	Mean age (yrs) (SD)	Gender male (%)	Mean BMI (SD)	Smoker (%)	Diabetes (%)	RT dose (Gy)	Mean weeks btw. neoadjuvant therapy and surgery (SD)	Previous pelvic RT (%)	ASA score (%)		CT (%)				CN+ *n.* (%)	CM+ *n.* (%)	Histologic grading	
										1–2	3–4	Is-1	2	3	4			Low	High
Coco 2013 [9]	22	62.6 (10.7)	68.2	–	–	–	50	8.4 (1.0)	0.0	–	–	0	4 (18.2)	18 (81.8)	0	14 (63.6)	0	22 (100)	0
Bujko 2013 [12]	89	68 (9.6)	52	–	–	–	56/54/29/25	7 (2.2)	0.0	–	–	77 (86.5)	12 (13.5)	0	0	0	0	–	–
Guerrieri 2014 [7]	297	70.3 (10.9)	63.3	26.4 (3.6)	31.3	13.1	50.4/25	8.1 (0.7)	0.0	242 (81.5)	55 (18.5)	1 (0.3)	174 (58.6)	117 (39.4)	5 (1.7)	18 (6.1)	1 (0.3)	229 (77.1)	68 (22.9)
Stipa 2014 [8]	43	67.8 (10.3)	62.8	25.2 (3.2)	37.2	20.9	45	6.7 (1.7)	14.0	23 (53.5)	20 (46.5)	0	27 (62.8)	16 (37.2)	0	–	–	37 (86)	6 (14)
Perez 2014 [13]	23	61.3 (13.0)	65.2	–	–	–	54/50.4	11.9 (3.1)	0.0	–	–	0	12 (52.2)	11 (47.8)	0	3 (13)	0	–	–
Arezzo 2014 [10]	14	70.0 (13.8)	50.0	–	–	–	25	6.8 (3.1)	0.0	–	–	2 (14.3)	10 (71.4)	2 (14.3)	0	0	0	11 (78.6)	3 (21.4)
Restivo 2015 [11]	29	73.9 (8.8)	58.6	25.8 (4.2)	20.7	20.7	54/45	9.8 (3.0)	0.0	18 (42.1)	11 (37.9)	1 (3.4)	4 (13.8)	24 (82.8)	0	6 (20.7)	0	29 (100)	0
Total	517	68.3 (11.2)	60.7	26.2 (3.6)	21.0	10.1		10.6 (13.5)	1.1	283 (51.8)	86 (15.8)	81 (15.7)	243 (47.0)	188 (36.4)	5 (0.9)	40 (8.2)	1 (0.2)	328 (60)	77 (14.1)

Hb hemoglobin, *RT* radiotherapy, *yrs* years, *SD* standard deviation

two-sided exact method at the conventional 5% significance level. Data were analyzed as of August 2017 by R 3.4.1 (The R Foundation for Statistical Computing, Vienna-Austria, http://www.R-project.org) [6].

Results

In all, 15 articles, with a total of 1165 patients, were selected and the corresponding authors contacted (Fig. 1). Only 7 centers provided the individual participant data (IPD) series [7–13], for a total of 517 patients who underwent neoadjuvant radiotherapy followed by transanal local excision for rectal cancer.

Patient characteristics of the entire cohort

Table 1 shows patient characteristics collected before surgery per each center. The median age was 68 years (IQR 61–77), 43.4% of them were > 70 years old, and majority was male (60.7%). Their median body mass index (BMI) was 27 kg/m^2(IQR 24–29), their median hemoglobin level was 12.05 g/dl, the prevalence of active/former smokers and of diabetes was 31.1% and 14.7%, respectively. An American Society of Anesthesiologists (ASA) score of 3–4 was assigned to 23.3% of cases, 37.3% had a cT3, 8.6% cN+ while only 0.2% were cM+.

Table 2 shows the ypTNM of patients included per center. Forty-four patients (8.5%) had a ypT3 tumor. Eighty per cent of the entire cohort had neoadjuvant CRT (nCRT).

Table 3 shows neoadjuvant therapy and intraoperative patient characteristics, stratified per center. The most frequently administered RT regimen was long course (81.4%).

Morbidity is reported in Table 4. Dehiscence occurred in 13.1% of patients, while 3.7% required a stoma. The median hospital stay was 3 days (IQR 3–6) and 47 patients needed to be readmitted after transanal local excision procedure.

