Available online at www.sciencedirect.com

ScienceDirect

EJSO the Journal of Cancer Surgery

EJSO xx (2016) 1–8 www.ejso.com

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

Q. Denost [a,*], C. Kontovounisios [b,c], S. Rasheed [b,c], R. Chevalier [a], R. Brasio [b], M. Capdepont [a], E. Rullier [a], P.P. Tekkis [b,c]

[a] CHU of Bordeaux, Department of Surgery, Saint-Andre Hospital, University of Bordeaux, Bordeaux, France
[b] Department of Colorectal Surgery, The Royal Marsden Hospital, Fulham Road, London, SW3 6JJ, UK
[c] Department of Surgery and Cancer, Imperial College London, London, SW7 2AZ, UK

Accepted 6 September 2016
Available online ■ ■ ■

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: 1.02–2.59; $p = 0.041$), 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 preferrence 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.[1] A total of 5–10% of rectal cancers are considered to be T4b at the time of diagnosis,[2] defined by the invasion to other adjacent organs according to the definition of the 7th UICC/TNM staging system.[3] By definition, patients with mrT4b rectal cancer, have tumour invading the mesorectal fascia on the pre-treatment pelvic MRI,[4] meaning that curative surgery (R0 resection) cannot be achieved with conventional TME surgery. In order to achieve a clear circumferential resection margin (>1 mm),[5,6] 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.[7–9]

* Corresponding author. Service de Chirurgie Digestive, Hôpital Saint-André, 33075 Bordeaux, France. Fax: +33 5 56 79 58 61.
E-mail address: quentin.denost@chu-bordeaux.fr (Q. Denost).

http://dx.doi.org/10.1016/j.ejso.2016.09.004

Please cite this article in press as: Denost Q, et al., Individualizing surgical treatment based on tumour response following neoadjuvant therapy in T4 primary rectal cancer, Eur J Surg Oncol (2016), http://dx.doi.org/10.1016/j.ejso.2016.09.004

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 is which 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 (mrT4bNxM0) 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 pelvis 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.[4] 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 (5FU, oxaliplatine) or triplet cytotoxic drugs (5-FU, oxaliplatin, irinotecan).

Adjuvant chemotherapy (5-fluorouracil and oxaliplatin) 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

Please cite this article in press as: Denost Q, et al., Individualizing surgical treatment based on tumour response following neoadjuvant therapy in T4 primary rectal cancer, Eur J Surg Oncol (2016), http://dx.doi.org/10.1016/j.ejso.2016.09.004