Long-Term Outcome of Patients with Complete Pathologic Response after Neoadjuvant Chemoradiation for cT3 Rectal Cancer: Implications for Local Excision Surgical Strategies

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ABSTRACT

Background. Neoadjuvant chemoradiotherapy (CRT) followed by radical surgery including total mesorectal excision (TME) is standard treatment in patients with locally advanced rectal cancer. Emerging data indicate that patients with complete pathologic response (ypCR) after CRT have favorable outcome, suggesting the possibility of less invasive surgical treatment. We analyzed long-term outcome of cT3 rectal cancer treated by neoadjuvant CRT in relation to ypCR and type of surgery.

Methods. The study population comprised 139 patients (93 men, 46 women; median age 62 years) with cT3N0–1M0 mid and distal rectal adenocarcinoma treated by CRT and surgery (110 TME and 29 local excision) at our institution between 1996 and 2008. At pathology, ypCR was defined as no residual cancer cells in the primary tumor.

Results. Tumors of 42 patients (30.2%) were classified as ypCR. After a median follow-up of 55.4 months, comparing patients with ypCR to patients with no ypCR, 5-year disease-free survival was 100% vs. 65.5% (P = 0.024), and 5-year local recurrence-free survival was 92.9% vs. 66.7% (P = 0.047).

Conclusions. With retrospective analysis limitations, our data confirm favorable long-term outcome of cT3 rectal cancer with ypCR after CRT and warrant clinical trials exploring local excision surgical strategies.

Neoadjuvant chemoradiotherapy (CRT) followed by radical surgery including total mesorectal excision (TME) has been shown to effectively improve local control and is the recommended treatment in patients with locally advanced (T3–4 or any N1–2) mid-distal rectal cancer. 1–5 Tumor regression after CRT is observed in most of the patients, and an absence of residual neoplasia in the resected specimen, known as complete pathologic response (ypCR), has been reported in up to one-third of cases, with its incidence largely varying among different studies. 6

Accumulating evidences indicate that patients with locally advanced rectal cancer showing ypCR after CRT have more favorable long-term outcome compared to patients with less degree or no pathologic response. 7–12 Moreover, tumor regression after neoadjuvant CRT may be observed not only in the primary tumor but also in mesorectal metastatic lymph nodes. 13–18 In view of these data, along with the available information on outcome of locally advanced rectal cancer treated by local excision (LE), organ-preserving strategies have been considered for the
subset of patients with ypCR after CRT. In addition, given the encouraging long-term results of a nonoperative treatment in patients with complete clinical response to CRT, a watch-and-wait policy has been also advocated. The decision making of optimal treatment for patients with locally advanced rectal cancer is a crucial issue because the risk of surgery-related morbidity, mortality, and quality of life has to be balanced with the risk of local and distal recurrence. Therefore, data on the long-term outcome in relation to the grade of pathologic response and to the type of surgical treatment in patients with locally advanced rectal cancer treated by neoadjuvant CRT are greatly needed.

Because patients with clinical T3 (cT3) rectal cancer showing ypCR after neoadjuvant CRT represent the potential target population for a conservative surgical approach including organ preservation, the aim of this study was to analyze the long-term outcome in a subset of such patients, which also included a number of patients who underwent full-thickness LE, treated at our institution during a 12-year period.

METHODS

All consecutive patients treated by neoadjuvant CRT and surgery for cT3 rectal cancer between January 1996 and September 2008 were identified from our institutional, prospectively maintained rectal cancer database. Patients with synchronous distant metastasis were excluded from the study. All patients had biopsy-proven adenocarcinoma of the rectum. The distance of the tumor from the anal verge was measured by rigid rectoscopy. Pre- and post-CRT primary tumor and nodal staging were evaluated by endorectal ultrasound and/or pelvic magnetic resonance imaging. Lymph nodes ≥ 5 mm in size were considered positive. In cases with discrepancy between the two imaging techniques the higher stage was considered. Distant metastasis was excluded by thoracoabdominal and pelvic computed tomographic scan.