CT and RT protocols

Stipa et al. [8] adopted a RT protocol delivering a total dose of 45.0 Gy with daily doses of 1.8 Gy on weekdays during 5 weeks. Concomitant CT was administered by infusion of 5-fluorouracil ($n = 33$) or oral capecitabine ($n = 10$).

Table 2 Oncologic characteristics of patients

Author	*n*	Pre-op chemotherapy (%)	YpT (%)					YpN+ (%)	Lymphovascular invasion+ (%)
			0	1	2	3	4		
Coco 2013 [9]	22	100	17 (77.3)	3 (13.6)	2 (9.1)	0	0	0	0
Bujko 2013 [12]	89	28	42 (47.2)	23 (25.8)	18 (20.2)	6 (6.7)	0	–	–
Guerrieri 2014 [7]	297	99.0	122 (41.1)	117 (39.4)	47 (15.8)	11 (3.7)	0	–	0
Stipa 2014 [8]	43	67.4	13 (30.2)	4 (9.3)	15 (34.9)	11 (25.6)	0	0	5 (11.6)
Perez 2014 [13]	23	100	0	0	12 (52.2)	11 (47.8)	0	3 (13.0)	2 (8.7)
Arezzo 2014 [10]	14	0.0	2 (14.3)	7 (50)	5 (35.7)	0	0	0	–
Restivo 2015 [11]	29	72.4	9 (31)	9 (31)	6 (20.7)	5 (17.2)	0	1 (3.5)	2 (6.9)
Total	517	80.1	205 (39.7)	163 (31.5)	105 (20.3)	44 (8.5)	0	4 (0.8)	9 (1.7)

Table 3 Neoadjuvant and intra-operative characteristics of patients

Author	*n*	Pre-op chemotherapy (%)	Radiotherapy regimen (%)		Mean tumor size before NT (mm) (SD)	Mean tumor size after NT (mm) (SD)	Mean distance from ano-rectal junction (mm) (SD)	Mean operative time (min) (SD)
			LC	SC				
Coco 2013 [9]	22	100	22 (100)	0	37.4 (7.7)	12.2 (5.3)	38.9 (23)	–
Bujko 2013 [12]	89	28	25 (28.1)	64 (71.9)	–	21 (20.5)	51 (24.9)	–
Guerrieri 2014 [7]	297	99.0	279 (93.9)	18 (6.1)	53.8 (28.8)	15.5 (13)	74 (26.9)	62.5 (37.7)
Stipa 2014 [8]	43	67.4	43 (100)	0	37.8 (15.8)	20.6 (18.4)	55.8 (20.4)	161.5 (58.9)
Perez 2014 [13]	23	100	23 (100)	0	37.4 (15)	22.3 (16.3)	34.8 (17)	–
Arezzo 2014 [10]	14	0.0	0	14 (100)	29.6 (9.9)	26 (11.8)	60.7 (30.2)	77.5 (42.1)
Restivo 2015 [11]	29	72.4	29 (100)	0	34.5 (9.9)	4.8 (6.6)	49.3 (17.5)	76.7 (17.1)
Total	517	80.1	421 (81.4)	96 (17.5)	48.4 (26.4)	16.5 (14.9)	63.6 (28.2)	75.3 (50.3)

LC long course radiotherapy, *SC* short course radiotherapy, *NT* neoadjuvant therapy, *SD* standard deviation

Table 4 Postoperative morbidity

Author	N	Gender male (%)	Dehiscence (%)	Vaginal fistula (%)	Urinary fistula (%)	Bleeding (%)	Gas incontinence (%)	Fecal incontinence (%)	Rectal pain (%)	Others (%)
Coco 2013 [9]	22	68.2	5 (22.7)	0	0	0	0	0	1 (4.5)	3 (13.6)
Bujko 2013 [12]	89	52	18 (20.2)	1 (2.3)	N/A	6 (6.7)	N/A	N/A	N/A	N/A
Guerrieri 2014 [7]	297	63.3	14 (4.7)	2 (1.8)	1 (0.3)	19 (6.4)	25 (8.4)	22 (7.4)	9 (3)	22 (7.4)
Stipa 2014 [8]	43	62.8	1 (2.3)	0	0	3 (7)	5 (11.6)	2 (4.7)	9 (20.9)	10 (23.3)
Perez 2014 [13]	23	65.2	13 (56.5)	0	0	2 (8.7)	N/A	N/A	13 (56.5)	N/A
Arezzo 2014 [10]	14	50.0	7 (50)[a]	0	0	0	0	0	3 (21.4)	3 (21.4)
Restivo 2015 [11]	29	58.6	10 (34.5)	1 (8.3)	0	6 (20.7)	5 (17.2)	5 (17.2)	5 (17.2)	2 (6.9)
Total	517	60.9	68 (13.1)	4 (0.8)	1 (0.2)	36 (7)	35 (6.8)	29 (5.6)	40 (7.7)	40 (7.7)

[a]Including two cases of enterocutaneous fistula

Restivo et al. [11] used a RT scheme delivering a total dose of 54.0 Gy ($n=24$) or 45.0 Gy ($n=3$) or 40.0 Gy ($n=2$). The CT protocols adopted were oral capecitabine ($n=19$), 5-fluorouracil ($n=2$) and no CT in 9 cases.

