Individualizing surgical treatment based on tumour response following neoadjuvant therapy in T4 primary rectal cancer

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Accepted 6 September 2016
Available online 17 September 2016

Abstract

Background: Rectal cancer involving at least one adjacent organ (mrT4b) requires multi-visceral resection to achieve clear resection margin (R0). Performing pelvic compartment preservation according to the tumour response has not been considered. This study assesses the impact of changing the surgical strategy according to tumour response in rectal cancer mrT4b.

Methods: Patients with non-metastatic T4b rectal cancer at two tertiary referral centres between 2008 and 2013 were grouped as “Responders” ypT0-3abNx versus “Non-responders” ypT3cd-4Nx and divided into three surgical procedures: total mesorectal excision (TME), extended-TME (eTME) and beyond-TME (b-TME). End-points were circumferential resection margin, postoperative morbidity, definitive stoma formation, 3-years local recurrence (3y-LR) and 3-years disease-free survival (3y-DFS) according to both tumours’ response and surgical procedures.

Results: Among 883 patients with rectal cancer, 101 were included. Responders had a higher rate of induction chemotherapy (59.7% vs. 38.2%; p = 0.04). Morbidity and definitive stoma formation were significantly higher in Non-responders. R0 was not impacted by either the tumour response or the surgical procedures. The 3y-LR was lower in Responders (14%) compared to Non Responders (32%) (HR 1.6; 95% CI: 1.02 e 2.59; p = 0.041), and was two-fold higher in e-TME compared to b-TME in Non-responders, whereas no difference was found in Responders. The 3y-DFS was higher in Responders irrespective to the surgery (71% vs. 47%; p = 0.07).

Conclusion: In Responders, TME or e-TME are technically and oncologically feasible and should be considered in preference to b-TME. In Non-responders, allowing for high rates of morbidity and local recurrence in patients with e-TME, b-TME procedures should be preferred.

Keywords: Rectal cancer; T4 cancer; Locally advanced rectal cancer; Total mesorectal excision; Beyond-total mesorectal excision; Pelvic exenteration

Introduction

The incidence of rectal cancer in the European Union (EU) is 15−25/100 000 per year and represents 35% of the total colorectal cancer incidence. A total of 5−10% of rectal cancers are considered to be T4b at the time of diagnosis, defined by the invasion to other adjacent organs according to the definition of the 7th UICC/TNM staging system. By definition, patients with mrT4b rectal cancer, have tumour invading the mesorectal fascia on the pre-treatment pelvic MRI, meaning that curative surgery (R0 resection) cannot be achieved with conventional TME surgery. In order to achieve a clear circumferential resection margin (>1 mm), a multivisceral resection involving en bloc removal of the tumour and adjacent infiltrated organs, which has been defined as beyond-TME procedure, currently remains the optimal surgery.
Guidelines do not recommend adapting the surgical procedure to the tumour response after neoadjuvant treatment in order to perform a less extensive resection with potentially lower morbidity.\(^2\) Currently, one of the main questions in rectal cancer management is knowing if response to neoadjuvant treatment can safely offer organ preservation in patients undergoing rectal surgery. Previous studies aimed to address this question for early stage rectal cancer over the last 10 years,\(^{10–12}\) whereas changing surgical planes in accordance of the tumour response for T4b primary rectal cancer has not been routinely considered.\(^{13,14}\)

The introduction of preoperative chemoradiotherapy\(^15\) has decreased the rate of local recurrence after surgery but has not been proven to decrease the risk of metastatic disease and cancer-specific survival.\(^16\) However, patients with locally advanced rectal cancer\(^17\) still have a high risk of both local and systemic failure.\(^9,18–20\) In this context, intensification of the neoadjuvant treatment in case of the involvement of other anatomical structures into the pelvis represents a fashionable alternative to control both “potential” systemic and local disease.\(^21,22\) The question arises with intensification of neoadjuvant treatment which is patients with initial T4b rectal cancer could obtain a clear resection margin with TME procedure and which one really need a beyond-TME surgical approach.

The present study aims to assess the impact of changing the surgical strategy according to tumour response assessed by post-treatment MRI on long-term oncological outcome in patients presenting with primary T4b rectal cancer.

Methods

Inclusion criteria

Patients with non-metastatic primary rectal cancer involving at least one adjacent organ on the pre-treatment pelvic MRI (mT4bNxM0) treated at Saint-Andre Hospital (Bordeaux, France) and at The Royal Marsden Hospital (London, UK) between January 2008 and September 2013 were included from their two prospective computer databases and analysed retrospectively.