Preoperative CRT

Preoperative CRT was provided according to several preoperative sequential treatment protocols developed at our institute between 1994 and 2008, including 5-fluoro-uracil (5-FU) bolus with leucovorin and 45 Gy with or without adjuvant 5-FU/leucovorin, raltitrexed, and 50.4 Gy plus 10 Gy intraoperative radiotherapy (IORT), capecitabine, and 50.4 Gy, continuous infusion (c.i.) 5-FU with gefitinib and 50.4 Gy plus 10 Gy IORT, and capecitabine with or without oxaliplatin and 50.4 Gy (ongoing study). The radiotherapy (RT) clinical target volume (CTV2) included the primary tumor, the mesorectum, and the internal iliac lymph nodes. A second CTV1 included the mesorectum corresponding to the primary tumor with 2-cm radial margin. RT fractionation was of 180 cGy/day, 5 fractions per week. More details on the RT technique have been previously reported.

Surgery

Patients underwent surgery 6–8 weeks after completion of neoadjuvant CRT. Surgical procedures included abdominoperineal resection (APR), low anterior resection (LAR), and full-thickness transanal LE. Radical resection was performed according to TME principles. Reasons for the use of LE included patient refusal of APR, medical comorbidity, and patient preference after a major (complete) clinical response. Toward the last study period, patients with disease with major response to CRT, even if they did not absolutely refuse APR, were offered the option of LE after appropriate informed consent. IORT to high-risk area (presacral region) was provided after surgical resection, according to the study protocols mentioned above.

Postoperative Chemotherapy

Adjuvant 5-FU-based chemotherapy was provided according to study protocol, or in selected cases including patients with metastatic lymph nodes.

Pathology

Pathologic tumor staging was performed according to the guidelines of the American Joint Committee on Cancer and College of American Pathologists. Histopathologic examination of the surgical specimens was performed by gastrointestinal experienced pathologists by using a standardized protocol according to Quirke and Dixon. Cases with no residual cancer cells in the surgical specimen were considered pathologic complete responders (ypCR/ypT0). Mucous lakes without identifiable carcinoma cells were not considered as residual tumor.

Follow-up

Postoperatively, patients were examined at follow-up visits every 3 months for the first 2 years and every 6 months thereafter. At each follow-up control, carcinoembryonic antigen level was determined. Abdominal and pelvic computed tomographic scan or liver ultrasound and chest x-ray were performed alternately every 3–6 months. Colonoscopy was performed yearly. All patients were
followed up at a dedicated outpatient multidisciplinary clinic.

**Statistical Analysis**

Chi-square test or Fisher’s exact test were used to compare percentages between disease that responded completely and disease that did not respond completely, and the Wilcoxon rank test was performed for median age comparison. Cumulative probabilities of overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS), distant metastasis–free survival (DMFS), and local recurrence-free survival (LRFS) were estimated by Kaplan-Meier survival methods, and differences between subgroups were assessed by the log rank test. Duration of follow-up was calculated as the time from surgery to the event of interest. Patients without event were censored at the date of last follow-up. In cases of local and distant metastasis, both events were recorded and computed at any time of occurrence. To better assess the oncologic implications of ypCR, the Cox proportional hazards model was used for adjusting the hazard ratios and corresponding 95% confidence intervals. Because of the limitation of sample size and number of events, only three variables were entered in the multivariate model: cN stage (cN0 vs. cN1), type of surgery (TME vs. LE), and ypCR (yes vs. no). A P value of ≤ 0.05 was considered statistically significant (two tailed). SAS software, version 9.2 (SAS Institute, Cary, NC), was used to perform the data analysis.