Coco et al. [9] used a RT protocol consisting of 50 Gy delivered with daily doses of 1.8 Gy on weekdays.

Different CT protocols were adopted: cisplatin and 5-fluorouracil, raltitrexed and oxaliplatin (TOMOX protocol), or oxaliplatin and capecitabine (CAPOX and XELOX protocols).

Bujko et al. [12] administered 5×5 Gy plus 4 Gy boost ($n=64$) or 55.8 Gy in 31 fractions with 5-fluorouracil and leucovorin ($n=25$).

Guerreri et al. [7] adopted a daily dose of 1.8 Gy with a total dose 50.4 Gy in 28 fractions. Patients < 70 years old having a good performance status received preoperative CT with continuous infusion of 5-fluorouracil (200 mg/m^2/day) while from 2003 they received capecitabine (1650 mg/m^2/day).

Perez et al. [13] administered 50.4–54 Gy during 6 weeks (45 Gy to the pelvis and 5.4–9 Gy boost to the primary tumor and perirectal fat) concomitant with 5-fluorouracil CT (450 mg/m^2).

Arezzo et al. [10] used a total dose of 25 Gy fractioned in 5 Gy daily and in 1 case a total dose of 45 Gy 2 Gy per day. No patient received CT.

Risk factors impacting on the local, systemic or overall recurrence

Oncologic results and follow-up are reported in Table 5. The cumulative survival of the 517 patients at 2 and 5 years was 93.9% and 82.1%, respectively, with 28 events at 2 years and 68 events at 5 years. The median OS was not reached.

Figures 2, 3 and 4 show the univariate and multivariate logistic models for local, systemic and overall recurrence, respectively. A local, systemic or overall recurrence after transanal local excision occurred in 54, 48 and 84 patients, respectively.

The first multivariate logistic model was dedicated to the estimation of local recurrence determinants. Four covariates were used in the multivariate model: gender, ypT, neoadjuvant CRT, tumor size post RT. The multivariate analysis showed ypT3 stage (OR 4.79, 95% CI 2.25–10.16, $p<0.001$), tumor size after radiotherapy > 10 mm (OR 5.86, 95% CI 2.33–14.74, $p<0.001$), and lack of combined CT (OR 3.68, 95% CI 1.78–7.62, $p<0.001$) to be associated with a higher incidence of local recurrence.

The second multivariate logistic model was dedicated to the estimation of causes of systemic recurrence. Five covariates were used in the multivariate model: distance from the anal verge, neoadjuvant CRT, tumor size post RT, leak. The

Table 5 Oncologic results and follow-up

Author	*n*	Local recurrence (%)	Systemic recurrence (%)	Overall survival (%)	Median follow-up (months) (range)
Coco 2013 [9]	22	1 (4.5)	2 (9)	19 (86.4)	99 (32–173)
Bujko 2013 [12]	89	13 (16.0)[a]	8 (9)	77 (86.5)	26.1 (2.4–85)
Guerrieri 2014 [7]	297	7 (2.4)	13 (4.4)	297 (100)	60.8 (12–243)
Stipa 2014 [8]	43	15 (34.9)	9 (20.9)	16 (37.2)	48 (3.7–252)
Perez 2014 [13]	23	3 (13)	6 (26.1)	20 (86.9)	44 (3–89)
Arezzo 2014 [10]	14	2 (14.2)	0	14 (100)	17.6 (1.6–55.5)
Restivo 2015 [11]	29	4 (13.8)	3 (10.3)	20 (69)	19.7 (3–214)
Total	517	45 (8.7)	41 (7.9)	463 (89.5)	38,8 (1.6–252)

[a]8 patients had immediate conversion to radical surgery and where excluded from the calculation

