Locally recurrent rectal cancer

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Original Article

Locally recurrent rectal cancer: oncological outcomes with different treatment strategies in two tertiary referral units

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Abstract

Background: The optimal treatment for patients with locally recurrent rectal cancer (LRRC) is controversial. The aim of this study was to investigate different treatment strategies in two leading tertiary referral hospitals in Europe.

Methods: All patients who underwent curative surgery for LRRC between January 2003 and December 2017 in Catharina Hospital, Eindhoven, the Netherlands (CHE), or Karolinska University Hospital, Stockholm, Sweden (KAR), were studied retrospectively. Available MRIs were reviewed to obtain a uniform staging for optimal comparison of both cohorts. The main outcomes studied were overall survival (OS), local re-recurrence-free survival (LRFS), and metastasis-free survival (MFS).

Results: In total, 377 patients were included, of whom 126 and 251 patients came from KAR and CHE respectively. At 5 years, the LRFS rate was 62.3 per cent in KAR *versus* 42.3 per cent in CHE ($P = 0.017$), whereas OS and MFS were similar. A clear surgical resection margin (R0) was the strongest prognostic factor for survival, with a hazard ratio of 2.23 (95 per cent c.i. 1.74 to 2.86; $P < 0.001$), 3.96 (2.87 to 5.47; $P < 0.001$), and 2.00 (1.48 to 2.69; $P < 0.001$) for OS, LRFS, and MFS respectively. KAR performed more extensive operations, resulting in more R0 resections than in CHE (76.2 *versus* 61.4 per cent; $P = 0.004$), whereas CHE relied more on neoadjuvant treatment and intraoperative radiotherapy, to reduce the morbidity of multivisceral resections ($P < 0.001$).

Conclusion: In radiotherapy-naive patients, neoadjuvant full-course chemoradiation confers the best oncological outcome. However, neoadjuvant therapy does not diminish the need for extended radical surgery to increase R0 resection rates.

Introduction

The treatment of locally recurrent rectal cancer (LRRC) has evolved from mostly palliative care to advanced and specialized multimodal treatment, often with curative intent. At present, a clear standard of care has not been established in LRRC management. This contrasts with locally advanced rectal cancer (LARC), for which neoadjuvant chemoradiotherapy is broadly accepted as the standard of care[1–3]. However, it is clear that, regardless of neoadjuvant treatment, achieving clear surgical resection margins (R0) is the single most important prognostic factor for survival.

Currently, the treatment for LRRC is mainly based on local protocols and a limited evidence base. Because of the similarities with LARC, LRRC is generally treated, if possible, with neoadjuvant chemoradiotherapy. This treatment regimen is recommended by the European Society for Medical Oncology[4] and supported by the consensus statement of the Beyond TME Collaborative[5]. However, there is no consensus on the optimal treatment for patients previously treated with radiotherapy. In this scenario, different protocols exist worldwide, such as reirradiation at different doses, with or without concomitant chemotherapy, induction chemotherapy before radiation, or use of neoadjuvant chemotherapy and intraoperative radiotherapy[6–10]. However, the evidence to support any one protocol is limited. In addition to improved oncological treatment, the boundaries of what is considered to be potentially surgically resectable have also been extended[11–13]. Comparisons between studies published to date are difficult because of the heterogeneity in the presentation of LRRC and the treatments reported, and the relatively small number of patients with LRRC.

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Table 1 Patient and treatment characteristics according to hospital