The study was approved by the local ethics committee in UK and France.

Preoperative staging

The initial evaluation included physical examination, colonoscopy with biopsy, pelvic magnetic resonance imaging (MRI), chest, abdominal and pelvic computed tomography (CT scan) and tumour marker measurement. Pelvic compartment involvement was defined using the first pelvic MRI, including anterior (prostate, vagina, uterus, bladder, urethra), posterior (presacral fascia, sacrum), lateral (ureter, hypogastric plexuses, internal iliac vessels, obturator neurovascular bundle or muscle, sciatic notch and nerve roots) and inferior compartment (levator ani muscle, external anal sphincter).\(^23\)

Re-staging of the tumour was performed 4 weeks after the end of chemoradiotherapy by a new MRI (axial, sagittal and coronal planes). This pelvic MRI described the tumour response and assessed the predicted pathological circumferential resection margin by the evaluation of the distance between the tumour and the mesorectal fascia. This margin was considered as negative if greater than 1 mm.\(^3\) Modifications of surgical strategy were based on this re-staging MRI.

Neoadjuvant and adjuvant treatment

According to the European Guidelines,\(^17\) all patients included in this study received neoadjuvant treatment using 50 Gy in 25 fractions over 5 weeks with concomitant chemotherapy (5-fluorouracil) followed by surgery 6–8 weeks later. In the second half of the study period, patients received neoadjuvant induction chemotherapy in addition to the long course chemoradiotherapy based on doublet (SFU, oxaliplatine) or triplet cytotoxic drugs (5-FU, oxaliplatine, irinotecan).

Adjuvant chemotherapy (5-fluorouracil and oxaliplatine) was given for patients with positive lymph nodes at the specimen (ypN+) and/or with R1 resection status.\(^5,6\)

Surgery

Surgery was performed 6–8 weeks after completion of neo-adjuvant treatment and was grouped into three categories of surgical procedures:

- Total mesorectal excision (TME) group: mesorectal fascial dissection with preservation of the hypogastric and pelvic plexuses was performed\(^24,25,\)
- extended-TME (e-TME) group: a partial resection of the adjacent organ(s) of the rectum was performed en bloc with the TME specimen with curative intent, in order to achieve a R0 resection.\(^9\) This procedure included the posterior wall of the prostate or the vagina, the uterus, the seminal vesicles, the hypogastric plexuses, the ureter and partial resection of the bladder;
- beyond-TME (b-TME) group: includes posterior pelvic exenteration (PPE), total pelvic exenteration (TPE), previously defined in the Beyond TME collaborative consensus\(^2\) and extra-levator abdominoperineal excision (ELAPE) for inferior compartment involvement with or without sacral resection (posterior compartment involvement- Sacrectomy).

In both institutions, surgical and oncological management was discussed in Multi-Disciplinary Team (MDT) meetings. Surgical strategies were different in these two tertiary centres. Surgical procedures were mainly performed according to the pre-treatment MRI in the Marsden
Pathological assessment

The operative specimen was addressed freshly to the pathological department and assessed by using the pathologic checklist for colorectal cancer recommended by the US guidelines. Tumours were classified by using the 7th UICC/TNM staging system. Circumferential resection margin was measured in millimetres and was considered as positive (R1) if less than or equal to 1 mm.

The tumour response assessment was defined by using the parietal and nodal (ypTN) system with the down staging grading. Good responders were ypT0-2N0, mid responders were ypT0-2N+ or ypT3abN+ and bad responders were ypT3cd-4N+. Patients with good and mid response were pooled together, taking into account that for both good and mid responders, the surgical resection plane to achieve an R0 resection could theoretically be the TME plane. They were defined as Responders and were compared to patients with bad response, defined as Non-responders.

End-points

Short-term outcomes included the post-operative morbidity, the length of hospital stay and the rate of definitive stoma formation. Post-operative morbidity was defined in accordance with Dindo et al. and only major complications, i.e. Dindo III–V, were reported.

The quality of surgery through the rate of R0 resection and the accuracy of the restaging MRI to predict negative circumferential resection margin through the negative predictive value were also analysed.

Long-term outcomes included both the 3-year local recurrence (3y-LR) and the 3-year disease free survival (3y-DFS), including any event, irrespective of cause, except loss to follow-up.

