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ORIGINAL ARTICLE

# Outcome and prognostic factors of local recurrent rectal cancer: a pooled analysis of 150 patients

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**Abstract**
*Background* Surgery is the only curative treatment in patients with locally recurrent rectal cancer (LRRC). The aim of this study was to evaluate the outcome and the prognostic factors of tumour-free resection margin (R0) and overall survival (OS) in LRRC.
*Methods* Consecutive LRRC patients observed between 1987 and 2005 in three Italian university hospitals were evaluated. Survival curves were estimated using the Kaplan–Meier method and compared with the log-rank test. In order to identify factors associated with both R0 resection and OS, a logistic regression analysis was performed in patients who underwent surgery with curative intent.
*Results* Out of 150 patients with LRRC, 107 underwent surgery, but since 7 were found to have unresectable disease only 100 underwent surgical resection. Of them, 51 underwent radical and 49 extended resection. Sixty of the 107 patients underwent multimodality treatment. In 61 patients, R0 resection was achieved. Median OS after surgery was 43.4 months. In patients, who had surgery with curative intent, independent variables associated with R0 resection were: surgery for the primary tumour performed in other hospitals ($p = 0.042$) extended resection ($p = 0.025$) and use of positron emission tomography (PET) as a staging modality ($p = 0.03$). Independent variables associated with OS were: post-operative radiotherapy ($p = 0.004$), stage of the primary tumour ($p = 0.004$), R0 resection ($p = 0.00001$), and use of PET (0.02).
*Conclusions* Resection for LRRC results in improved survival. Other than the well-known prognostic factors R0 resection and OS, PET scan has an independent impact both on OS and R0 resection. It should therefore be included in routine clinical practice when staging LRRC.

**Keywords** Rectal cancer · Local recurrence · Surgery for local recurrence · Survival · PET

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## Introduction

Despite advances in treatment, 3–30 % of patients develop local recurrence of rectal cancer (LRRC) after curative resection, representing an important clinical challenge [1].

Without treatment, median life expectancy in patients with LRRC is 7 months, while with chemoradiotherapy (CRT) alone it is 17 months [2].

In 40–60 % of patients, LRRC is isolated, so attempting curative resection is an option for cure [3]. In fact, some series recently reported that 5-year survival was between 20 and 35 % after surgery [4, 5]. Surgery for LRRC often requires en-bloc resection to obtain negative margins, with a high rate of surgery-related morbidity [4–7].

The principal aim of the present study was to determine the outcome of patients undergoing surgery for LRRC. The secondary aim was to evaluate prognostic factors of curative resection and survival.

## Materials and methods

### Patients

We retrospectively evaluated data of consecutive patients presenting with recurrent rectal cancer between 1987 and 2005 from the prospective databases of three Italian centres adopting an identical follow-up programme: the Second University of Naples, the University of Florence, and the University of Padua.

Pre-operative work-up included: clinical examination, Carcinoembryonic antigen (CEA) dosage, colonoscopy, total body computed tomography (CT) scan, and magnetic resonance imaging (MRI) of the pelvis. Since 1998, positron emission tomography (PET) or PET–CT was routinely performed pre-operatively. The site of LRRC was classified using the nomenclature based on the anatomical region [8].

Criteria for unresectability changed in the course of the years shifting towards a more aggressive attitude. Contraindications to surgery were similar between centres and consisted of: poor performance status or patients who were medically unfit (i.e. those with severe cardiopulmonary impairment); sciatic nerve involvement; circumferential pelvic bone involvement; extension of the tumour through the sciatic notch; encasement of the external iliac vessels; high sacral involvement—resection above the S3; unresectable distant metastases; predicted R2 resection. However, surgery was individualized and discussed with the patient.

Pre-operative chemoradiotherapy (pCRT) was offered to patients who were pelvic radiotherapy (RT) naïve, unless contraindicated, while re-irradiation of those who received pelvic RT for the primary cancer was considered in selected cases.

Resection was defined as either "radical" (radical resection, RR) if LRRC resection was achieved without resection of any other pelvic organ or "extended" (extended resection, ER) if LRRC resection involved at least one adjacent major vessel/organ/bone (ureters, bladder, prostate, vagina, fallopian tubes, ovary, uterus, iliac vessels, small bowel, sacrum).

Resection status was defined as R0 (no residual disease after surgery), R1 (microscopic residual cancer), R2 (macroscopic residual cancer).

Perioperative mortality was defined as death occurring within 30 days of surgery. Survival analyses were performed only in patients who underwent surgery with curative intent.

After surgery patients were followed up every 3 months for the first year, every 6 months for the subsequent 4 years, and then at least once a year. CEA levels were always determined. Patients had a CT scan 6 months after surgery, and then yearly. When possible, a PET scan was always added to CT evaluation.