	KAR ($n = 126$)	CHE ($n = 251$)	Overall ($n = 377$)	P†
Sex				0.187
F	54 (43)	90 (36)	144 (38.2)	
M	72 (57)	161 (64.1)	233 (61.8)	
Age (years)*	64.6 (56–74)	64.1 (58–71)	64.3 (58–72)	
Neoadjuvant RT, primary	78 (62)	168 (66.9)	246 (65.3)	0.334
Surgery, primary				0.727
Anterior resection	82 (69)	167 (66.5)	249 (67.3)	
Abdominoperineal excision	37 (31)	83 (33)	120 (32.4)	
Total exenteration	0 (0)	1 (0.4)	1 (0.3)	
Adjuvant chemotherapy, primary	40 (32)	42 (17)	82 (22)	0.001
Pathological tumour category, primary				0.504
pT0–2	19 (17)	54 (22)	73 (20)	
pT3	79 (69)	161 (65.4)	240 (66.7)	
pT4	16 (14)	31 (13)	47 (13)	
Pathological node category, primary				0.322
pN0	50 (40)	114 (45.4)	164 (43.5)	
pN1+	76 (60)	137 (54.6)	213 (56.5)	
Pathological metastasis category, primary				0.03
pM0	104 (87.4)	235 (94)	339 (91.9)	
pM1	15 (13)	15 (6)	30 (8)	
Induction chemotherapy	3 (2)	64 (26)	67 (18)	<0.001
Neoadjuvant treatment				<0.001
No RT at all	24 (20)	0 (0)	24 (6.5)	
Full-course (chemo)RT	19 (16)	80 (32)	99 (27)	
Reirradiation	2 (2)	171 (68.1)	173 (46.8)	
RT solely for primary tumour	74 (62)	0 (0)	74 (20)	
Primary compartment, LRRC				0.373
Central	43 (39)	95 (43)	138 (42.1)	
Anterior	17 (16)	34 (16)	51 (16)	
Posterior	12 (11)	34 (16)	46 (14)	
Lateral	37 (34)	56 (26)	93 (28)	
CRM involvement (mm)				0.003
> 1	77 (61)	110 (44.7)	187 (49.7)	
≤ 1	49 (39)	136 (55.3)	185 (50.3)	
Surgery				0.02
Low anterior resection	3 (2)	25 (10)	28 (7)	
Abdominoperineal excision	16 (13)	43 (17)	59 (16)	
Multivisceral resection	62 (49)	121 (48.2)	183 (48.5)	
Resection NOS	10 (8)	21 (8)	31 (8)	
Total pelvic exenteration	31 (25)	41 (16)	72 (19)	
Hemipelvectomy	4 (3)	0 (0)	0 (1)	
Additional organs removed				
Urinary bladder	41 (33)	46 (18)	87 (23)	0.002
Prostate (M only in analysis)	25 (20)	30 (12)	55 (15)	0.041
Vagina (F only in analysis)	26 (21)	45 (18)	71 (19)	0.526
Ureter	49 (39)	41 (16)	90 (24)	<0.001
Sacrum	36 (29)	81 (32)	117 (31)	0.464
IORT	7 (6)	228 (90.8)	235 (62.3)	<0.001
Resection margin				0.004
R0	96 (76)	154 (61.4)	250 (66.3)	
R1/R2	30 (24)	97 (39)	127 (33.7)	
Adjuvant RT, LRRC (EBRT/brachytherapy)	6 (5)	0 (0)	6 (2)	<0.001
Adjuvant chemotherapy	6 (5)	5 (2)	11 (3)	0.132
Complications (Clavien–Dindo grade)				0.742
0–II	86 (68)	172 (69.9)	258 (69.4)	
III–V	40 (32)	74 (30)	114 (30.6)	

Values in parentheses are percentages unless indicated otherwise; *values are mean (i.q.r.). KAR, Karolinska University Hospital, Stockhom, Sweden; CHE, Catharina Hospital, Eindhoven, the Netherlands; RT, radiotherapy; LRRC, locally recurrent rectal cancer; CRM, circumferential resection margin; NOS, not otherwise specified; IORT, intraoperative RT; EBRT, external-beam RT. †χ^2 or Fisher's exact test.

The aim of this study was to evaluate the long-term oncological outcomes of the different treatment regimens for LRRC used in two leading tertiary referral hospitals in Europe.

Methods

Patients

The outcomes of all patients who underwent surgical resection for potentially curable LRRC between January 2003 and December 2017 at Catharina Hospital Eindhoven, the Netherlands (CHE), or Karolinska University Hospital, Stockholm, Sweden (KAR) were studied retrospectively. Both hospitals have proven experience in treating this specific group of patients and serve as tertiary referral hospitals within their country. Patients were excluded if they either had a second or third recurrence, synchronous metastasis, a recurrence after transanal endoscopic microsurgery, local excision of the primary tumour, or failure of a watch-and-wait trajectory. Data were collected from both hospitals, which comprised patient characteristics, and clinical data on neoadjuvant and adjuvant treatment, surgery,

pathology, imaging, and follow-up. Every patient underwent pelvic MRI at baseline and after neoadjuvant therapy, when administered, as standard of care. If the quality of the images permitted reassessment, these were reviewed by experienced and dedicated radiologists at CHE and KAR, according to a set protocol to obtain a uniform staging[14]. All patients were discussed by the dedicated LRRC multidisciplinary teams at KAR or CHE, both of which have extensive and broadly recognized experience in treatment and research for patients with LRRC. Data from the two hospitals were compared. Follow-up was complete until 12 January 2022.

Neoadjuvant treatment

The two hospitals had different local standards of care. In CHE, all patients received neoadjuvant treatment with either full-course chemoradiotherapy or reirradiation in patients who had undergone irradiation before. Full-course chemoradiotherapy was delivered with a cumulative dose of 45–50.4 Gy in fractions of 1.8–2 Gy with concomitant capecitabine (825 mg/m^2 twice a day on radiotherapy days). Reirradiation consisted of a cumulative dose of 30 Gy in 15 fractions of 2 Gy, mostly with concomitant capecitabine at a dose equivalent to that used in chemoradiotherapy. During the last years of the interval described, induction chemotherapy was considered the standard of care for all LRRCs and applied whenever possible in CHE. This generally consisted of four cycles of CAPOX (capecitabine and oxaliplatin) or five cycles of FOLFOX (leucovorin, 5-fluorouracil, and oxaliplatin). Intraoperative electron-beam radiotherapy (IOERT) was delivered during surgery after removal of the tumour in patients who had neoadjuvant reirradiation or if deemed necessary to strive for clear resection margins, and, second, to attempt organ preservation with possibly closer margins if deemed possible. A single dose of 10–12.5 Gy was then delivered depending on the frozen section of the area at risk, with the larger dose given in cases of microscopically involved margins[15,16].