Statistical analysis

Data were collected prospectively on the computer databases of the Colorectal Units of Saint-Andre Hospital, Bordeaux and The Royal Marsden Hospital, London, and extracted retrospectively for the purpose of this study. Data were expressed as medians with ranges. Differences between groups were determined by the χ² test or Fisher’s exact test and by the Mann Whitney or Wilcoxon test when appropriate. A p-value of less than 0.05 was considered as statistically significant. Disease-free survival and disease recurrence were evaluated by using the Kaplan–Meier method and compared with the log-rank test and Cox regression analysis.

Results

Demographics data

At total of 883 patients were operated for primary rectal cancer in two colorectal tertiary centres of which 101 (11.4%) patients were operated for T4b primary rectal cancer (mrT4bNxM0) between January 2008 and September 2013.

Patient demographic characteristics are reported in Table 1. There were 57 male patients and the median age was 64 (33–84) years old, without any difference between the responder and non-responder groups. The two most frequently pelvic compartments involved, before neoadjuvant treatment, were the anterior and inferior compartments, and more than 20% of patients had more than 2 compartments involved, without any difference between groups.

Characteristics of the induction chemotherapy

Neoadjuvant chemotherapy was given in 53 patients (52.5%). Two main different drug regimens were given: 5-fluorouracil (or capecitabine) and oxaliplatin (n = 41) or 5-fluorouracil and oxaliplatin in association with irinotecan (n = 12). The rate of neoadjuvant induction chemotherapy, irrespective of drug regimen, was significantly higher in Responders group compared to Non-responders group (59.7% vs. 38.2%; p = 0.041).

Surgical characteristics and morbidities

The three categories of surgical procedures, TME, e-TME and b-TME were performed for Responders with a
homogeneous distribution, 28.3%, 34.3% and 37.4%, respectively. According to the definition, TME was never performed for Non-responders as the primary rectal cancer still involved the TME surgical plane after neoadjuvant treatment. In the group of Non-responders, e-TME was performed in 55.9% of cases and b-TME in 44.1%.

The rate of definitive stoma formation ($p = 0.006$) and length of hospital stay ($p < 0.001$) were both significantly higher in non-responders. Details of surgical procedures performed are given in Tables 2a and 2b. Removing the posterior wall of the prostate was performed in 5 cases, only in the responder group. One patient with e-TME procedure died postoperatively in Non-responders group (mortality 0.9%). The rate of major morbidity (Dindo III–V) was significantly higher in Non-responders (6% vs. 20.6%, $p = 0.04$). Moreover, this rate was two-fold higher for patients who underwent e-TME (26.3%) compared to those with b-TME procedures (13.3%) in cases of Non-response (Table 3).

**Pathologist assessment**

The rate of R1 resection after neoadjuvant treatment was two-fold lower in Responders compared to Non-responders, 9% vs. 20.6%, respectively (see Table 4). In both Responders and Non-responders groups, the rates of R1 resection were similar between eTME and b-TME, 13% vs. 8% and 21% vs. 20%, respectively. Only one patient with TME was R1.

A positive nodal status (ypN+) was reported in 25% of ypT0-2 (7/28), in 38.5% of ypT3a/b (15/39), and in 41.2% of ypT3c-ypT4 (14/34). Moreover, in this population with only mrT4b rectal cancers, the rates of ypT0 (complete response) and ypT1 (sub-complete response) were 5% and 12% with 20% (1/5) and 25% (3/12) with nodal involvement, respectively.

**Accuracy of the restaging MRI**

In 39 patients, restaging MRI predicted clear mesorectal fascia after neoadjuvant treatment, which was confirmed by pathological assessment in 35 patients. Therefore, the negative predictive value of the restaging MRI with regards to the involvement of the mesorectal fascia was 89.7%. In contrast, restaging MRI predicted an involvement of the mesorectal fascia in 62 patients, whereas 30 had a free mesorectal fascia in pathologic assessment, hence the positive predictive value of the restaging MRI with regards to the involvement of the mesorectal fascia was 48.4%.

**Long-term outcome**

Overall, the median follow-up was 40 (ranges, 0–84) months, without a significant difference between groups. 34 patients had a recurrence (33.7%) during the follow-up. The 3-year local and distance distant recurrence rates were 18% and 24%, respectively. The 3-year local recurrence rate was significantly lower in Responders compared to Non-responders (14% vs. 32%, Hazzard ratio = 1.6 (95% CI: 1.02 to 2.59), $p = 0.041$) (Fig. 1 a). Patients who underwent TME did not have any local recurrences.