Fig. 2 Univariate and multivariate logistic regression for local recurrence

		Univariate		Multivariate	
		OR (95% CI)	p	OR (95% CI)	p
Age	>70 vs ≤70 years	1.20 (0.65-2.22)	0.553		
Gender	M vs F	0.58 (0.32-1.08)	0.086	0.66 (0.32-1.36)	0.259
cT	3-4 vs 1-2	1.13 (0.61-2.11)	0.699		
ypT	*3 vs 1-2*	*9.20 (4.72-17.93)*	*<0.001*	*4.79 (2.25-10.16)*	*<0.001*
ypT			<0.001		
	2 vs 0-1	4.91 (2.28-10.58)	<0.001		
	3 vs 0-1	15.60 (6.83-35.67)	<0.001		
Tumor grade	high vs low	0.88 (0.33-2.38)	0.801		
Tumor size	>40 vs ≤40 mm	0.71 (0.34-1.48)	0.365		
Distance from anorectal junction	>60 vs ≤60 mm	0.86 (0.46-1.61)	0.638		
Preoperative CRT	*no vs yes*	*5.69 (3.02-10.71)*	*<0.001*	*3.68 (1.78-7.62)*	*<0.001*
Tumor size post RT	*>10 vs ≤10 mm*	*9.52 (3.93-23.08)*	*<0.001*	*5.86 (2.33-14.74)*	*<0.001*
Dehiscence	yes vs no	1.06 (0.43-2.60)	0.905		
RT dose	LC vs SC	0.39 (0.20-0.76)	0.006		
Time between CRT and surgery	>8 vs ≤8 weeks	1.44 (0.68-3.03)	0.337		

CRT: chemo-radio therapy, RT: radiotherapy, LC: long course radiotherapy, SC: short course radiotherapy

Fig. 3 Univariate and multivariate logistic regression for systemic recurrence

		Univariate		Multivariate	
		OR (95% CI)	p	OR (95% CI)	p
Age	>70 vs ≤70 years	0.78 (0.40-1.49)	0.449		
Gender	M vs F	1.26 (0.64-2.46)	0.501		
cT	3-4 vs 1-2	1.35 (0.71-2.56)	0.366		
ypT	*3 vs 1-2*	*7.68 (3.85-15.33)*	*<0.001*	*5.93 (2.83-12.43)*	*<0.001*
ypT			<0.001		
	2 vs 0-1	10.59 (4.51-24.86)	<0.001		
	3 vs 0-1	18.87 (7.27-48.99)	<0.001		
Tumor grade	high vs low	0.73 (0.24-2.17)	0.567		
Tumor size	>40 vs ≤40 mm	0.88 (0.43-1.80)	0.728		
Distance from anorectal junction	>60 vs ≤60 mm	0.40 (0.19-0.82)	0.013	0.53 (0.24-1.15)	0.106
Preoperative CRT	no vs yes	1.99 (0.99-4.00)	0.053	1.15 (0.50-2.64)	0.737
Tumor size post RT	>10 vs ≤10 mm	2.35 (1.18-4.69)	0.015	1.51 (0.71-3.22)	0.285
Dehiscence	yes vs no	2.42 (1.13-5.20)	0.024	1.34 (0.54-3.31)	0.530
RT dose	LC vs SC	1.06 (0.46-2.48)	0.890		
Time between CRT and surgery	>8 vs ≤8 weeks	1.64 (0.77-3.49)	0.197		

CRT: chemo-radio therapy, RT: radiotherapy, LC: long course radiotherapy, SC: short course radiotherapy

Fig. 4 Univariate and multivariate logistic models for overall recurrence

		Univariate		Multivariate	
		OR (95% CI)	p	OR (95% CI)	p
Age	>70 vs ≤70 years	0.93 (0.56-.1.53)	0.765		
Gender	M vs F	0.88 (0.53-1.46)	0.627		
cT	3-4 vs 1-2	1.32 (0.80-2.19)	0.280		
ypT	*3 vs 1-2*	*11.07 (6.11-20.05)*	*<0.001*	*6.43 (3.33-12.42)*	*<0.001*
ypT			<0.001		
	2 vs 0-1	7.78 (4.12-14.68)	<0.001		
	3 vs 0-1	23.33 (10.92-49.86)	<0.001		
Tumor grade	high vs low	0.72 (0.31-1.68)	0.446		
Tumor size	>40 vs ≤40 mm	0.78 (0.44-1.37)	0.378		
Distance from anorectal junction	>60 vs ≤60 mm	0.66 (0.39-1.11)	0.114		
Preoperative CRT	*no vs yes*	*3.38 (1.98-5.76)*	*<0.001*	*2.09 (1.10-3.97)*	*0.024*
Tumor size post RT	*>10 vs ≤10 mm*	*4.88 (2.72-8.75)*	*<0.001*	*3.14 (1.68-5.87)*	*<0.001*
Dehiscence	yes vs no	1.82 (0.95-3.50)	0.070	0.99 (0.45-2.19)	0.989
RT dose	LC vs SC	0.60 (0.33-1.08)	0.091		
Time between CRT and surgery	>8 vs ≤8 weeks	1.78 (0.99-3.22)	0.056		