**RESULTS**

A total of 188 consecutive patients with rectal adenocarcinoma treated by neoadjuvant CRT followed by surgery with TME (LAR and APR) or LE at our institution between January 1996 and September 2008 were identified. Initially considered for this study were 150 cT3 rectal cancer patients. Of these, 11 were excluded because they had synchronous distant metastasis, leaving a total of 139 patients for analysis. Complete pathologic response in the 42 ypCR patients, while TME surgery, IORT, and adjuvant chemotherapy were used significantly more in the group of ypCR patients, compared to no-ypCR patients. Clinicopathologic differences in ypCR patients compared to no-ypCR patients, while TME surgery, IORT, and adjuvant chemotherapy were used significantly more in the group of no-ypCR patients. Clinicopathologic and treatment characteristics according to the type of surgery in the 42 ypCR patients are reported in Table 2.

**Patients and Treatment Characteristics**

There were 93 male (67%) and 46 female (33%) patients. The median age was 62 years (range, 25–87 years). Seventy-two patients had disease staged as cT3N0 (52%) and 67 as cT3N1 (48%). Median distance of the tumor from the anal verge was 5 cm (range, 1–12 cm). Total RT dose was 45 Gy in 41 patients (29%) and 50.4 Gy in 98 patients (71%). TME surgery was performed in 110 patients (83%) (92 LAR, 18 APR), while LE was performed in 29 patients (17%). Documented reasons for the use of LE were preference after a major clinical response in 22 cases, patient absolute refusal of APR in 4 cases, and medical comorbidity in 3 cases. In 41 patients (29%), IORT was applied in the context of clinical studies. Postoperative chemotherapy was administered in 39 patients (28%).

**Clinical and Pathologic Response**

Clinical restaging before surgery demonstrated primary tumor downstaging (defined as ycT ≤ 2) in 96 patients (69%), 15 of whom (11%) had disease that was restaged as ycT0. Pathologic tumor staging was ypT0 in 42 patients (30%), ypT1 in 11 (8%), ypT2 in 45 (32%), and ypT3 in 41 (30%). Therefore, ypCR was achieved in 30% of the patients. Among the 15 ycT0 tumors, 11 (73%) were found to be ypT0, 2 ypT1, and 2 ypT2. Pathology information about lymph node metastatic status were available in all the 110 patients treated by TME surgery. The median number of lymph nodes examined was 14 (range, 2–32). Metastatic lymph nodes were identified in 27 patients (25%) (19 ypN1, and 8 ypN2). All patients with disease initially staged as cN0 resulted in ypN0 disease. Metastatic lymph nodes were found in 3 (all cN positive) of 25 ypCR patients (12%), and in 24 (29%) of 85 no-ypCR patients (P = NS). In the 60 patients with disease initially staged as cN positive, no metastatic lymph nodes were identified in 12 (80%) of 15 ypCR patients, and in 21 (47%) of 45 no-ypCR patients (P = 0.055). Table 1 outlines the distribution of clinicopathologic and treatment characteristics according to ypCR. There were no statistically significant clinicopathologic differences in ypCR patients compared to no-ypCR patients, while TME surgery, IORT, and adjuvant chemotherapy were used significantly more in the group of no-ypCR patients. Clinicopathologic and treatment characteristics according to the type of surgery in the 42 ypCR patients are reported in Table 2.