Overall survival (OS) was defined as the interval time between the date of surgery and the date of death for any cause or last follow-up control.

**Table 1** Patient, tumour and treatment characteristics of the 150 patients with locally recurrent rectal cancer

| | *n* (%) |
|---|---|
| Male | 99 (66) |
| Median age, years (range) | 62 (36–85) |
| pT | |
| pT1/T2 | 44 (29.3) |
| pT3 | 79 (52.7) |
| pT4 | 27 (18) |
| pN | |
| pN− | 73 (48.6) |
| pN+ | 71 (51.4) |
| Surgical treatment of the primary tumour | |
| Local excision | 10 (6.6) |
| Sigmoid colectomy | 7 (4.6) |
| Anterior resection | 94 (62.4) |
| Hartmann procedure | 15 (10) |
| Abdominoperineal excision | 24 (16) |
| Re-staging according to Suzuki et al. [32] | |
| F0 | 9 (6) |
| F1 | 69 (46) |
| F2 | 55 (36.7) |
| F3 | 17 (11.3) |

### Statistical analysis

Statistical analysis was performed with Statistical Package for Social Sciences (SPSS®) version 17.0 (SPSS Inc., Chicago, IL, USA). Dichotomous variables were analysed by means of Fischer's exact test. Univariate and multivariate regression analyses were performed in the whole group (150 patients) to identify predictors of OS. Logistic regression was used to identify predictors of OS and R0 resection in patients undergoing surgery with curative intent (100 patients). The Kaplan–Meier method was used to generate survival curves. Univariate and multivariate survival analyses were performed using the log-rank test and Cox hazard model, respectively. Only predictors that were found to be statistically significant at the univariate analyses were included in the multivariate regression analyses. The $p$ value was two-sided; $p < 0.05$ was considered statistically significant.

## Results

### Characteristics of patients and of the primary tumour

One hundred and fifty patients with LRRC after primary R0 resection were identified. Demographic characteristics at recurrence, pT and pN stage, and surgical treatment of the primary tumour are summarized in Table 1. Surgery for the primary tumour was performed elsewhere in 102 (68 %) cases. Thirty-eight patients (25 %) received RT and/or chemotherapy as adjuvant or neoadjuvant treatment. The pTNM [9] stage of the primary rectal cancer was: I ($n = 22$, 14.7 %), II ($n = 51$, 34 %), III ($n = 74$, 49.3 %), and IV (resectable liver metastases) ($n = 3$, 2 %).

### Local recurrence

Median time to local recurrence was 19 months (range: 2–87 months). Ninety-seven patients (64.6 %) experienced symptoms from disease relapse. PET or PET–CT was performed in 42 (28 %) patients. The CEA values were found to be increased in 73 (48.6 %) cases. The site of recurrence was found to be central in 53 patients (49.5 %), anterior in 16 (14.9 %), posterior in 13 (12.1 %), antero-posterior in 2 (1.8 %), lateral in 7 (6.5 %), anterolateral in 8 (7.4 %), and posterolateral in 8 (7.4 %).

In 43 (28.7 %) patients, the recurrence was considered unresectable pre-operatively and surgery was not performed. The most frequent causes of unresectability were distant metastases not amenable to resection (16 patients, 37.2 %) and infiltration of major vessels (9 patients, 20.9 %). Re-staging for LRRC is reported in Table 1. Patients with F4 had worse OS compared with other groups.

### Neoadjuvant and adjuvant treatment for LRRC

Of 107 patients who underwent surgery, 60 received the following adjuvant or neoadjuvant treatments: pCRT ($n = 26$, 24.3 %), post-operative RT ($n = 22$, 20.6 %), double-cycle hyperfractionated CRT ($n = 7$, 6.5 %), pre- and post-operative RT ($n = 3$, 2.8 %), and intraoperative radiotherapy (IORT) ($n = 2$, 1.8 %). Five patients who had already received RT as part of treatment of the primary tumour were re-irradiated with a total dose of 23.4 Gy plus concomitant 5-fluorouracil and folinic acid. In order to assess resectability, patients were re-staged by means of MRI or CT scan—with PET scan if available—4–6 weeks after completion of the neoadjuvant regimen and, if suitable for surgery, patients were operated on 6–8 weeks after completion of RT. Post-operative RT was carried out when R0 resection was not achieved or dubious.