CRT: chemo-radio therapy, RT: radiotherapy, LC: long course radiotherapy, SC: short course radiotherapy

Fig. 5 Univariate and multivariate Cox proportional hazard models for overall survival

		Univariate		Multivariate	
		HR (95% CI)	p	HR (95% CI)	p
Age	*>70 vs ≤70 years*	*2.45 (1.62-3.68)*	*<0.001*	*2.57 (1.68-3.91)*	*<0.001*
Gender	M vs F	0.79 (0.53-1.17)	0.236		
cT	*3-4 vs 1-2*	1.36 (0.67-1.63)	0.626		
ypT	3 vs 1-2	*2.87 (1.80-4.59)*	<0.001	*2.33 (1.42-3.82)*	*0.001*
ypT					
	2 vs 0-1	2.57 (1.64-4.02)	<0.001		
	3 vs 0-1	3.96 (2.30-6.81)	<0.001		
Distance from anorectal junction	*>60 vs ≤60 mm*	*0.63 (0.42-0.95)*	*0.028*	*0.64 (0.42-0.97)*	*0.036*
Preoperative CRT	*no vs yes*	*2.68 (1.69-4.25)*	*<0.001*	*2.24 (1.37-3.65)*	*0.001*
Tumor size post RT	>10 vs ≤10 mm	1.63 (1.09-2.45)	0.018	1.29 (0.85-1.96)	0.237
Dehiscence	yes vs no	1.52 (0.87-2.63)	0.139		
Local recurrence	yes vs no	4.80 (3.02-7.63)	<0.001		
Systemic recurrence	yes vs no	13.86 (8.85-21.71)	<0.001		
Overall recurrence	yes vs no	8.65 (5.77-12.96)	<0.001		
RT dose	LC vs SC	0.90 (0.45-1.81)	0.768		
Tumour grade	high vs low	0.76 (0.41-1.41)	0.390		
Time between CRT and surgery	>8 vs ≤8 weeks	0.82 (0.44-1.53)	0.525		

CRT: chemo-radio therapy, RT: radiotherapy, LC: long course radiotherapy, SC: short course radiotherapy

only independent risk factor identified was ypT3 (OR 5.93, 95% CI 2.83–12.43, $p < 0.001$).

The third multivariate logistic model was dedicated to the estimation of predictors of overall recurrence. Four covariates were used in the multivariate model: ypT, neoadjuvant CRT, tumor size post RT, leak. The larger number of events allowed a more detailed estimation of determinants. Again, the multivariate analysis showed ypT3 stage (OR 6.43, 95% CI 3.33–12.42, $p < 0.001$), tumor size after radiotherapy > 10 mm (OR 3.14, 95% CI 1.68–5.87, $p < 0.001$), and lack of combined CT (OR 2.09, 95% CI 1.10–3.97, $p = 0.024$) to be associated with a higher incidence of overall recurrence.

Main risk factors impacting on OS

Figure 5 shows the univariate and multivariate Cox proportional hazard models for OS. At a median follow-up of 4.9 years (IQR 2.0–7.9, while the maximum notably reached 20.7 years), 98 patients (18.9%) died for all causes. At the maximum follow-up, 54.6% of patients were still alive and under observation.

Since in the Cox univariate model series most of the risk factors were statistically significant, the multivariate model was fundamental to properly control for confounding variables. Five covariates were used in the multivariate model: age, ypT, distance from the anal verge, neoadjuvant CRT, tumor size post RT. Four independent predictors were confirmed OS was negatively influenced by age > 70 years (HR 2.57, 95% CI 1.68–3.91, $p < 0.001$), ypT3 (HR 2.33, 95% CI 1.42–3.82, $p < 0.001$), distance from the anal verge < 6 cm

(HR 0.64, 95% CI 0.42–0.97, $p = 0.036$) and lack of combined CT (HR 2.24, 95% CI 1.37–3.65, $p < 0.001$). No risk factor showed a time-dependent behavior, so the assumption of proportional hazard was fully respected.