**Recurrence and Survival**

There was no postoperative mortality. During a median follow-up of 55.4 months, 12 patients (8.6%) developed local recurrence only, 9 (6.5%) developed local recurrence and distant metastasis (7 liver and 2 lung), and 18 (12.9%) distant metastasis only (9 liver, 4 lung, 4 liver and lung, and 1 lung and brain). In the entire patient population, OS, DSS, DFS, DMFS, and LRFS were 79.1, 83.4, 72.2, 80.5, and 84.3%, respectively. In the subset of 42 patients with ypCR, 1 patient (2.4%) developed local recurrence only, 1 patient (2.4%) local recurrence and liver metastasis, and 3 patients (7.1%) distant metastasis only (1 liver, and 2 liver and lung). Comparing patients with ypCR (n = 42) to
patients with no ypCR ($n = 97$), the 5-year OS was 89.5% versus 74.7%, respectively ($P = 0.026$), the 5-year DSS was 95.8% versus 78.0% ($P = 0.004$), the 5-year DFS was 90.1% versus 64.0% ($P = 0.004$), the 5-year DMFS was 92.5% versus 74.9% ($P = 0.038$), and the 5-year LRFS was 94.9% versus 79.6% ($P = 0.023$) (Fig. 1). In ypCR patients, no statistically significant differences were observed in any of the outcome end points comparing patients treated by surgery including TME and patients treated by LE (Fig. 2). In the subset of 29 patients treated by CRT followed by LE, comparing patients with ypCR ($n = 17$) to patients with no ypCR ($n = 12$), the 5-year OS was 92.3% versus 65.5%, respectively ($P = NS$), the 5-year DSS was 100% versus 65.5% ($P = 0.024$), the 5-year DFS was 87.4% versus 58.3% ($P = NS$), the 5-year DMFS was 87.4% versus 69.4% ($P = NS$), and the 5-year LRFS was 92.9% versus 66.7% ($P = 0.047$) (Fig. 3).

At multivariate analysis, ypCR was a significant prognostic factor for OS, DSS, DFS, DMFS, and LRFS, independent from cN stage and type of surgery (Table 3).

**DISCUSSION**

In the present study, we evaluated the oncologic outcome of consecutive patients with cT3 low and mid rectal cancer with ypCR after neoadjuvant CRT, treated and

| Variable | Total, $n$ (%) | ypCR, $n$ (%) | No ypCR, $n$ (%) | $P$-value |
|----------|----------------|---------------|------------------|-----------|
| Sex | | | | |
| Female | 46 (33.1) | 15 (35.7) | 31 (32.0) | 0.67 |
| Male | 93 (66.9) | 27 (64.3) | 66 (68.0) | |
| Age (years) | | | | |
| Median (range) | 62 (25–87) | 65 (40–85) | 62 (25–87) | 0.16 |
| Distance from anal verge (cm) | | | | |
| $\leq$5 | 86 (61.9) | 29 (69.1) | 57 (58.8) | |
| >5 | 53 (38.1) | 13 (30.9) | 40 (41.2) | 0.25 |
| Clinical lymph node status | | | | |
| cN0 | 72 (51.8) | 22 (52.4) | 50 (51.6) | |
| cN1 | 67 (48.2) | 20 (47.6) | 47 (48.4) | 0.93 |
| Dose of radiotherapy delivered | | | | |
| 45 Gy/25 | 41 (29.5) | 13 (30.9) | 28 (28.9) | 0.80 |
| 50.4 Gy/28 | 98 (70.5) | 29 (69.1) | 69 (71.1) | |
| Type of chemotherapy | | | | |
| 5-FU/LV | 39 (28.1) | 13 (30.9) | 26 (28.6) | |
| 5-FU c.i. + gefitinib | 21 (15.1) | 7 (16.7) | 14 (14.4) | |
| CAPE | 26 (18.7) | 7 (16.7) | 19 (19.6) | |
| Raltitrexed | 32 (23.0) | 7 (16.7) | 25 (25.8) | |
| CAPE + OXA | 21 (15.1) | 8 (19.0) | 13 (13.4) | 0.72 |
| Type of surgery | | | | |
| LE | 29 (20.9) | 17 (40.5) | 12 (12.4) | 0.0002 |
| TME (LAR or APR) | 110 (79.1) | 25 (59.5) | 85 (87.6) | |
| Pathologic lymph node status | | | | |
| ypN0 | 83 (75.4) | 22 (88.0) | 61 (71.8) | 0.097 |
| ypN1–2 | 27 (24.6) | 3 (12.0) | 24 (28.2) | |
| IORT | | | | |
| No | 98 (70.5) | 31 (73.8) | 67 (69.1) | 0.32 |
| Yes | 30 (29.5) | 11 (26.2) | 30 (30.9) | |
| Adjuvant chemotherapy | | | | |
| No | 100 (71.9) | 37 (88.1) | 63 (64.9) | |
| Yes | 39 (28.1) | 5 (11.9) | 34 (35.1) | 0.006 |