**Table 2** Post-operative complications (48) in 29 of 100 patients undergoing surgery with curative intent

| Complication | Radical resection | Extended resection | *p* |
|---|---|---|---|
| Haemorrhage | – | 2 | 0.237 |
| Myocardial infarction | – | 1 | 0.490 |
| Pneumonia | 2 | 1 | >0.99 |
| Ileus | 2 | 2 | >0.99 |
| Anastomotic leak | 2 | 1 | >0.99 |
| Perineal wound breakdown | 3 | 5 | 0.482 |
| Persistent perineal sinus | 1 | 2 | 0.613 |
| Wound infection | 4 | 4 | >0.99 |
| Pelvic collection | 4 | 6 | 0.520 |
| Urinary injury | 1 | – | >0.99 |
| Urinary retention | 2 | 2 | >0.99 |
| Sexual dysfunction | – | 1 | 0.490 |
| Total | 21 | 27 | 0.229 |
| Complications according to Clavien–Dindo classification [33] | | | 0.558 |
| I | 8 | 8 | |
| II | 3 | 4 | |
| III | 10 | 14 | |
| IV | – | 1 | |
| V | – | – | |

### Surgery for LRRC

Out of 107 (71 %) patients who underwent surgery, 7 (6.5 %) were found to have an unresectable recurrence and in 5 of them, the site of recurrence was posterolateral.

The remaining 100 patients (62 male, median age 62 years, range 36–85 years) underwent a potentially curative resection of the recurrent disease.

When evidence of direct invasion was found, pelvic structures were dissected en-bloc, otherwise an attempt to dissect them free was made.

A RR was performed in 51 patients (47.6 %): anterior resection (AR) in 9 patients, AR with a coloanal anastomosis in 5, abdominoperineal excision (APE) in 30, and Hartmann procedure in 7. An ER was performed in 49 patients (45.7 %). In these patients, the site of recurrence was: anterior in 19 (6 pelvic exenteration, 8 APE with bladder excision, 5 pubic bone excision), lateral in 6 (pelvic wall structures vessels, ureter, and kidney excision), posterior in 8 (5 APE with sacrectomy up to S3, 3 pelvic exenteration with sacrectomy), and involved small bowel, ovary and/or fallopian tubes in 16.

A myocutaneous flap was used to cover the perineal defect in selected patients, in collaboration with surgeons with expertise in flap procedures. Twelve patients received

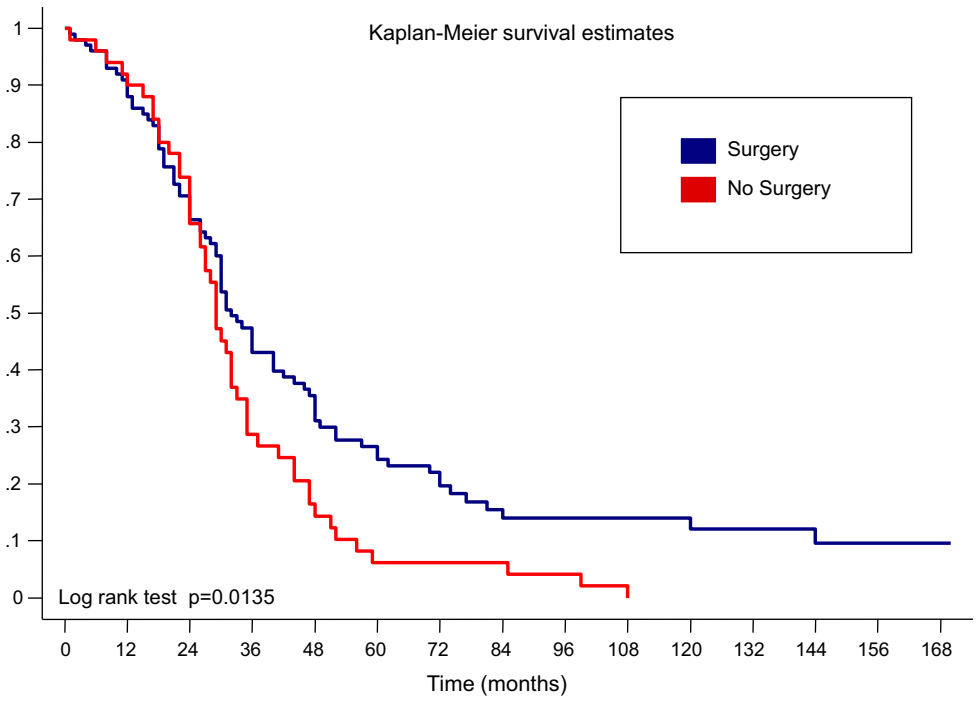


**Fig. 1** Overall survival of all patients with locally recurrent rectal cancer, according to treatment. *Blue graph* patients undergoing surgery; *red graph* patients unfit for or refusing surgery ($p = 0.0135$)

a vertical rectus abdominis myocutaneous (VRAM) flap, while 3 underwent a gluteus maximus flap reconstruction in the prone jack-knife position.

Ileal conduits were fashioned in 15 and ureterostomies in 8 ER patients. In the RR group, a terminal colostomy was fashioned in 37 patients, while 14 had a temporary diverting ileostomy. In the ER group, 38 had a terminal colostomy, while an ileostomy was made in 11.