In KAR, depending on the tumour and patient characteristics, patients received no neoadjuvant radiotherapy at all, full-course chemoradiotherapy, or, sporadically, short-course radiotherapy, which comprised a cumulative dose of 25 Gy in five fractions of 5 Gy. In patients with primarily unresectable recurrence, induction chemotherapy was administered before surgery, with CAPOX or FOLFOX as in CHE. Reirradiation was not part of local standard of care. In KAR, a number of patients were considered eligible for surgery without the use of neoadjuvant therapy for a variety of reasons, including previous radiotherapy for prostate cancer or gynaecological cancer, being too frail, too much small bowel in the irradiation field, or when it was predicted that the tumour could be resected safely without neoadjuvant radiotherapy.

Surgery

In both hospitals, the type of surgery depended on the location of the recurrence and involvement of other organs and structures. The procedures were categorized as follows: low anterior resection; abdominoperineal excision; extra-anatomical resection, defined as resection without formal oncological resection of the bowel; multivisceral resection, defined as formal oncological resection of the bowel and at least one other organ or structure, such as the uterus and ovaries, prostate, vesicles, or sacrum; posterior and total pelvic exenteration, defined as resection of the rectum, bladder, and prostate with vesicles or uterus with ovaries; and hemipelvectomy, defined as the removal of half of the pelvis including one leg.

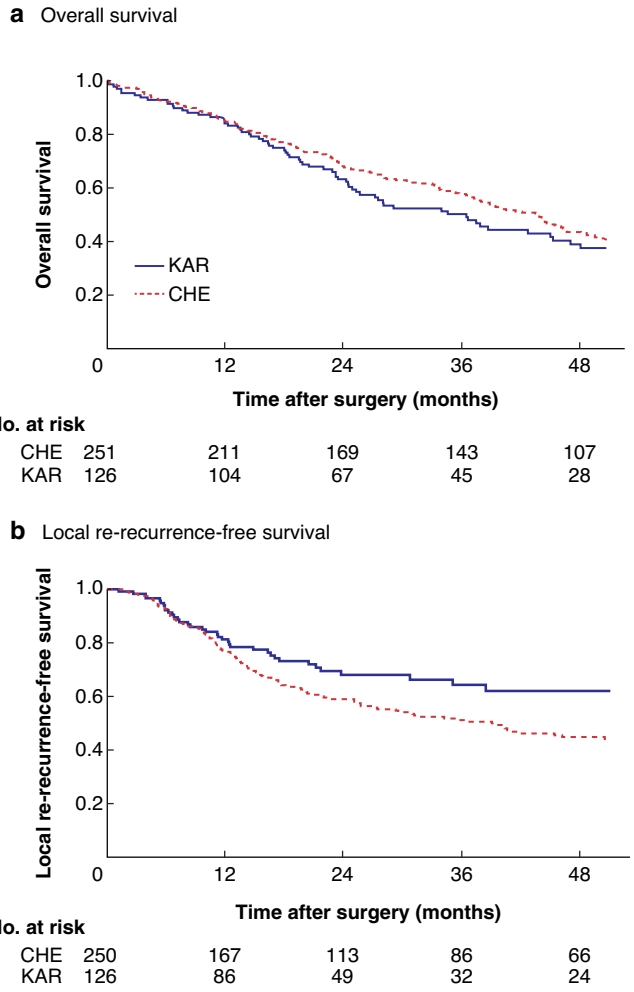

Fig. 1 Kaplan–Meier analysis of overall and local re-recurrence-free survival in the two hospitals

a Overall and **b** local re-recurrence-free survival. KAR, Karolinska University Hospital, Stockhom, Sweden; CHE, Catharina Hospital, Eindhoven, the Netherlands. **a** $P = 0.495$, **b** $P = 0.017$ (log rank test).

Other surgical specialists, such as urologists, plastic surgeons, and vascular surgeons were consulted, depending on the extent of the resection.

Adjuvant treatment

In both hospitals, adjuvant chemotherapy was not the standard of care for patients with LRRC. In KAR, adjuvant external-beam radiotherapy (EBRT) was applied as an optional additional treatment in patients with suspected involved margins. After 2008, EBRT was replaced by brachytherapy, for which catheters were placed and left behind during surgery.

Follow-up

The standard follow-up protocol was similar in both hospitals, and consisted of carcinoembryonic antigen (CEA) measurement once every 3 months and thoracoabdominal CT once every 6 months during the first 3 years after surgery. In years 4 and 5, CEA levels were measured once every 6 months, and thoracoabdominal CT was performed annually. In patients with suspected local recurrence, further imaging was undertaken using MRI of the pelvis. If metastasis suspected, further examination was done depending on the location of the metastases.