5-FU 5-fluorouracil, LV leucovorin, c.i. continuous infusion, CAPE capecitabine, OXA oxaliplatinum, LE full-thickness local excision, TME total mesorectal excision, LAR low anterior resection, APR abdominal perineal resection, IORT intraoperative radiotherapy
TABLE 2 Clinicopathologic and treatment characteristics according to type of surgery in 42 cT3 rectal cancer patients with complete pathologic response (ypCR) after neoadjuvant chemoradiation

| Variable                          | Total, n (%) | TME (n = 25), n (%) | LE (n = 17), n (%) | P-value |
|----------------------------------|-------------|---------------------|-------------------|---------|
| **Sex**                          |             |                     |                   |         |
| Female                           | 15 (35.7)   | 8 (32.0)            | 7 (41.2)          |         |
| Male                             | 27 (64.3)   | 17 (68.0)           | 10 (58.8)         | 0.54    |
| **Age (years)**                  |             |                     |                   |         |
| Median (range)                   | 66 (43–86)  | 61 (43–80)          | 67 (46–86)        | 0.11    |
| **Distance from anal verge (cm)**|             |                     |                   |         |
| ≤5                               | 29 (69.1)   | 12 (48.0)           | 17 (100)          |         |
| >5                               | 13 (30.9)   | 13 (52.0)           | 0 (0)             | 0.0003  |
| **Clinical lymph node status**   |             |                     |                   |         |
| cN0                              | 22 (52.4)   | 10 (40.0)           | 12 (70.6)         |         |
| cN1                              | 20 (47.6)   | 15 (60.0)           | 5 (29.4)          | 0.051   |
| **Dose of radiotherapy delivered**|         |                     |                   |         |
| 45 Gy /25                        | 13 (30.9)   | 6 (24.0)            | 7 (41.2)          |         |
| 50.4 Gy /28                      | 29 (69.1)   | 19 (76.0)           | 10 (58.8)         | 0.24    |
| **Type of chemotherapy**         |             |                     |                   |         |
| 5-FU/LV                          | 13 (30.9)   | 6 (24.0)            | 7 (41.2)          |         |
| 5-FU c.i. + gefitinib            | 7 (16.7)    | 5 (20.0)            | 2 (11.8)          |         |
| CAPE                             | 7 (16.7)    | 3 (12.0)            | 4 (23.5)          | 0.38    |
| Raltitrexed                      | 7 (16.7)    | 6 (24.0)            | 1 (5.9)           |         |
| CAPE + OXA                       | 8 (19.0)    | 5 (20.0)            | 3 (17.6)          |         |
| **Adjuvant chemotherapy**        |             |                     |                   |         |
| No                               | 37 (88.1)   | 22 (88.0)           | 15 (88.2)         |         |
| Yes                              | 5 (11.9)    | 3 (12.0)            | 2 (11.8)          | 0.98    |

*TME* total mesorectal excision, *LE* full-thickness local excision, 5-FU 5-fluorouracil, LV leucovorin, c.i. continuous infusion, CAPE capecitabine, OXA oxaliplatin, IORT intraoperative radiotherapy

FIG. 1 Kaplan-Meier estimates for disease-specific survival according to complete pathologic response (ypCR) to neoadjuvant chemoradiation in 139 cT3 rectal cancer patients