<table>
<thead>
<tr>
<th>Table 2a</th>
<th>Surgical characteristics.</th>
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<tbody>
<tr>
<td>Patient group</td>
<td>Responders (n = 67)</td>
</tr>
<tr>
<td>TME</td>
<td>19 (28.3)</td>
</tr>
<tr>
<td>e-TME*</td>
<td>23 (34.3)</td>
</tr>
<tr>
<td>b-TME**</td>
<td>25 (37.4)</td>
</tr>
<tr>
<td>Anastomosis</td>
<td>38 (56.7)</td>
</tr>
<tr>
<td>-Handsewn</td>
<td>28</td>
</tr>
<tr>
<td>-Mechanical</td>
<td>10</td>
</tr>
<tr>
<td>Definitive stoma</td>
<td>30 (44.8)</td>
</tr>
<tr>
<td>Length of stay</td>
<td>12 (5–31)</td>
</tr>
</tbody>
</table>

*extended-TME; **beyond-TME.

The values $p < 0.05$ are represented in bold.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Postoperative morbidity.</th>
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</thead>
<tbody>
<tr>
<td>Patient group</td>
<td>Responders (n = 67)</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>(Dindo III–V)</td>
<td>4 (6.0)</td>
</tr>
<tr>
<td>-TME</td>
<td>0 (0)</td>
</tr>
<tr>
<td>-eTME</td>
<td>2/23 (8.7)</td>
</tr>
<tr>
<td>-b-TME</td>
<td>2/25 (8.0)</td>
</tr>
</tbody>
</table>

*extended-TME; **beyond-TME.

The value $p < 0.05$ is represented in bold.
and c, respectively. In Non-responders, the 3-year local recurrence rate was 32% with almost a two-fold higher risk for patients who underwent an e-TME (39%), compared to those with b-TME (22%) (Fig. 1b). The distant recurrence rate was also significantly lower in Responders compared to Non-responders (19% vs. 37.5%; p = 0.05). The highest rate of distant metastases was observed for Non Responders with bTME procedures (53.3%). The association of local and distant recurrences were 4.8% and 15.5% in Responders and Non-responders respectively (p = 0.11) (Table 5b).

The 3-year disease-free survival was 63% in the whole population, 71% vs. 47% (p = 0.07) in Responders and Non-responders respectively (Fig. 2a). The worse 3-year DFS was observed for Non Responders with having bTME surgery (40%) mainly due to distant metastases (Fig. 2b), whereas the better 3-year DFS was reported for Responders with having TME surgery (84%) (Fig. 2c).

Discussion

The present study describes a pooled analysis of 101 patients who initially presented with locally advanced primary rectal cancer with involvement of at least one adjacent organ (mrT4b) who were managed and operated in two European colorectal tertiary centres. These patients, represented 11.4% of the 883 rectal cancers treated in these institutions. The selection criteria included a short and recent period of study observation (2008–2013) to allow for homogeneous group of patients using contemporary neo-adjuvant treatments without compromising patients’ follow-up (40 months). In this study, we showed that Responders had more induction neo-adjuvant treatment than Non-responders and subsequently that both the 3y-LR and the 3y-DFS were higher in Responders. Moreover, the study results suggest that changing surgical strategy and planes of dissection in an effort to achieve pelvic compartment preservation is technically and oncologically feasible in case of tumour down staging in patients with mrT4b primary advanced rectal cancer. In the absence of tumour downsizing (Non-responders to neo-adjuvant therapy), a beyond-TME procedure may be required. An attempt to preserved adjacent organs using an extended-TME procedure often led to higher morbidity and local recurrence compared to more radical beyond-TME surgery.

To our knowledge, this is the first study of its kind assessing short-term adverse events and oncological outcomes based on the tumour response after neoadjuvant treatment together with the impact of surgical changing strategy, in patients presenting with mrT4b rectal cancer.
The present study has drawbacks of which include small number of patients, lack of standardized tumour regression grading system and type II statistical error. Further studies are required to validate the results and confirm our current recommendations.

Pathologic response assessment has been variable in the literature in either parietal and nodal (ypTN) response or either cellular response (Tumour Regression Rate or TRG). The TRG system includes several gradings focused on the ratio between tumour cellularity and remodelling fibrous tissue in the rectal wall, without any consensus. The relation between TRG and DFS is still debated, probably due to the lack of standardisation and the fact that response to neoadjuvant radiotherapy can result in tumour fragmentation rather than shrinkage indicating that deep rectal wall layers can be involved by residual tumour cells. The ypTN system is based on the location of residual tumour cells in the different layers of the rectal wall and lymph node status and is divided in two main grading: the complete pathological response (ypT0N0 or ypCR) and the downstaging with good (ypT0-2N0) or bad (ypT3-4) responders. Regarding the rate of pCR lower than 10% in case of cT4 rectal cancer, the downstaging grading system appeared more appropriate for tumour response assessment in our study.