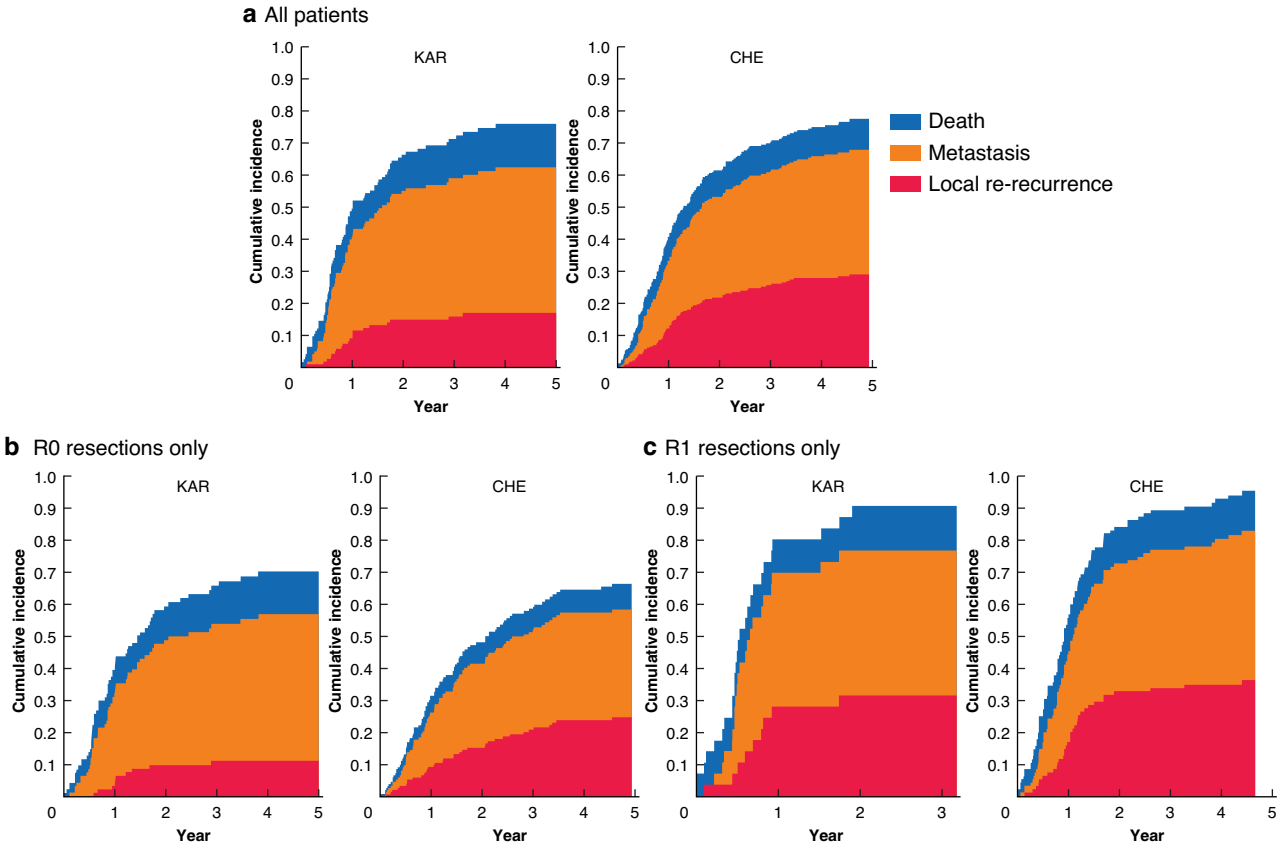

Fig. 2 Proportional subhazard models with parametric stacked cumulative incidences

a All patients, **b** R0 resections only, and **c** R1 resections only. KAR, Karolinska University Hospital, Stockhom, Sweden; CHE, Catharina Hospital, Eindhoven, the Netherlands.

Statistical analysis

The endpoints included overall survival (OS), local re-recurrence-free survival (LRFS), and metastasis-free survival (MFS). OS was calculated from the date of surgery until the date of death or the patient was censored at the last follow-up. LRFS and MFS were calculated from the date of surgery until the date on which local recurrence or metastasis was detected by imaging or histology, or the patient was censored at the last follow-up, or death.

Continuous data are reported as mean or median, as appropriate (with i.q.r. or 95 per cent c.i.), and categorical data as counts with percentages. Group comparisons were performed using χ^2 test, Fisher's exact test, or the Mann–Whitney *U* test, as appropriate. Survival rates and cumulative incidences were calculated using the Kaplan–Meier method, and comparisons made using the log rank test. Univariable Cox regression analysis was used to calculate the association between OS and patient and tumour characteristics. All variables with a significance level of $P \leq 0.050$ in univariable analysis were entered into a multivariable analysis. Two-sided $P \leq 0.050$ was considered statistically significant. Cumulative incidence functions were used in a proportional (stacked) subhazard model to estimate and graphically display the probability of death, taking competing risks into account. Statistical analyses were done using SPSS® Statistics for Windows® version 25.0 (IBM, Armonk, NY, USA), and Stata® version 12 (StataCorp, College Station, TX, USA) was used for the proportional hazards model.

Results

Patients

Between 1 January 2003 and 31 December 2017, 377 patients with LRRC underwent surgery, of whom 126 and 251 patients were treated in KAR and CHE respectively. Patient and treatment characteristics are shown in *Table 1*. Median follow-up was 36 (i.q.r. 17–62) months.

Type of neoadjuvant treatment for LRRC

In CHE, all patients received neoadjuvant radiotherapy; 80 patients underwent full-course chemoradiotherapy (32 per cent) and 171 had reirradiation (68.1 per cent). In KAR, most patients received no neoadjuvant therapy for the LRRC (82 per cent), whereas 19 patients received full-course chemoradiotherapy (16 per cent), and two underwent reirradiation (2 per cent). Induction chemotherapy was administered in three patients in KAR (2 per cent) and 64 (26 per cent) in CHE.

