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Rapid Research Communication

Sphincter-saving surgery after neoadjuvant therapy for ultra-low rectal cancer where abdominoperineal resection was indicated: 10-year results of the GRECCAR 1 trial

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Introduction

Management of ultra-low rectal cancer (ULRC) continues to be a challenge. Despite surgical improvements, the rate of conservative surgery for ULRC continues to be less than 50 per cent and varies between countries and surgeons. This is due to both technical challenges and concern for local recurrence.

In 2001, the GRECCAR group initiated a prospective randomized trial to address some of the issues of sphincter preservation for ULRC. Here, the authors report the 10-year oncological long-term follow-up of these patients.

Methods

GRECCAR 1 was a French national, phase III, multicentre, open-label, randomized study (registration number NCT00979680; http://www.clinicaltrials.gov).

Inclusion criteria were defined as an ultra-low T2–3 M0 adenocarcinoma of the rectum with the inferior margin of the tumour located less than 2 cm from the upper part of the levator ani. At study entry, the surgeon determined that the tumour required an abdominoperineal resection (APR). Patients were then randomized to high-dose radiotherapy (HDR) (45 Gy, over 5 weeks to the pelvis with a 18 Gy boost to the tumour[1]) or radiochemotherapy (RCT) (45 Gy plus 5-fluoruracil200 mg per m^2 per day).

The final decision on sphincter preservation was based on the clinical tumour margin status at surgery, performed 6 weeks after completion of radiotherapy. A standardized total mesorectal excision technique was used in all patients. For sphincter-sparing resection (SSR), three types of endoanal dissection[2] were defined: mucosectomy, and partial (PISR) or complete (CISR) intersphincteric resection.

Results

From April 2001 to April 2005, 195 patients formed the study population (HDR 100, RCT 95). For most clinical parameters, no difference was found between the two preoperative treatments. The mean distance from the upper part of the levator ani to the caudal tumour edge (Inferior Pole–LA) was 0.5 (range 0–2) cm in each group. Some 75 patients had a distance of 0 cm between IP–LA (ultra-low tumours).

The sphincter was preserved in 165 (84.6 per cent) of the 195 patients, with no difference between the HDR and RCT group (83.0 *versus* 86 per cent respectively). The difference in sphincter

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preservation rate was −3.3 (90 per cent c.i. −11.5 to 5.5) per cent. According to the study design, the treatment arms were considered equivalent because the equivalence margin lay outside the confidence interval. An APR was performed in 17 patients in the HDR group and 13 in the RCT group. Key technical features were an ISR rate of 85.5 per cent (141 of 165) and a CISR rate of 36.4 per cent (60 of 165). The postoperative morbidity rate was 28.0 per cent; for HDR and RCT respectively, the rates were: 11 *versus* 9 per cent for fistula, 3 *versus* 5 per cent for pelvic abscess, 5 *versus* 4 per cent for colonic necrosis, 8 *versus* 5 per cent for anastomotic stricture, and 4 *versus* 3 per cent for postoperative occlusion. No postoperative mortality was recorded.

Sterilized specimen rates were 8 and 15 per cent in the HDR and RCT arms respectively (P =0.456). The median radial and inferior safety margins were 5 mm and 1 cm respectively, with a median of 12 nodes examined in the two arms. Defining a circumferential resection margin (CRM) of 1 mm or more and a negative distal resection margin (DRM) as a curative resection, the R0 resection rate became 95 per cent (86 per cent for APR, 100 per cent for mucosectomy, 96 per cent for PISR and 97 per cent for CISR).

The median duration of follow-up was 10.1 (95 per cent c.i. 8.2 to 12.3) years. Oncological outcomes at 10 years for each group are outlined in *Fig. 1*. There were no significant differences between HDR and RCT groups in the 10-year rates of overall survival (OS) (69.4 (95 per cent c.i. 57.3 to 78.6) *versus* 70 (58 to 79) per cent respectively; P = 0.977), disease-free survival (DFS) (57.4 (46.0 to 67.3) *versus* 56.5 (44.6 to 66.7) per cent; P = 0.977), local relapse-free survival (RFS) (90.8 (82.3 to 95.3) *versus* 86 (76 to 92) per cent; P = 0.303), and metastases-free survival (MFS) (67.6 (56.0 to 76.7) *versus* 72 (61 to 81) per cent; P = 0.587).