Of 100 patients with resectable LRRC, 61 underwent a R0 (33 RR, 28 ER), 27 a R1 (13 RR, 14 ER), and 12 a R2 (5 RR, 7 ER) resection. There was no statistically significant association between R resection and type of surgical resection (RR and ER).

Twenty-nine patients developed 48 post-operative complications (Table 2). One patient died post-operatively. Patients undergoing ER had longer mean length of hospital stay compared with RR ($14 \pm 9.3$ vs. $11 \pm 9.5$ days, $p = 0.02$).

In the whole group ($n = 150$) of patients, with a median follow-up of 47 months (range: 0.9–151 months), the median OS was 31.3 months [95 % confidence interval (CI), range 26.02–37.2 months]. Significantly longer OS was observed in patients undergoing surgery compared with those who refused or did not meet surgery criteria (43.4 vs. 9.8 months, $p = 0.0135$) (Fig. 1).

Univariate and multivariate regression analyses were also performed in order to identify significant predictors of OS. In the whole group ($n = 150$), advanced stage of the primary disease ($p = 0.0006$) and unwillingness/unfitness to undergo surgery ($p = 0.0135$) were significant predictors of shorter life expectancy. When considering the 100 patients who underwent surgical resection (Table 3), independent negative factors associated with OS were: stage of the primary tumour ($p = 0.004$), the residual disease ($p < 0.001$), and post-operative radiotherapy ($p = 0.004$). Conversely, pre-operative PET scan assessment was an independent factor associated with longer survival ($p = 0.021$). OS curves comparing patients who underwent an R0 versus R1–R2 resection are shown in Fig. 2.

Findings of the univariate regression analysis performed to identify the predictors of free resection margins are summarized in Table 4. At multivariate analysis, factors independently associated with a non-radical resection (R1–R2) were: surgery for the primary tumour performed elsewhere, PET–CT not performed on staging LRRC, and RR instead of ER.

## Discussion

The aim of this multicentre retrospective study was to evaluate the outcome of patients undergoing surgery for LRRC and to investigate prognostic factors of curative resection and survival. We found that resection for LRRC may result in improved survival. The median OS in all 150 patients with LRRC was 31.3 months. Patients who underwent surgery with curative intent had significantly longer OS than those who did not (43.4 vs. 9.8 months, $p = 0.0135$). R0 resection and stage of the primary play a

**Table 3** Univariate and multivariate regression to identify independent prognostic factor of survival in 100 patients undergoing surgery (HR >1 related to shorter overall survival)

| Factor | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR | *p* | HR | *p* |
| Sex: male versus female | 1.378 (0.765, 2.482) | 0.284 | – | – |
| Age: >70 versus <70 years | 0.765 (0.393, 1.487) | 0.430 | – | – |
| CEA[a]: increased versus normal value | 0.431 (0.121, 0.902) | 0.048 | 0.877 (0.514, 1.494) | 0.629 |
| Stage of primary tumour: III versus I, II | 2.108 (1.185, 3.460) | 0.002 | 1.908 (1.192, 3.541) | 0.004 |
| PET scan versus no PET scan | 0.543 (0.143, 0.703) | 0.003 | 0.806 (0.121, 0.901) | 0.021 |
| Surgery of recurrence: ER versus RR | 0.582 (0.311, 1.091) | 0.091 | – | – |
| Residual disease: | | | | |
| R1/R2 versus R0 | 4.269 (2.139, 7.739) | <0.001 | 4.069 (1.939, 10.040) | <0.001 |
| R1 versus R0 | 2.967 (1.943, 4.765) | <0.001 | 2.304 (1.032, 5.270) | 0.003 |
| R2 versus R0 | 4.643 (3.754, 7.876) | <0.001 | 4.843 (3.061, 9.876) | <0.001 |
| Pre-operative chemoradiotherapy: yes versus no | 0.871 (0.322, 0.924) | 0.016 | 0.965 (0.230, 1.158) | 0.143 |
| Post-operative radiotherapy: yes versus no | 1.941 (1.520, 3.695) | 0.001 | 1.541 (1.070, 3.967) | 0.004 |

Values in parentheses are 95 % confidence interval

*HR* hazard ratio, *CEA* carcinoembryogenic antigen, *ER* extended resection, *RR* radical resection; *PET* Positron emission tomography