Type of surgery for LRRC

In both hospitals, a large proportion of patients (49 per cent in KAR and 48.2 per cent in CHE) underwent multivisceral resection. However, surgery in KAR was more extensive in terms of the resection rate of specific pelvic organs or structures. Resections of the urinary bladder, prostate (men analysed separately), and ureter were significantly more common in KAR, whereas no differences were evident in resection of the vagina (women analysed separately) or sacrum. The R0 resection rate was 76 and 61.4 per cent in KAR and CHE respectively ($P = 0.004$).

Table 2 Patient characteristics according to baseline neoadjuvant treatment of locally recurrent rectal cancer and primary tumour

	No RT at all ($n = 24$)†	RT solely for primary tumour ($n = 74$)†	Full-course RT ($n = 99$)	Reirradiation ($n = 173$)	P§
Age (years)*	68.8 (58.25–78.25)	62.7 (55.75–70.5)	66.0 (61–73)	63.2 (57.5–71)	
Primary origin					<0.001
Rectum	8 (33)	73 (99)	69 (69)	173 (100)	
Sigmoid	16 (67)	1 (1)	30 (30)	0	
Hospital					<0.001
KAR	24 (100)	74 (100)	19 (19)	2 (1)	
CHE	0 (0)	0 (0)	80 (81)	171 (98.8)	
Pathological tumour category, primary					0.163
pT0–2	4 (17)	12 (18)	14 (15)	42 (25)	
pT3	14 (58)	47 (71)	66 (69)	111 (65.3)	
pT4	6 (25)	7 (11)	16 (17)	17 (10)	
Pathological node category, primary					0.030
pN0	11 (46)	25 (34)	55 (56)	72 (42)	
pN1+	13 (54)	49 (66)	44 (44)	101 (58.4)	
Pathological metastasis category, primary					0.157
pM0	21 (88)	61 (88)	88 (90)	165 (95.4)	
pM1	3 (13)	8 (12)	10 (10)	8 (5)	
Surgery, primary					<0.001
Anterior resection	22 (92)	36 (52)	95 (96)	92 (53)	
Abdominoperineal excision	2 (8)	33 (48)	4 (4)	81 (47)	
Total exenteration	0 (0)	0 (0)	0 (0)	1 (1)	
No. of lesions‡					0.773
1	17 (94)	60 (88)	81 (95)	140 (92.1)	
2	1 (6)	6 (9)	3 (4)	8 (5)	
≥ 3	0 (0)	2 (3)	1 (1)	4 (3)	
Compartment‡					<0.001
Central	9 (50)	21 (31)	56 (66)	50 (33)	
Anterior	3 (17)	12 (18)	8 (9)	27 (18)	
Posterior	3 (17)	8 (12)	10 (12)	25 (17)	
Lateral	3 (17)	27 (40)	11 (13)	49 (33)	
Extramural vascular invasion	5 (28)	24 (35)	18 (21)	36 (24)	0.252
Induction chemotherapy	0 (0)	0 (0)	7 (7)	58 (34)	<0.001
Surgery, LRRC					<0.001
Low anterior resection	1 (4)	0 (0)	23 (23)	3 (2)	
Abdominoperineal excision	2 (8)	8 (11)	19 (19)	28 (16)	
Multivisceral resection	14 (58)	35 (47)	41 (41)	90 (52)	
Resection NOS	3 (13)	22 (30)	4 (4)	18 (10)	
Hemipelvectomy	4 (17)	5 (7)	0 (0)	0 (0)	
Additional organs removed					
Urinary bladder	5 (21)	28 (38)	13 (13)	40 (23)	0.002
Prostate (M only in analysis)	2 (8)	17 (23)	11 (11)	25 (15)	0.123
Vagina (F only in analysis)	3 (13)	21 (28)	9 (9)	36 (21)	0.008
Ureter	8 (33)	33 (45)	18 (18)	29 (17)	<0.001
Sacrum	6 (25)	19 (26)	30 (30)	59 (34)	0.534
IORT	2 (6)	3 (5)	74 (75)	156 (90.2)	<0.001
mrTRG					0.705
Definitely complete	n.a.	0 (0)	0 (0)	3 (2)	
Probably complete	n.a.	1 (9)	8 (10)	14 (9)	
Possibly residual/possibly complete	n.a.	1 (9)	19 (23)	22 (15)	
Probably residual	n.a.	5 (46)	24 (29)	51 (35)	
Definitely residual	n.a.	4 (36)	16 (19)	36 (25)	
Not possible to judge	n.a.	0 (0)	17 (20)	19 (13)	
Complications (Clavien–Dindo grade)					0.705
0–II	17 (71)	47 (64)	67 (68)	120 (71)	
III–V	7 (29)	27 (37)	31 (32)	49 (29)	
Resection margin					<0.001
R0	21 (88)	50 (68)	78 (79)	95 (55)	
R1/2	3 (13)	24 (32)	21 (21)	78 (45)	
CRM involvement (mm)					0.001
> 1	18 (75)	36 (49)	59 (61)	68 (40)	
≤ 1	6 (25)	38 (51)	38 (39)	102 (60)	

Values in parentheses are percentages unless indicated otherwise; *values are mean (i.q.r.). †Including 16 patients who received solely chemotherapy for locally recurrent rectal cancer (LRRC). ‡From 328 patients for whom MRI was revised. RT, radiotherapy; KAR, Karolinska University Hospital, Stockhom, Sweden; CHE, Catharina Hospital, Eindhoven, the Netherlands; NOS, not otherwise specified; IORT, intraoperative RT; mrTRG, MRI tumour regression grade; n.a., not applicable. §χ^2 or Fisher's exact test.