When considering the type of surgery (*Fig. 2*), significant differences were found between APR and SSR in the 10-year rates of OS (55 (95 per cent c.i. 31 to 73) *versus* 72.2 (63.4 to 79.2) per cent respectively; P = 0.026), DFS (38 (19 to 58) *versus* 60.1 (51.3 to 67.8) per cent; P = 0.015), RFS (excluding deaths) (45 (25 to 63) *versus* 61.2 (52.5 to 68.8) per cent; P = 0.030), and MFS (52 (31 to 69) *versus* 73.1 (64.5 to 79.9) per cent; P = 0.009). When the four subgroups of surgery type were studied, this statistically significant difference disappeared for OS (P = 0.145) and DFS (P = 0.111) at 10 years, although the worst prognosis remained for APR.

Ten-year survival rates according to the CRM showed a strongly unfavourable prognosis for a CRM of less than 1 mm for OS (22.2 (95 per cent c.i. 3.4 to 51.3) per cent) and DFS (22.2 (3.4 to 51.3) per cent), whereas 10-year OS rates were similar for a CRM of 1 mm (68.9 (46.9 to 83.2) per cent) and CRM greater than 1 mm (72.7 (63.4 to 80.0) per cent) (CRM below 1 mm versus CRM greater than or equal to 1 mm; P < 0.001). The stoma closure rate after SSR was 93 per cent.

Discussion

The avoidance of mutilating surgery for ultra-low rectal carcinoma can follow different paths. The general trend is to increase preoperative treatment and adapt the operative strategy to the tumoral response and operative risk. Sphincter-saving surgery is limited by concern over functional results and oncological concerns regarding potential local recurrence. The present oncological long-term results are a strong argument to validate this conservative strategy in the guise of curative resection. In this multicentre study, standardization of the endoanal surgery and decision-making following the neoadjuvant treatment were key points.