Of the entire cohort of patients, divided by age, the cumulative survival of those ≤ 70 years old (286 patients) at 2 and 5 years was 94.5% and 85.8%, respectively, with 14 events at 2 years and 31 events at 5 years. The median OS was not reached. The cumulative survival of those > 70 years old (231 patients) at 2 and 5 years was 93.2% and 77.1%, respectively, with 14 events at 2 years and 37 events at 5 years. The median OS was 10.0 years.

The cumulative survival (CS) of those with distal margins of tumors located ≤ 60 mm from the anal verge (293 patients) at 2 and 5 years was 91.5% and 78.1%, respectively, with 22 events at 2 years and 46 events at 5 years. The median OS was 18.7 years. The CS of those > 60 mm (224 patients) at 2 and 5 years was 96.9% and 86.9%, respectively, with 6 events at 2 years and 22 events at 5 years. The median OS was not reached.

The CS of those who did not undergo combined CT (103 patients) at 2 and 5 years was 88.6% and 64.2%, respectively, with 9 events at 2 years and 18 events at 5 years. The median OS was 8.5 years. The CS of those who did undergo a combined CT (441 patients) at 2 and 5 years was 94.7% and 84.7%, respectively, with 20 events at 2 years and 50 events at 5 years. The median OS was not reached.

cTNM and ypTNM impact on the overall survival

A multivariate dedicated Cox model revealed that the main independent risk factor ypT3 (HR 2.33, 95% CI 1.42–3.82, $p = 0.001$), while the role of cT3-4 (HR 1.36, 95% CI 0.67–1.63, $p = 0.626$) was negligible.

While the overall probability of survival curves for cT1–2 and cT3–4 are almost overlapping (Fig. 6a), the overall

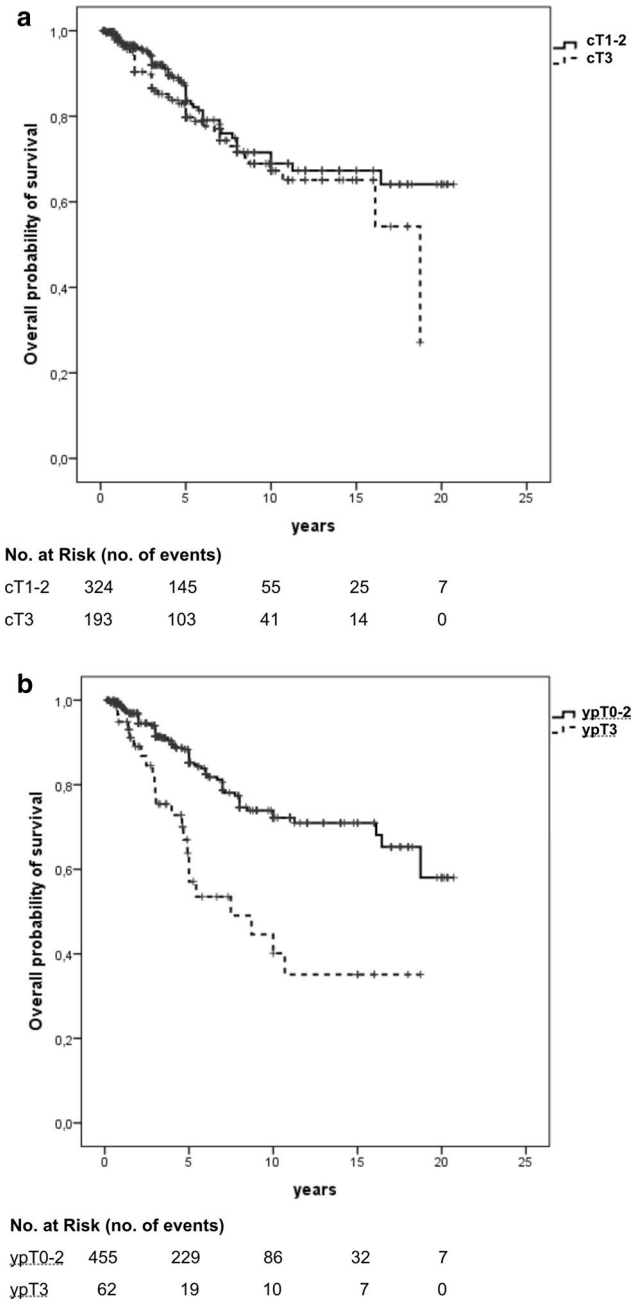

Fig. 6 Overall probability of survival curves for cT1–2 and cT3–4 (**a**) and for ypT0–2 and ypT3 (**b**)