Changing surgical strategy in accordance with the tumour response after chemoradiotherapy in rectal cancer is a very attractive and fashionable concept from the organ preservation strategy to the sphincter-saving resection procedures for good responders. However, for primary advanced rectal cancer with involvement of additional pelvic structures identified on the pre-treatment pelvic MRI (mrT4b), patients are currently treated with en bloc resections of these structures with the primary tumour, i.e. beyond-TME procedures. Moreover, the literature on pelvic exenteration focused specifically on T4b rectal cancer is scarce, the wide majority combining primary and recurrent tumour. The oncologically accuracy (R0 resection) of extended-TME for T4 rectal cancer has been reported, specifically in case of prostate involvement, however, intra-operative urethral injury during posterior

Table 5b 3-years disease-free survival.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Responders (n = 67)</th>
<th>Non-responders (n = 34)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-years DFS</td>
<td>71%</td>
<td>47%</td>
<td>0.07</td>
</tr>
<tr>
<td>-TME</td>
<td>84%</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>-e-TME</td>
<td>63%</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>-b-TME</td>
<td>65%</td>
<td>40%</td>
<td></td>
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</tbody>
</table>

Figure 1c. 3-years local recurrence in Responders according to the surgical procedures.

Figure 2a. 3-years disease-free survival according to the tumour response.

Figure 2b. 3-years disease-free survival in Non-responders according to the surgical procedures.
prostatic shaving occurred in 36% of cases resulting in a rate of postoperative urinary fistula formation of nearly 20%. Authors did not assess the role of the tumour downstaging on their results. All series of extended-TME or pelvic exenteration highlighted the major impact of the negative resection margin (R0) on survival, but never consider the interest of the tumour downstaging on both survival and surgical strategy. Nevertheless, authors of the Scandinavian phase III randomized trial, comparing radiotherapy alone vs. chemoradiotherapy in initial “non-resectable” rectal cancer (T3 with CRM ≤ 1 mm and T4), reported 60% of TME procedure after downstaging with 5% of local recurrence, in agreement with the literature. We reported only 28% of TME but for rectal cancer initially more advanced (all T4b). Our results showed that local recurrence and 3-years DFS were similar between TME, e-TME and b-TME in Responders, whereas Non-responders had a higher rate of local recurrence in case of e-TME. Moreover, the worse 3-years DFS was reported for patients with b-TME procedures in Non-responders due to the high risk of distant metastases in this situation highlighting the poor biological features and behaviour of these tumours which required an extensive surgery to control the disease locally but which failed at distance. This data reinforce the requirement of an intensified neoadjuvant treatment to control “potential” distant disease.

The value of MRI in restaging locally advanced rectal cancer after neoadjuvant therapy is controversial but it appears in a recent review that MRI can be used for evaluation of the tumour status (ymrT0-2 vs. ymrT3-4) and involvement of the CRM after neoadjuvant treatment. The detection of small clusters of residual tumour cells within fibrosis remains one of the main problem and the major risk is the overassessment of the mesorectal fascia involvement in the post-chemoradiotherapy MRI. Authors reported a positive and a negative predictive values of CRM involvement at the restaging MRI of 42.9% and 100%, respectively, which are very closed to our reported values: 48.4% and 89.7%.

In conclusion, patients who respond well to neo-adjuvant therapy, conventional TME or extended-TME procedures are technically and oncolologically feasible and pelvic compartment preservation ought to be considered in preference to more radical multi-visceral beyond-TME procedures. Patients who do not respond to neo-adjuvant treatment, allowing for the high postoperative morbidity and the high risk of local recurrence in patients with extended-TME, more radical multi-visceral beyond-TME procedures should be considered in order to achieve optimum post-operative and oncological outcomes. Non-responders had significantly less neo-adjuvant chemotherapy and a higher risk of both local and distant metastases compared to Responders highlighting the possibility for using total neo-adjuvant treatment for such high risk patients. This may allow to improve the rate of Responders and thus the rate of pelvic compartment preservation in these patients presenting with local advanced rectal cancer.

Conflicts of interest and source of funding

The authors report no financial or other conflict of interest relevant to the subject of this article.

Acknowledgements

The study was supported by Bordeaux University Hospital and The Royal Marsden Medical Research Centre.

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