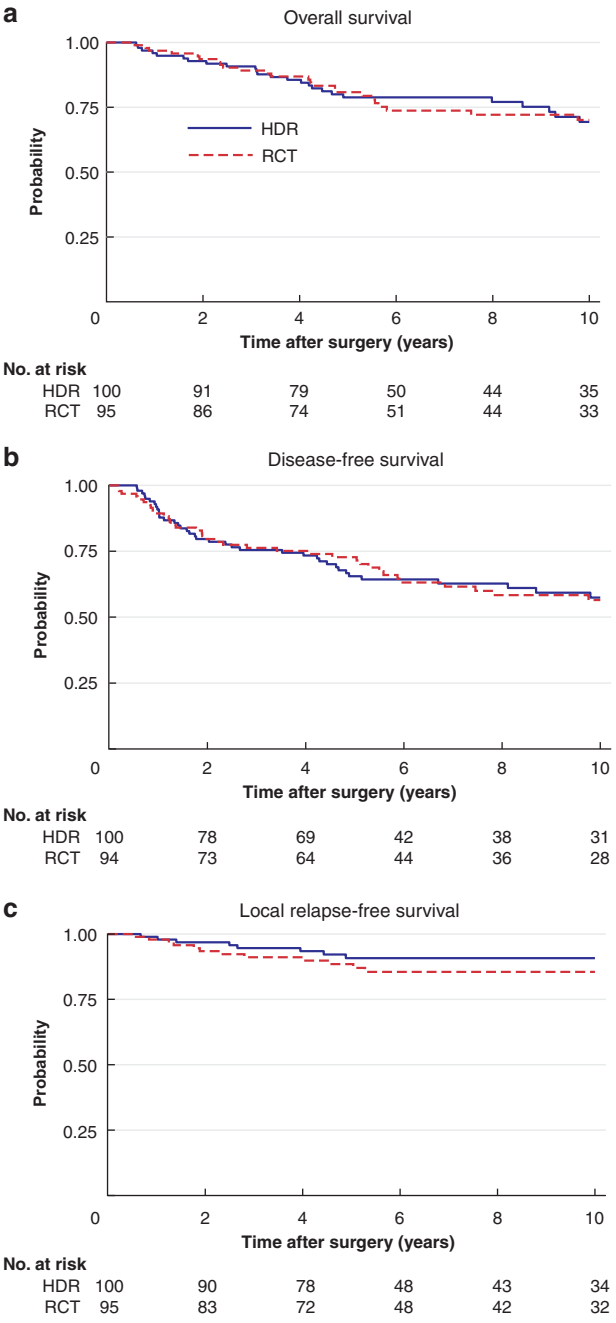

Fig. 1 Kaplan–Meier analysis of overall, disease-free, and relapse-free survival according to preoperative treatment, high-dose radiotherapy or radiochemotherapy

a Overall survival (hazard ratio (HR) 1.00, 95 per cent c.i. 0.56 to 1.77; P =0.977); **b** disease-free survival (HR 0.99, 0.63 to 1.57; P=0.977); **c** local relapse-free survival (HR 1.59, 0.65 to 3.90; P =0.303). HDR, high-dose radiotherapy; RCT, radiochemotherapy.

Finding data regarding the rate of APR by country is challenging. Data from an English national database[3] showed that the APR rate decreased from 29.4 to 21.2 per cent between 1996 and 2004. In a US review[4], the APR rate was 20.4 per cent for all rectal cancers, but could be above 40 per cent for low rectal cancers. Even a highly specialized US centre reported an APR rate of 25 per cent for all rectal cancers in 2009–2015[5]. Between 2005 and 2015, the APR rate in Germany was 29 per cent[6]. The French hospital discharge database PMSI (Programme de Médicalisation des Systèmes d'Information) indicates that the APR rate decreased