Adjuvant treatment for LRRC

No adjuvant radiotherapy was given in CHE, whereas EBRT or brachytherapy was administered in six patients (5 per cent) in KAR. Adjuvant chemotherapy was administered sporadically to six patients (5 per cent) in KAR and five (2 per cent) in CHE.

Oncological outcomes

OS and MFS were not significantly different between the KAR and CHE groups. On the other hand, the 5-year LRFS was significantly better in KAR than in CHE (62.3 per cent in KAR *versus* 42.3 per cent in CHE, $P = 0.017$) (*Table S1*, *Figs 1* and *2*).

In a sensitivity analysis of treatment failure (first event) that included only patients who had R0 resection, LRFS was still significantly better in KAR ($P = 0.013$), whereas MFS was better in CHE ($P = 0.044$). OS was not significantly different between the hospitals ($P = 0.495$) (*Fig. 2*).

For patients who had R1 resection, there was no significant difference in oncological outcomes between the hospitals (*Fig. 2*).

Results according to neoadjuvant treatment

After combining the data from both hospitals, they were stratified according to the type of neoadjuvant radiotherapy received, including potential radiotherapy for the primary tumour. These treatments were grouped as no neoadjuvant radiotherapy at all (24 patients), radiotherapy solely for the primary tumour (74), full-course chemoradiotherapy (99), and reirradiation (173). There were significant differences at baseline between these categories in surgery for the primary tumour, pN category, primary compartment of the recurrence, administration of induction chemotherapy, surgery for the recurrence, additional resected organs, application of IOERT, resection margin, and circumferential resection margin (CRM) involvement (*Table 2*).

Table 3 Oncological outcomes according to neoadjuvant radiotherapy received for locally recurrent rectal cancer

	No RT at all	Full-course RT	Reirradiation	RT solely for primary tumour	P*
Overall survival					0.007
1 year	73	90	83.2	82	
3 years	50	60	55.6	45	
5 years	38	47	29.2	21	
Local re-recurrence-free survival					<0.001
1 year	78	88	72.8	76	
3 years	72	76	41.8	50	
5 years	72	66	34.0	45	
Metastasis-free survival					0.051
1 year	58	79	71.6	63	
3 years	52	59	47.9	37	
5 years	26	52	39.2	33	

Values in parentheses are percentages. *Log rank test.