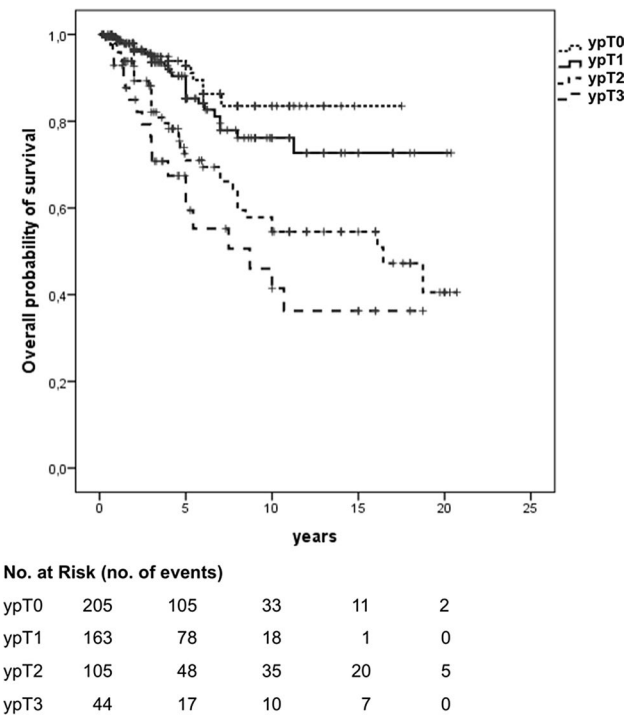

Fig. 7 Overall probability of survival curves for ypTis, ypT1, ypT2 and ypT

probability of survival curves for ypT0–2 shows a consistent improvement compared to those for ypT3 (Fig. 6b). The analysis of survival curves shows that the stratification of OS correlates with ypT and not with cT. The overall probability of survival curves for ypT0, ypT1, ypT2 and ypT3 are shown in Fig. 7. Of the entire cohort of patients, the CS of those ypT0 (205 patients), ypT1 (163 patients), ypT2 (105 patients) and ypT3 (44 patients) at 2 years was 96.1%, 96.6%, 89.3% and 85.0%, respectively, with 7, 5, 10 and 6 events. At 5 years the CS was 85.3%, 92.7%, 71.0% and 59.5%, respectively, with 21, 9, 24 and 14 events. The median OS was 16.4 years for ypT2 and 8.7 years for ypT3, while it was not reached for ypT0 and ypT1.

Discussion

Aim of the present study was to verify if and when an organ-preserving strategy may be a valid alternative in the treatment of selected patients with rectal cancer after neoadjuvant RT. The multivariate logistic model showed that the association of simultaneous CT and neoadjuvant RT was the most important protective factor for local and overall recurrence. Local recurrence rates have mirrored the risk of mesorectal nodal metastases. Of note, transanal local excision allows the surgeon to selectively perform larger resections that include part of the mesorectal tissue. However, conventional local excision is a procedure that typically removes the primary cancer with no associated mesorectal tissue. Thus, oncological failures after transanal local excision have been associated with the risk of unsuspected and not removed metastatic mesorectal nodes. In this setting, the potential effects of nCRT on primary tumor size, depth of tumor penetration, and mesorectal nodal sterilization could result in a residual tumor amenable to local excision even in the setting of an incomplete response to nCRT. And in fact, tumor size after RT > 10 mm was the main risk factor for local and overall recurrence, suggesting that only tumors showing a good shrinkage with downsizing and probably downstaging should be considered a good indication for local excision with curative intent. This is in line with results of two previous studies [14, 15], where the local recurrences were exclusively observed among poor responders to nCRT. To strengthen this finding, the analysis of OS curves shows that the stratification of survival correlates with ypT and non with cT. Although this might be partially dependent on the difficulty to assess correctly the T stage of rectal cancer preoperatively in some cases, it is likely that this depends on the different biological characteristics of the tumor. In other words, tumors responding to nCRT may be less aggressive, while tumors not responding may be more aggressive and, therefore, have a worse prognosis. We have noticed that poorly differentiated tumors did not do worse compared to well differentiated tumors, as would be expected. A specific Kaplan–Meier OS curve was generated and the curves were almost overlapping. We believe the lack of statistically significant difference should not be related to small numbers, as in fact we included in this sub-analysis > 400 patients, with a 1:4 ratio. It would be expected that low-grade tumors would be more sensitive to CT at least, but is not demonstrated by our data. This probably influences disease-free survival rather than OS.