[a] increased: >2.5 in non-smokers, >5 ng/ml in smokers

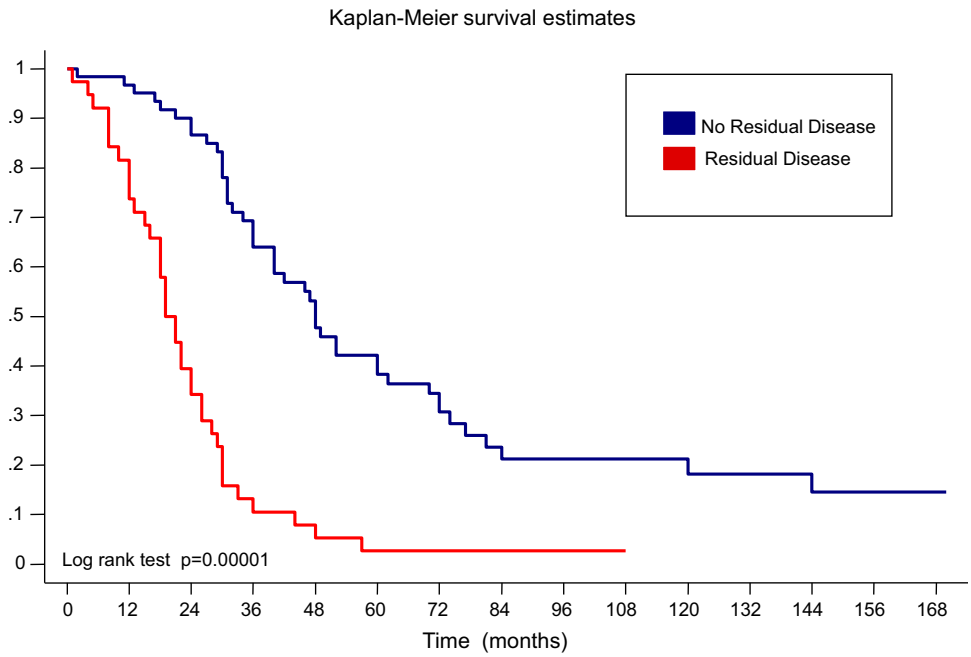


**Fig. 2** Overall survival of patients undergoing surgery for local recurrence with curative intent, stratified for the resection margin achieved: *blue graph* patients with curative (R0) resections; *red graph* patients with microscopic (R1) or gross (R2) tumour residual ($p < 0.0001$)

key role as prognostic factors. Interestingly, R0 resection is affected by the institution where the primary tumour was resected, and the use of PET is an independent prognostic factor for OS and predictor of R0 resection.

We identified several independent predictors of longer survival in patients receiving surgery (Table 3). Patients receiving R0 resections were almost five times more likely to have a significant life gain over R2 ($p < 0.001$), while those with residual microscopic disease (R1) had two times the risk of shorter survival ($p = 0.003$). Actually, R1 resection may offer better results than non-operative management in patients with unresectable LRRC [10], but expected benefits in the long term should not be overestimated.

Node-positive primary cancers significantly impaired survival [hazard ratio (HR) 1.9 95 % CI 1.1–3.5, $p = 0.004$], mainly as a result of a systemic spread and distant metastases. Pre-operative CRT showed a protective effect at univariate analysis, but it did not reach significance at multivariate analysis.

Patients receiving post-operative RT had shorter survival (HR 1.5 95 % CI 1–3.9, $p = 0.004$, Fig. 3): advanced disease and certainty of residual disease, as well as adverse events due to re-irradiation might account for this. We

**Table 4** Univariate and multivariate regression to identify predictors of disease-free resection margins in 100 patients undergoing surgery for local recurrence (HR >1 related to R0)

| Factor | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR | *p* | HR | *p* |
| Primary surgery: referred versus institutional | 1.751 (1.024, 2.371) | 0.002 | 1.231 (1.043, 1.870) | 0.042 |
| Institution: I (39 patients) | | | | |
| II (19 patients) | 0.204 (0.036, 1.144) | 0.071 | – | – |
| III (42 patients) | 0.613 (0.098, 3.842) | 0.602 | | |
| Sex: male versus female | 1.212 (0.347, 3.123) | 0.942 | – | – |
| Age: >70 versus <70 years | 0.950 (0.897, 1.005) | 0.072 | – | – |
| CEA[a]: increased versus normal value | 1.321 (0.921, 3.023) | 0.043 | 0.990 (0.948, 1.035) | 0.664 |
| Resectability assessment: CT or MRI + FDG-PET versus CT or MRI alone | 1.931 (1.328, 5.701) | 0.002 | 1.151 (1.222, 7.898) | 0.03 |
| Stage of primary tumour: III versus I, II | 0.980 (0.422, 2.276) | 0.962 | – | – |
| Pre-operative radiotherapy for primary tumour: yes versus no | 0.321 (0.078, 1.327) | 0.117 | – | – |
| Post-operative radiotherapy for primary tumour: yes versus no | 0.431 (0.267, 0.618) | 0.035 | 0.640 (0.074, 5.576) | 0.686 |
| Pre-operative chemoradiotherapy: yes versus no | 1.320 (1.032, 3.561) | 0.021 | 1.016 (0.828, 5.367) | 0.092 |
| Surgery: ER versus RR | 2.672 (1.336, 8.387) | 0.001 | 1.253 (1.077, 3.839) | 0.025 |