FIG. 2 Kaplan-Meier estimates for disease-specific survival according to type of surgical treatment [total mesorectal excision (TME) surgery vs. full-thickness local excision (LE)] in 42 cT3 rectal cancer patients with complete pathologic response (ypCR) to neoadjuvant chemoradiation
prospectively followed up at a single institution during a 12-year period. At pathologic examination of the surgical specimen, ypCR was observed in 30.2% of the cases. In an updated analysis on a total of 4,732 rectal cancer patients treated by preoperative CRT in 81 prospective arms from phase II and III trials, Sanghera et al.\(^6\) have recently reported a ypCR rate of 14.8%, varying from 0 to 43% in the different arms. In their study, factors associated with ypCR were the use of two drugs, c.i. 5-FU administration, and RT dose of \(\geq 45\) Gy. These findings could account for the relatively high ypCR rate observed by us because 71% of our patients received 50.4 Gy; in addition, c.i. 5-FU and two drugs regimens were provided to a large number of our patients.

Our retrospective survival analysis indicates that patients with ypCR have statistically significantly better oncologic outcomes than those without ypCR, and that in patients with ypCR, the risk of developing local recurrence and distant metastasis during follow-up is considerably lower, with 5-year DMFS and LRFS of 92.5 and 94.9%, respectively. Our results are consistent with data reported by others. Maas et al.\(^7\) in a recent pooled analysis of data from 3,105 locally advanced rectal cancer cases treated by preoperative CRT, reported that ypCR disease (\(n = 484\)) had significantly better results, with 5-year DFS and LRFS of 83.3 and 97.2%, respectively. De Campos-Lobato et al.\(^10\) have recently reported that in a series of 238 locally advanced rectal cancer cases treated by preoperative CRT during a 10-year period, 5-year OS, DFS, and LRFS were 92.7, 92.4, and 100%, respectively, in the 58 ypCR patients. Rödel et al.\(^12\) evaluated pathologic tumor response on surgical specimens of 385 locally advanced rectal cancer patients treated within the preoperative CRT arm of the CAO/ARO/AIO-94 trial and found that ypCR was an independent prognostic factor for local and distant metastasis. Capirci et al.\(^9\) in an outcome analysis on a pool of 566 patients with locally advanced rectal cancer and ypCR after preoperative RT with or without chemotherapy, reported 5-year rates of OS, DSS, and DFS of 90, 94, and 85%, respectively, with a local recurrence rate of 1.6%. Other studies have observed better long-term outcome in patients with primary tumor downstaging (ypT0–2 vs. ypT3–4).\(^11,38\) On the basis of this evidence, it has been postulated that tumoral ypCR achievement might be indicative of a prognostically favorable biological tumor profile with less propensity for local or distant recurrence and improved survival.\(^7\) Alternatively, significantly lower local recurrence rate and distant metastasis rate in the subset of tumors displaying ypCR might be explained by a higher sensitivity to both radiation and chemotherapy.

In our study, when comparing pre-CRT lymph node staging and lymph node pathologic status, a trend association was observed between ypCR achievement and mesorectal lymph node downstaging. Moreover, we found metastatic lymph nodes in 12% of patients with ypCR and no metastatic lymph nodes in 79% of patients with no ypCR. Our data are similar to the figures reported by Hughes et al.\(^15\) in a study of 143 patients in which the incidence rate of metastatic mesorectal lymph nodes was 17% in the 23 patients with ypCR versus 35% in patients with no ypCR. However, other authors have reported lower incidence rates of metastatic mesorectal lymph nodes in patients with ypCR.

### Table 3

| Outcome            | ypCR \(n = 97\) vs. no ypCR \(n = 42\) | \(P\)-value |
|--------------------|----------------------------------------|-------------|
| OS                 | 0.26 (0.09–0.80)                       | 0.0185      |
| DSS                | 0.08 (0.01–0.63)                       | 0.0164      |
| DFS                | 0.23 (0.09–0.61)                       | 0.0034      |
| DMFS               | 0.30 (0.10–0.92)                       | 0.0353      |
| LRFS               | 0.15 (0.03–0.70)                       | 0.0155      |

*HR* hazard ratio, *CI* confidence interval, *OS* overall survival, *DSS* disease-specific survival, *DFS* disease-free survival, *DMFS* distant metastasis-free survival, *LRFS* local recurrence–free survival