The present study has several limitations. It is a retrospective analysis of an Individual Participant Database of prospective studies which adhered to the protocol. All were observational studies with evident selection as well as other kinds of bias. There is a further potential risk of bias in the selection of papers included as the data of only about half of the patients were gleaned from these studies. Moreover, CRT protocols adopted show extreme variability not only among studies but also within each study in the majority of cases, with five studies adopting only RT and no CT in at least some patients, with different RT administration (short course or long course) as well as different CT schemes, also due to the relatively long time of patient inclusion. The fragmentation of protocols adopted prevented a multivariate assessment of the role of short course or long course, as well as of the role of different CT drugs. Furthermore, in our attempt to include a large number of variables, we encountered problems with missing data. In compliance with the PRISMA-IPD Statement, we decided to sacrifice a number of variables when the rate of missing data was too high, this way excluding probably important variables such as BMI, tobacco use, diabetes, ASA class, lympho-vascular invasion, tumour budding or previous pelvic RT. Nevertheless, we were able to perform multivariate logistic regression with a consistent number of patients. Other variables such as ypN were included although most probably the exact rate of N+ patients was underreported because the surgical technique consisted of just a local excision. In spite of these limitations, the present study provides a unique source of data from which to quantify a number of risk factors for recurrence after local surgery for rectal cancer following neoadjuvant therapy. An accurate assessment of the risk of recurrence is crucial for shared decision-making in which patients are informed about up-to-date evidence and probable outcomes. To this end, several preoperative, intraoperative, and postoperative factors need to be considered as well as neoadjuvant treatment protocols. A review of the evidence supported by a large number of data, possibly collected from multiple centers, would minimize the role of local factors such as surgeon's skills and local care protocols. Following this rationale, we systematically reviewed the literature and performed a pooled analysis of available data.

Previously, the only randomized study comparing Transanal Endoscopic Microsurgery (TEM) to laparoscopic TME

in the management of cT2N0 rectal cancer after nCRT suggested similar local recurrence-free survival and postoperative morbidity favoring the TEM group [16], despite an update showing that patients undergoing TEM were more likely to develop recurrence [14]. Another prospective single-arm study reported low local recurrence rates after nCRT and local excision for the management of cT2N0 rectal adenocarcinomas, suggesting that this organ-preserving strategy could be oncologically safe [15]. The slightly lower rate of recurrence reported compared to previous systematic reviews [17] may be the effect of having included some of the largest series available, so that surgical skills and experience may have played a role. Nevertheless, because the standard strategy of systematic reviews and meta-analyses does not allow for detailed analysis of risk factors, since only patient clusters can be included in such types of analysis, we applied an individual participant data strategy to identify on a patient-by-patient base the risk factors influencing the outcome. This meant that all the participating study centers had to produce a consistent body of data ready for analysis.

From the technical point of view, it has to be considered that local excision in the setting of a previously irradiated field is challenging, may lead to significant difficulties in tissue healing and seems to justify the considerable rates of associated morbidity after this procedure [18, 19]. Wound complications, such as partial or complete dehiscence, occur in about 15% of patients after nCRT. This has several clinical consequences, including significant anal pain, requiring readmission, and even occasional diverting stomas. These data suggest that, when patients are treated with curative intent, local excision should be offered with extreme caution after nCRT to patients with selected rectal cancers [20]. Based on the results of the present study, the strategy to offer local excision to those patients who achieved a good response to nCRT (defined as downgrading to ypT0–2ypN0 and downsizing to ≤ 10 mm), seems reasonable. Those who do not have a good response, might be reconsidered for radical surgery, if not contraindicated. However, local excision should be considered for patients unfit for major surgery (OS at 5 years for ypT3 > 50%) and for palliative reasons. An organ-preserving strategy may be a valid alternative in the treatment of selected patients with rectal cancer after neoadjuvant radiotherapy [21, 22]. As the risk of local and systemic recurrence after rectal cancer surgery is multifactorial and certain factors are known to influence its occurrence, identifying them and quantifying their relative risk may assist surgeons to optimize surgical strategy and aid patients in understanding the risk involved before giving their consent, particularly regarding the question of whether radical surgery or just a local excision may be needed or not [23].

Conclusions

The present analyses of risk for tumor recurrence after nCRT followed by local excision for rectal cancer may assist surgeons in deciding whether to offer or not the chance of a surgical treatment with reduced invasiveness rather than radical surgery. Further studies should focus on comparing results of different protocols of RT and possible combined CT to maximize the neoadjuvant effect before local excision. The next step will be to develop a specific scoring and grading system for the risk of tumor recurrence based on results of local excision after nCRT.

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Data availability The datasets analysed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The author(s) declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patient included in the case report.

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