Values in parentheses are 95 % confidence interval

*OR* odds ratio, *CEA* carcinoembryogenic antigen, *ER* extended resection, *RR* radical resection, *CT* Computed tomography, *MRI* Magnetic resonance imaging, *FDG-PET* Fluorodeoxyglucose-positron emission tomography

[a] Increased: >2.5 in non-smokers, >5 ng/ml in smokers

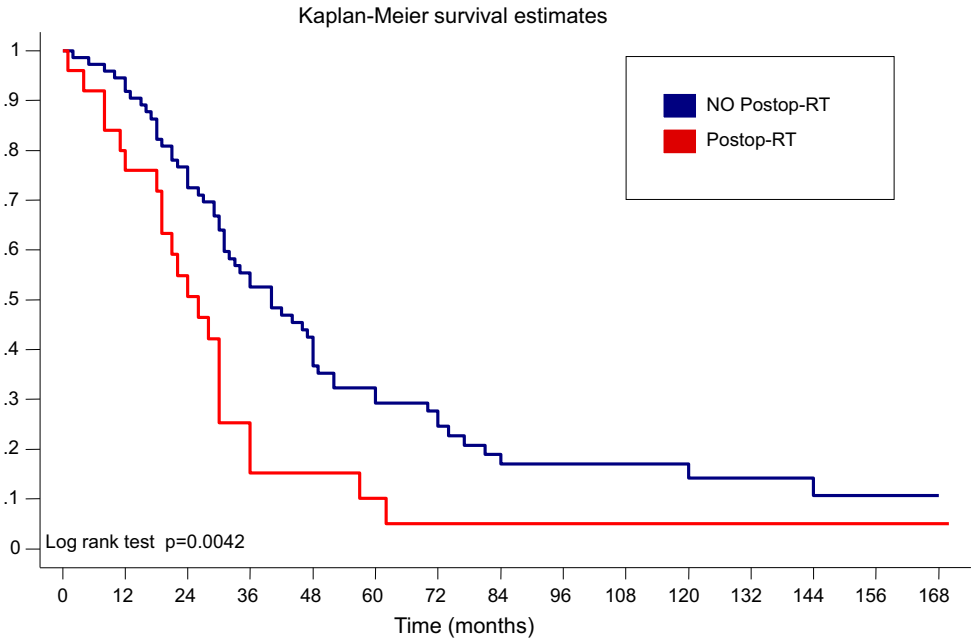


**Fig. 3** Overall survival of patients undergoing surgery for local recurrence with curative intent, stratified for post-operative radiotherapy (RT): *blue graph* patients not receiving post-operative RT; *red graph* patients receiving post-operative RT ($p = 0.004$)

would suggest to routinely rule out R1 in doubtful sites during surgery by means of intraoperative histological examination, in order to widen surgery and when possible to deliver IORT. Routine adjuvant RT should be abandoned even in LRRC patients with residual disease—since no additional benefits are likely to be observed—in order to avoid further life-threatening complications, favouring more focused techniques [11], by an individualized approach.

Unsurprisingly, PET scan conferred protection against shorter survival, because of the well-known capability of disclosing distant disease [12, 13], amenable to resection, ultimately leading to radicality, or unresectable, and ruling out surgery. All patients who underwent explorative

laparotomy and were found to have an unresectable disease (7 out of 107 operated on) did not have a PET scan pre-operatively, while PET detected unresectable LRRC in four patients who had a negative CT and/or MRI scan (2.6 %), allowing exclusion of these patients from an attempt at surgical treatment.

Most studies agree in identifying microscopic disease-free margins as the strongest predictor of survival [2–6, 14–18]. Every effort should be made to achieve R0, carefully balancing expected risks and benefits, because of a longer survival.

We attempted to identify predictors of R0 (Table 4). We found that two pre-operative conditions were significantly and independently associated with higher rates of radical resection: the hospital where primary surgery was carried out (HR 1.2 95 % CI 1.04–1.8, $p = 0.04$), and a PET scan performed prior to surgery for LRRC (HR 1.2 95 %CI 1.2–7.9 $p = 0.03$). It could be hypothesized that patients operated on for primary rectal carcinoma in hospitals with low case-loads in rectal surgery may have received inadequate surgery, and as a result had residual disease.