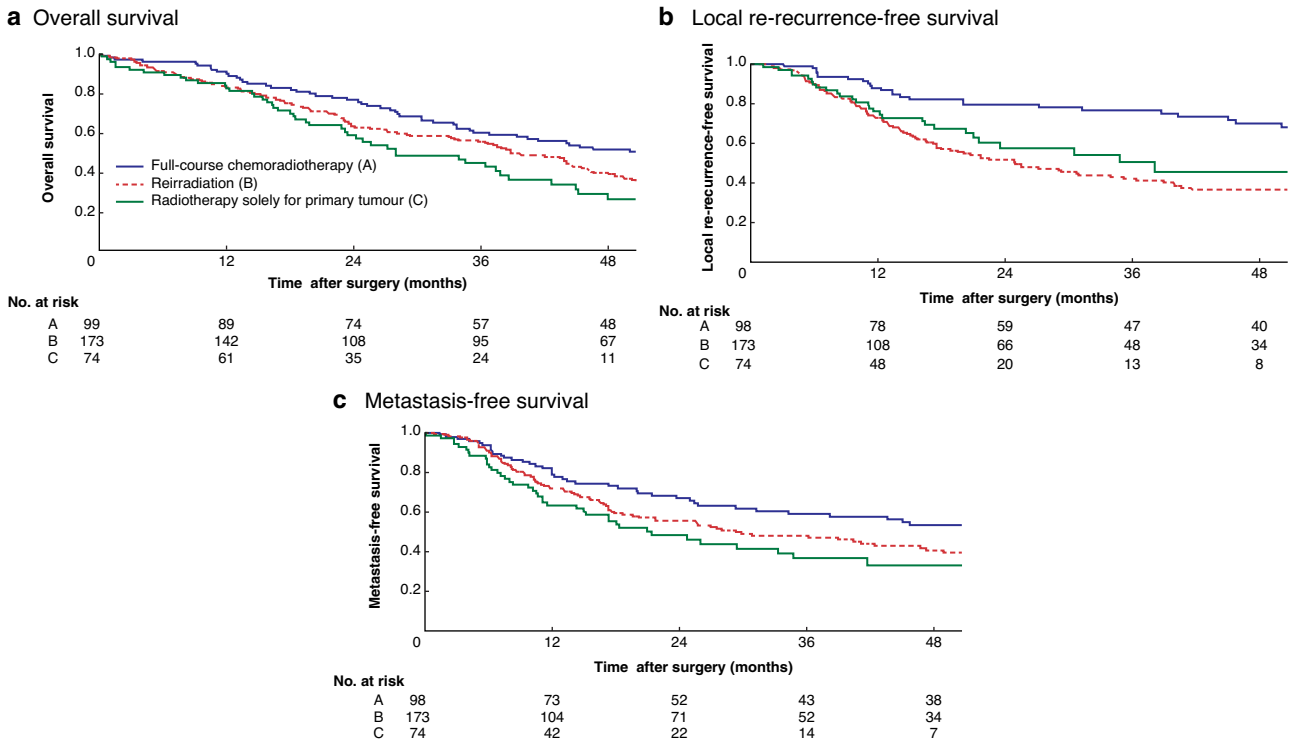

Fig. 3 Kaplan–Meier analysis of overall, local re-recurrence-free, and metastasis-free survival according to neoadjuvant therapy

a Overall, **b** local re-recurrence-free, and **c** metastasis-free survival. Pairwise comparisons: **a** $P = 0.005$ (A *versus* B), $P = 0.003$ (A *versus* C), $P = 0.207$ (B *versus* C); **b** $P < 0.001$ (A *versus* B), $P = 0.005$ (A *versus* C), $P = 0.197$ (B *versus* C); **c** P 0.066 (A *versus* B), $P = 0.010$ (A *versus* C), $P = 0.227$ (B *versus* C) (log rank test).

Survival analysis according to these categories was carried out. Twenty-four patients who had no neoadjuvant radiotherapy at all were not included in the Kaplan–Meier analysis (*Table 3*).

In univariable survival analysis, age, primary surgery, primary lymph node stage in the TNM classification, neoadjuvant radiotherapy treatment for recurrence, CRM, primary compartment of recurrence, and R0 resection were all individually associated with OS ($P \leq 0.050$). Based on these significant variables in univariable analysis, a multivariable regression model was built, which revealed that OS was worse in patients aged over 70 years or without a clear resection margin (R1/2) after resection of the local recurrence ($P < 0.001$ and $P = 0.001$ respectively) (*Table S2*).

R0 resection was the strongest prognostic factor for survival, with a hazard ratio of 2.23 (95 per cent c.i.1.74 to 2.86; $P < 0.001$), 3.96 (2.87 to 5.47; $P < 0.001$), and 2.00 (1.48 to 2.69; $P < 0.001$) for OS, LRFS, and MFS respectively.

Overall survival

The 5-year OS rate was 38 per cent for 24 patients treated with surgery only, 47 per cent for 99 patients who had full-course chemoradiotherapy, 29.2 per cent for 173 patients who underwent reirradiation, and 21 per cent for 74 patients treated with radiotherapy solely for the primary tumour ($P = 0.007$). *Post hoc* pairwise comparisons showed differences for full-course chemoradiotherapy *versus* reirradiation, and full-course chemoradiotherapy *versus* radiotherapy for the primary tumour alone ($P = 0.005$ and $P = 0.003$ respectively) (*Fig. 3*).

Local re-recurrence-free survival

The 5-year LRFS rate was 72 per cent for 24 patients treated with surgery only, 66 per cent for 98 patients treated with full-course chemoradiotherapy, 34.0 per cent for 173 patients who had reirradiation, and 45 per cent for 74 patients who had radiotherapy solely for the primary tumour ($P < 0.001$). *Post hoc* pairwise comparisons showed significant differences (*Fig. 3*).

Metastasis-free survival

The 5-year MFS rate was 26 per cent for 24 patients treated with surgery only, 52 per cent for 98 patients who underwent full-course chemoradiotherapy, 39.2 per cent for 173 patients who had reirradiation, and 33 per cent for 74 patients who received radiotherapy solely for the primary tumour ($P = 0.051$) (*Fig. 3*).

Discussion

This study investigated the outcomes of different treatment strategies for LRRC in two leading tertiary referral hospitals in the Netherlands and Sweden. The results, with regard to OS, LRFS and MFS, support full-course chemoradiotherapy as affording better oncological outcomes than reirradiation and no neoadjuvant radiotherapy in the treatment of LRRC.

Neoadjuvant treatment may improve the R0 resection rate, which is the most important prognostic factor for survival; however, a surgical strategy aimed at wider margins seems pivotal in increasing the probability of R0 resection. To achieve R0 resection, the focus should be on determining the extent of surgery, without relying on downstaging by neoadjuvant therapy[13,17–20]. The best oncological outcomes in both hospitals were found in the group of patients who underwent full-course chemoradiotherapy. Similar to findings regarding the treatment of LARC, this suggests that the response to neoadjuvant treatment can be attributed to better oncological outcomes by facilitating R0 resections[21]. The opposite was also found to be true: R1 margins predicted not only poor LRFS but also poor MFS and OS.

Previous studies have focused on intensification of neoadjuvant treatment in patients with LRRC, most of whom received neoadjuvant radiotherapy for the primary tumour. Dose limitations prevent the administration of neoadjuvant full-course chemoradiotherapy in these patients[6,10]. Intensification can be achieved by reirradiation with concomitant chemotherapy, neoadjuvant induction chemotherapy, and/or boosting the tumour area using IOERT[22,23]. The use of reirradiation did not seem to have an effect in this cohort. In previous studies, the effect of reirradiation was debatable. From retrospective research done in CHE, it seemed promising especially when induction chemotherapy was added[10,24–26]. The intensification of neoadjuvant therapy is currently being assessed by the GRECCAR 15 trial and PelvEx II study[27,28].