*Adjusted by pre-chemoradiation clinical lymph node status (cN0 vs. cN1) and type of surgery (total mesorectal excision vs. full-thickness local excision)
no-ypCR patients. Pucciarelli et al.\textsuperscript{17} in a study of 235 patients reported positive nodes rate of 2\% in ypT0 cases versus 38\% in ypT3 cases. Read et al.\textsuperscript{39} in 644 patients treated by preoperative RT or CRT, reported metastatic lymph nodes in 1 (2\%) of 42 ypT0 patients and in 158 (36\%) of 602 ypT1–4 patients. Similarly, Guillem et al.\textsuperscript{40} in a series of 188 cT3N rectal cancers treated by CRT and TME, found that metastatic mesorectal lymph nodes incidence increased from 3\% in ypT0 to 36\% in ypT3–4.

In our study, subset survival analysis in patients with ypCR demonstrated no outcome differences in the group of patients treated by LE compared to patients treated by TME. In the 17 ypCR patients treated by LE, 5-year DSS, DMFS, and LRFS were 100, 87.4, and 92.9\%, respectively. These findings confirm previous data reported by Bonnen et al.\textsuperscript{23} from M. D. Anderson Cancer Center, who found no 5-year OS, DFS, and LRFS differences in cT3 rectal cancer patients comparing 26 patients treated by LE (ypCR = 54\%) with 169 patients treated by TME (ypCR = 22\%). Callender et al., from the same institution, have recently compared outcomes in a larger cohort of patients and reevaluated the original patients after longer follow-up: 47 patients underwent LE (ypCR = 49\%) and 473 patients underwent TME (ypCR = 23\%). There was no statistically significant difference between the 10-year actuarial local recurrence rate for the LE group versus the TME group (10.6 and 7.6\%, respectively), and no significant difference in OS, DSS, and DFS between groups.\textsuperscript{16} Kundel et al.\textsuperscript{16} in 320 locally advanced rectal cancers, compared ypCR patients who had LE (n = 14) with those who underwent TME (n = 37). With a median follow-up of 48 months, no patients in LE group experienced recurrence, versus 4 in TME group, while OS, DFS, and LRFS were similar in both groups. Guerrieri et al.\textsuperscript{39} reported that in 61 cT3 rectal cancer treated by CRT and transanal endoscopic microsurgery, long-term local and distant metastasis failure probability were both 0\% in 9 ypCR patients, compared to 5 and 4\% in no-ypCR patients. Nair et al.\textsuperscript{21} in 44 cT2–3 rectal cancers treated by CRT and LE reported that local recurrence and distant metastasis rates were both 4\% in the 25 ypCR patients, compared to both 16\% in no-ypCR patients. Finally, Habr-Gama et al.\textsuperscript{27} reported long-term outcome results of their experience comparing operative and nonoperative treatment in 265 patients with rectal adenocarcinoma (mostly cT3) treated by CRT. Patients with incomplete clinical response were referred to TME surgery. Patients with incomplete clinical response treated by surgery resulting in ypCR were compared to patients with complete clinical response treated by nonoperative treatment. Five-year OS and DFS were 88 and 83\%, respectively, in the resection group and 100 and 92\% in the observation group.

In conclusion, within the limitations of retrospective analysis, our data confirm the existing evidence indicating that patients with ypCR rectal cancer after preoperative CRT have a favorable long-term outcome, with a low risk of local recurrence and distant metastasis regardless of the type of surgical treatment. Such patients appear to be good candidates for organ-preserving strategies to be explored in clinical studies. On the other hand, the poor outcome of no-ypCR patients treated by LE strongly indicates that conservative surgical treatment should be avoided in this subset of patients. In parallel, new functional imaging modalities and molecular factors that are predictive of response to treatment should be investigated because they might be used to select the best treatment and to develop strategies aimed at enhancing the effectiveness of CRT.

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