It can be predicted that an extensive (adequate) primary approach—even reducing the rates of local recurrence—may negatively affect the likelihood of achieving R0 margins, should subsequent surgery be needed. This may account for differences observed in patients presenting with LRRC who had primary surgery before and after the era of total mesorectal excision (TME), with TME requiring multimodal and more extensive approaches, outside the "holy plane" [19, 20]. With the suspicion of residual disease during surgery (i.e. bone involvement), the addition of IORT could be advantageous [14, 21]. In our series, IORT was performed in a restricted number of patients, limiting data evaluation. This factor may also have accounted for the insignificance of the difference in survival between RR and ER groups (Table 3). Pacelli et al. [22] retrospectively analysed data of 157 patients operated on in a single Institution presenting with LRRC, 58 of whom underwent surgery. Recurrences were more often located extraluminally (62 vs. 38 %). They found pre-operative CRT to be an independent prognostic factor for local control of recurrent disease, in agreement with previously reported experiences with pre-operative chemotherapy allowing radical resection in over 60 % of patients otherwise unfit for surgery [23]. We observed extremely unsatisfactory outcomes in patients who received pre- or post-operative RT for primary cancer, probably because of more advanced primary disease in this group. Also, fibrosis due to previous pelvic irradiation often makes surgery for LRRC technically demanding. Re-irradiation of patients with LRRC who received RT for primary cancer is an option, but late toxicity may increase after surgery [24]. Mirnezami et al. [12] recently recommended resection alone over neoadjuvant treatment in patients who are not *naïve* to RT. In our series, pre-operative CRT did not reach statistical significance in terms of increased resectability (HR 1.01 95 % CI 0.8–5.3 $p = 0.09$). This may be the result of different pre- and post-operative regimens adopted at the time of first surgery, as great variability between centres has been reported [25]. Yu et al. [26] found LRRC to be radioresistant compared with primary tumours, suggesting that improved or intensified CRT protocols are desirable for LRRC.

PET has been shown to play an important role in the follow-up of patients operated on for rectal cancer and can alter the management of patients with recurrent disease [13]. PET–CT is now recommended in surgical planning of patients presenting with suspected LRRC, making possible the distinction between scars and disease relapse, and detection of distant metastases. This functional evaluation and MRI scan should be considered complementary rather than concurrent [12]. The utility of FDG–PET in evaluating distant metastases is widely accepted, however, its role in increasing the rates of R0 has been poorly investigated. In our series, PET scan significantly increased the likelihood of R0 resection. One explanation of this finding might be that PET can disclose multiple localizations or sites of tumour cells with high-metabolic activity inside the pelvis, which may be missed during conventional imaging assessment, and another that PET was usually performed with CT scan, allowing better anatomical mapping and consequently a more precise surgical approach. This finding requires confirmation in studies on larger series.

Raised CEA did not independently predicted R0, and this may be justified by almost 65 % of patients presenting with symptoms raising suspicion of LRRC.

Extended surgical approaches conferred higher chances to obtain satisfactory tumour clearance (HR 1.2 95 % CI 1–3.8 $p = 0.02$). En-bloc resection of involved structures is the treatment of choice for LRRC spreading to surrounding tissues [5], a pivotal role being played by the site and pattern of recurrence. In our series, the most frequent localization was central (49.5 %), followed by anterior and posterior ones (27 %), which are more likely to involve sacrificable structures; lateral and anterolateral or posterolateral localizations were less frequent (21.3 %) but more difficult to treat. Lateral or high fixed recurrences may require a shift from an "anatomical" resection—typical of primary rectal cancer—towards "sarcoma-like" surgery (i.e. for vessel reconstruction), which is being observed in the very recent literature [27], in order to achieve R0 resections (Fig. 4a–c).

Surgery for LRRC is complex and often extensive, which may result in a significant degree of perioperative mortality and complications [5, 27–30]. However, in experienced hands, 30-day mortality is reported to be low