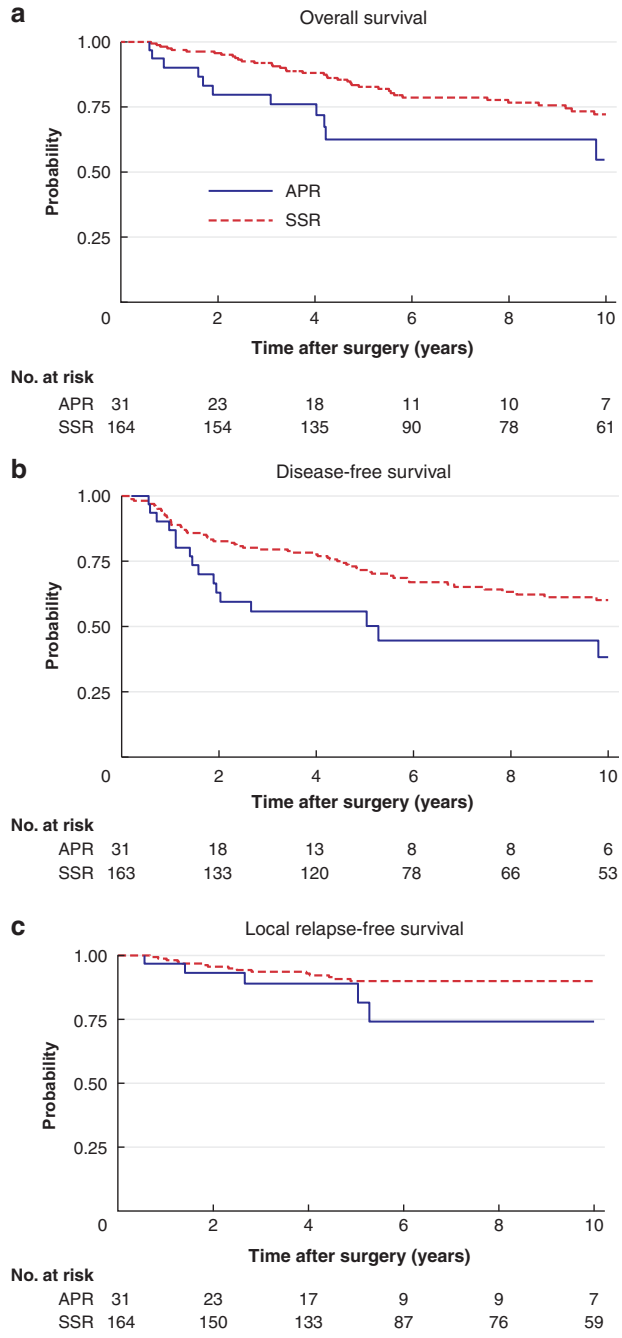

Fig. 2 Kaplan–Meier analysis of overall, disease-free, and relapse-free survival according to type of surgery, abdominoperineal resection or sphincter-saving resection

a Overall survival (hazard ratio (HR) 0.47, 95 per cent c.i. 0.24 to 0.93; P =0.026); **b** disease-free survival (HR 0.51, 0.29 to 0.89; P=0.015); **c** local relapse-free survival (HR 0.43, 0.16 to 1.20; P =0.097). APR, abdominoperineal resection; SSR, sphincter-saving resection.

from 20.7 per cent in 2010 to 16.8 per cent in 2018. In a tertiary Korean centre, the rate of ULRC was 21.4 per cent[7]. An analysis[8] of consecutive patients with low rectal cancer from 12 referring hospitals in seven countries reported an APR rate of 41 per cent in 2009–2013. From these data, objective explanations for variations in the APR rate are difficult to make, although high-volume and specialization seem to favour a lower rate.

ISR was first described in 1977 by Lyttle and Parks[9], and suggested for rectal carcinoma by Marks and colleagues[10], Kusunoki and co-workers[11], and Schiessel *et al.*[2]. Since these first publications, many authors have reported the feasibility, reliability, and safety of this method[12,13]. Absence of the mesorectum in very low rectal cancer underlines the interest in removing the internal sphincter, which is the technical specificity of the ISR to widen the CRM. A recent ISR review[14] reported a rate of 80.2 per cent for 5-year DFS, with a local recurrence rate of 5.8 per cent.

The present study confirms these data with a more aggressive approach for ISR. Two subgroups of rectal cancer were highlighted according to the topography—ultra-low (IP–LA = 0 cm) and low (IP–LA: 2 cm or less), and no differences were found for 10-year OS (76.7 *versus* 64.8 per cent respectively; $P = 0.158$) or DFS (56.7 *versus* 57.1 per cent; $P = 0.964$) rate. Thus, DRM is rarely a contraindication to ISR, because it is almost always possible to incise 1 cm below the lesion, even under the dentate line.

Sphincter preservation in low rectal cancer is affected by both surgeon experience and belief. Historically, a prominent factor was the distance from the tumour to the anal sphincters. Today, tumoral response to neoadjuvant treatment appears to be the key to transforming an initially mutilating surgery to a conservative approach[15,16]. The present study clearly demonstrates that meticulous transanal dissection with a rigorous intersphincteric resection tailored to the residual tumour enables good long-term local control, even for ultra-low rectal adenocarcinoma. A significant volumetric tumoral response after neoadjuvant therapy is essential. This is currently best assessed with both rectal examination and MRI evaluation[17]. However, the surgeon's operative technique, motivation, and understanding of the disease remain major key factors.