From comparison of the two groups of previously irradiated patients, it can be concluded that the surgical approach aiming at wide margins, based on the primary imaging as practised in KAR, resulted in a higher R0 resection rate than achieved in CHE. In CHE, the surgical plan was based on the restaging imaging after neoadjuvant treatment; the surgical approach was de-escalated when downstaging by neoadjuvant treatment seemed to allow a smaller, but still radical, resection[29,30]. During surgery, IOERT was used to treat any tumour cells not resected and frozen sections were taken to analyse the radicality of the resection. In KAR, any tissue that was initially interpreted as involved on the primary imaging was resected. However, a larger, but not statistically significant, proportion of patients in KAR developed distant metastases as the first event ($P = 0.144$). Interestingly, this difference was significant in the sensitivity analysis that included only patients who had R0 resection ($P = 0.044$). At baseline, the clinical TNM stage was unknown, which might partly explain the differences in treatment strategies and could have resulted in some sort of selection bias. Patients who did not receive neoadjuvant radiotherapy for the primary and recurrent tumour were excluded from the Kaplan–Meier analysis because of the great heterogeneity of the group.

The retrospective nature of this study leads to some important limitations. There is the possibility of selection bias, and data obtained retrospectively by review of patient records are unlikely to be as complete as those in a prospective study. Furthermore, as the aim of this study was to determine the differences in oncological outcomes by treatment regimen, the possibility of exploring the specific characteristics that influence or even predict these outcomes increased. Unfortunately, as apparent in the regression analysis, the limitation in sample size and the large number of substantial predictors made the multivariable model overfit. This suggests that the subgroups were probably too small for conclusions to be drawn.

Neoadjuvant therapy may facilitate R0 resection. However, apparent downstaging may lead to less radical surgery that risks failure to resect microscopic tumour deposits, resulting in R1 resection. This might explain why fewer R0 resections were observed in CHE compared with KAR, even though this did not result in worse oncological outcomes. In the published literature, the overall R0 resection rate for LRRC is approximately 60 per cent[31,32], which is comparable to the R0 resection rates from CHE (61.4 per cent).

As neoadjuvant treatment and a surgical approach based on the primary imaging seem effective in achieving R0 resections and better oncological outcomes, this changed current practice in both hospitals in the present study. As full-course chemoradiotherapy

was associated with better OS, it has become standard of care in KAR, whereas CHE has returned to the former strategy of determining the surgical approach on the basis of primary imaging, instead of the imaging after neoadjuvant treatment.

Neoadjuvant full-course chemoradiation in radiotherapy-naive patients independently leads to the best oncological outcome. However, neoadjuvant therapy does not diminish the need for a surgical approach aiming at wide resection margins to increase the probability of R0 resection. Therefore, the surgical approach for resection should depend on primary imaging of the LRRC before any treatment is started.

Disclosure. The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

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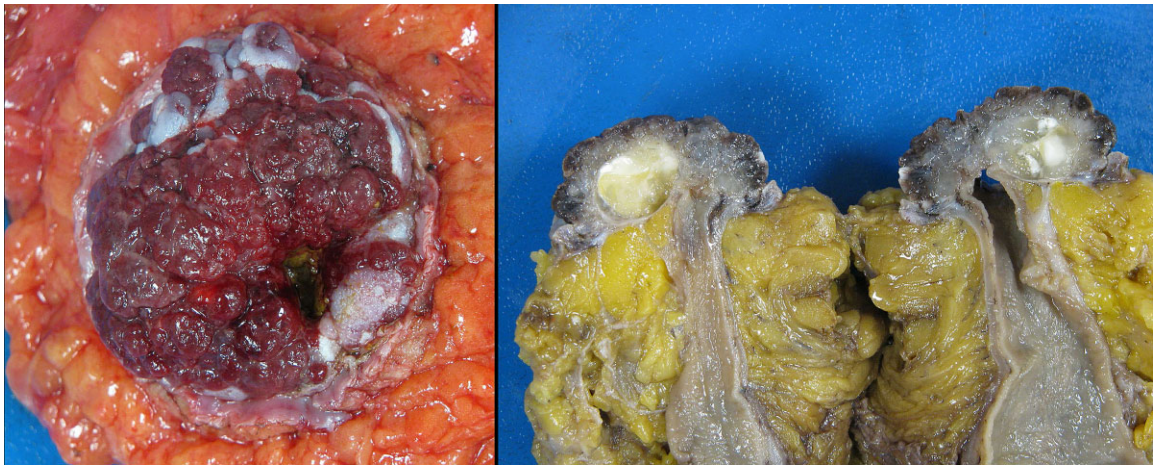
Surgical Snapshots

Colostomy granulomas, not always what they seem

A 53-year-old patient with a history of Crohn's disease had experienced painful bleeding from colostomy granulomas for 7 years. Repeat biopsies diagnosed a stomal adenocarcinoma; multiple previous biopsies had been negative for malignancy. A left colectomy was performed. Definitive histopathology showed a mucinous pT2N0 adenocarcinoma with a complete resection.



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