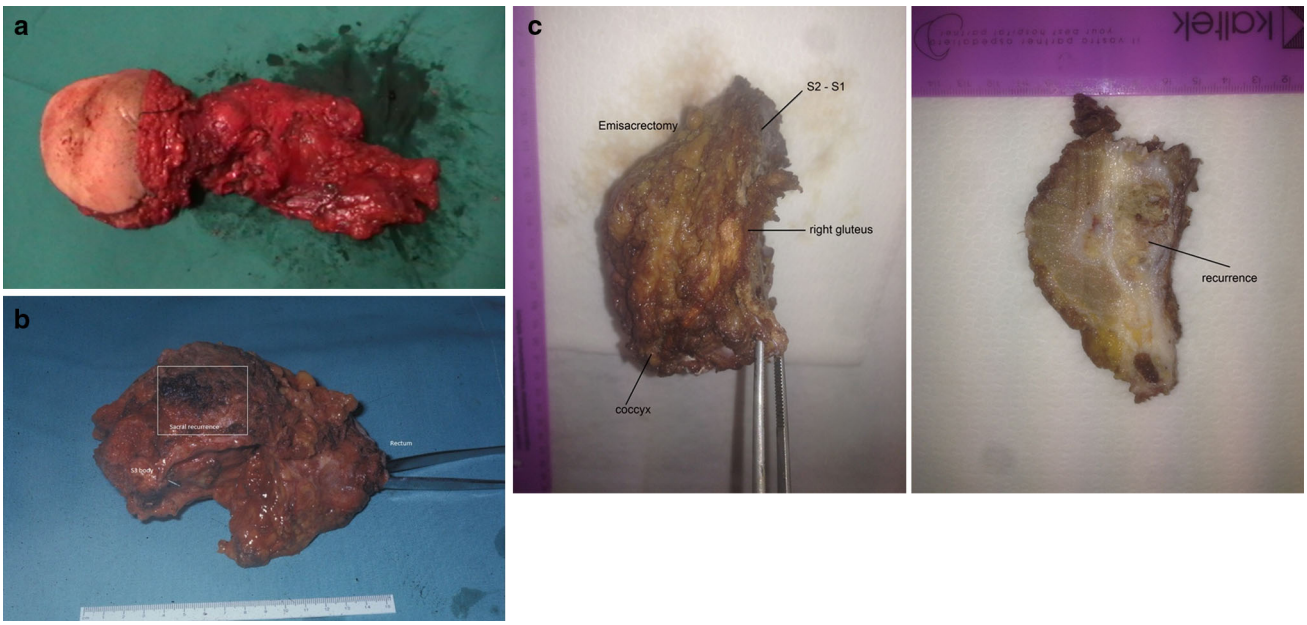


**Fig. 4** **a–c** Hemisacrectomy performed for pelvic recurrence after anterior resection for rectal adenocarcinoma infiltrating anastomotic line, prostate, ischiorectal fossae and sacrum

and is mainly caused by bleeding, sepsis and thromboembolic complications. In our series, there were no intraoperative deaths, and perioperative mortality was 1 %. The extent of surgery also influences perioperative complications. These vary considerably between reports, with incidence rates, which are not negligible, ranging from 15 to 68 % [5, 28–30]. We observed an acceptable complication rate when compared with data available in the literature, and no differences concerning the type of surgery (RR vs. ER), which suggests that these advanced procedures may be safely performed by experienced teams. Pelvic collections (20.7 %), perineal wound breakdown (16.7 %), and wound infections (16.7 %) accounted for more than half of all complications.

The present study has several limitations, shared with similar experiences reported in the literature. Data were gathered in a retrospective fashion and from the databases of three different centres. It reports on a long time span, therefore, conclusions may be limited by disparities in treatments as well as by evolution of disease management and staging. The evolution of surgery for LRRC has led to more aggressive approaches over time and may have had an influence on some factors tested in this study. The number of resections for LRRC may be limited (100 over 18 years). However, patients have been followed up thoroughly over years after repeated surgery. Nonetheless, even if lower than those reported in studies from the USA and Northern Europe, it is not dissimilar from those of other Italian reports (i.e. 44 resections over 15 years in a university hospital [22]), and all three centres had adequate expertise in LRRC treatment. The team volume increased over time, but a crude range of 2–3 cases of patients undergoing surgery for LRRC with curative intent per year per centre is observed, which falls in the range of all LRRC observed in most UK centres [31]. This allows easier interpretation and translation of data. Another limitation is the lack of homogeneous data concerning the management of patients with LRRC and synchronous distant metastases. Controversy exists over whether resectable synchronous lung or liver disease is a contraindication to attempted removal of LRRC [34]. Gagliardi et al. [19] showed that small liver metastases amenable to resection had no detrimental effects on survival in LRRC patients compared with those without extrapelvic recurrence. The role of synchronous pelvic and hepatic resection has been questioned [34], but authors [35] suggest that it may be reserved for selected patients [34]. In our series, this was carried out using a case-by-case approach. Long-term outcomes are yet to be published in large series, highlighting the need of further research.

The present study offers new insight into LRRC management, including the utility of PET scan in predicting likeliness of R0 resection, as a surrogate marker of survival, which was practically unexplored in the past. However, this observation should be read with caution, as PET was performed in a limited number of patients, and even if all candidates for surgery for LRRC were offered a PET scan, when available, a potential selection bias cannot be ruled out.

## Conclusions

Patients with LRRC are best treated by radical surgery. Multimodal treatment in specialized centres may increase the rates of curative surgery, but probably needs to be optimized.

Primary surgery performed in low case-load centres and a pre-operative PET scan examination may be independent predictors of R0 resection. Irrespective of primary surgery and LRRC localization, ER confers higher chances of obtaining disease-free resection margins.

Long-term OS is definitively impaired by residual disease after surgery. Patients fit for surgery should be encouraged to undergo surgical treatment, as those who are not fit or refuse surgery have shorter OS. The use of PET–CT scan seems to improve OS because it makes possible better selection of candidates for resection. Routine adjuvant RT in patients who had R1/R2 resections is questionable.

**Conflict of interest** None.

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