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References

1. Rouanet P, Fabre JM, Dubois JB, Dravet F, Saint Aubert B, Pradel J et al. Conservative surgery for low rectal carcinoma after high dose radiation. Functional and oncological results. Ann Surg 1995;**221**:67–73
2. Schiessel R, Novi G, Holzer B, Rosen HR, Renner K, Hölbling N et al. Technique and long-term results of intersphincteric resection for low rectal cancer. Dis Colon Rectum 2005;**48**:1858–1865
3. Tilney HS, Heriot AG, Purkayastha S, Antoniou A, Aylin P, Darzi AW et al. A national perspective on the decline of abdominoperineal resection for rectal cancer. Ann Surg 2008;**247**:77–84
4. Keller DS, Reif de Paula T, Kiran RP. Ready for the National Accreditation Programs for Rectal Cancer? Auditing rectal cancer outcomes in the United States. Colorectal Dis 2019;**21**:1213–1215
5. Roxburgh CSD, Strombom P, Lynn P, Cercek A, Gonen M, Smith JJ et al. Changes in the multidisciplinary management of rectal cancer from 2009 to 2015 and associated improvements in short-term outcomes. Colorectal Dis 2019;**21**:1140–1150
6. Ghadban T, Reeh M, Bockhorn M, Heumann A, Grotelueschen R, Bachmann K et al. Minimally invasive surgery for colorectal

cancer remains underutilized in Germany despite its nationwide application over the last decade. Sci Rep 2018;**8**:15146
7. Park JS, Park SY, Kim HJ, Cho SH, Kwak SG, Choi GS. Long-term oncologic outcomes after neoadjuvant chemoradiation followed by intersphincteric resection with coloanal anastomosis for locally advanced low rectal cancer. Dis Colon Rectum 2019; **62**:408–416
8. Ogura A, Konishi T, Cunningham C, Garcia-Aguilar J, Iversen H, Toda S et al. Neoadjuvant (chemo)radiotherapy with total mesorectal excision only is not sufficient to prevent lateral local recurrence in enlarged nodes: results of the multicenter lateral node study of patients with low cT3/4 rectal cancer consortium. J Clin Oncol 2019;**37**:33–43
9. Lyttle JA, Parks AG. Intersphincteric excision of the rectum. Br J Surg 1977;**64**:413–416
10. Marks G, Mohiuddin M, Masoni L. The reality of radical sphincter preservation surgery for cancer of the distal 3 cm of rectum following high-dose radiation. Int J Radiat Oncol Biol Phys 1993; **27**:779–783
11. Kusunoki M, Shoji Y, Yanagi H, Fujita S, Hatada T, Sakanoue Y et al. Modified anoabdominal rectal resection and colonic J-pouch anal anastomosis for lower rectal carcinoma: preliminary report. Surgery 1992;**112**:876–883
12. Rullier E, Laurent C, Bretagnol F, Rullier A, Vendrely V, Zerbib F. Sphincter-saving resection for all rectal carcinomas: the end of the 2-cm distal rule. Ann Surg 2005;**241**:465–469
13. Saito N, Moriya Y, Shirouzu K, Maeda K, Mochizuki H, Koda K et al. Intersphincteric resection in patients with very low rectal cancer: a review of the Japanese experience. Dis Colon Rectum 2006;**49(Suppl)**:S13–S22
14. Collard M, Lefevre J. Ultimate functional preservation with intersphincteric resection for rectal cancer. Front Oncol 2020; **10**:297
15. Weiser MR, Quah HM, Shia J, Guillem JG, Paty PB, Temple LK et al. Sphincter preservation in low rectal cancer is facilitated by preoperative chemoradiation and intersphincteric dissection. Ann Surg 2009;**249**:236–242
16. Han YB, Oh SN, Choi MH, Lee SH, Jang HS, Lee MA et al. Clinical impact of tumor volume reduction in rectal cancer following preoperative chemoradiation. Diagn Interv Imaging 2016;**97**: 843–850
17. Nougaret S, Castan F, de Forges H, Gallix B, Gourgou S, Rouanet P; GRECCAR Study Group. Early MRI predictors of disease-free survival in locally advanced rectal cancer from the GRECCAR 4 trial. Br J Surg 2019;**106**:1530–1541