European Journal of Surgical Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Feasibility study of a Response Surveillance Program in locally advanced mid and low rectal cancer to increase organ preservation

Mehdi Boubaddi [a], Christina Fleming [a], Veronique Vendrely [b], Nora Frulio [c], Cécile Salut [c], Eric Rullier [a], Quentin Denost [a, *]

[a] Department of Colorectal Surgery, CHU, Bordeaux, France
[b] Department of Radiation Oncology, CHU, Bordeaux, France
[c] Department of Radiology, CHU, Bordeaux, France

ARTICLE INFO

Article history:
Received 13 June 2022
Received in revised form
2 August 2022
Accepted 25 August 2022
Available online xxx

Keywords:
Rectal cancer
Organ preservation
Watch and wait
Response assessment
Complete response
Neoadjuvant therapy

ABSTRACT

Background: Assessment of tumor response in rectal cancer after neoadjuvant treatment by MRI (Tumour Regression Grade, TRG 1–5) is well standardized. The overall timing and method of defining complete response (cCR) remain controversial. The aim of this work was to evaluate the feasibility of a defined Response Surveillance Program (RSP) to increase organ preservation for locally advanced rectal cancer after neoadjuvant treatment.

Methods: A standardized program of clinical (CR), radiological (RR) and metabolic (MR) assessment of tumor response is defined over a 6 month period from completion of NACRT with formal assessment performed every 2 months (M). Patients with TRG1-3 at M2 and TRG1-2 at M4 continue in the program up to M6 assessment. Patients managed with this protocol from 2016 to 2020 were analyzed. The primary endpoint was rectal preservation rate. Secondary endpoints included disease-free survival and overall survival at 3 years.

Result: 314 potentially suitable patients were enrolled in the RSP and 50 patients completed the six month program and were successfully enrolled into watch and wait. Fourteen (28%) were T2 tumor stage, 27 (54%) T3 and nine (18%) were T4. During watch and wait, patients with locoregional recurrence (n = 11) were treated with local excision (n = 3), endocavitary radiotherapy (n = 1), TME (n = 5) and APR (n = 2). With a median follow-up of 32 months, the rectal preservation rate was 88%, with a 3-year disease-free survival of 67% and an overall survival of 98%.

Conclusion: This study validates the feasibility of the practical implementation of a Response Surveillance Program to increase organ preservation rates without compromising oncological outcomes in rectal cancer.

1. Introduction

Management of locally advanced rectal adenocarcinoma (T2-T4 N0/N + M0) is evolving with new neoadjuvant treatments and organ preservation strategies emerging [1,2]. Complete response can be observed in as many as 30% of patients who receive induction chemotherapy and neoadjuvant chemoradiotherapy which confers more favorable cancer outcomes [3]. This finding raises the question about the requirement of total mesorectal excision (TME) in all cases of locally advanced rectal cancer (LARC) as surgical morbidity is reported in 30% of cases. Organ preservation for rectal cancer is gaining interest as optimization of neoadjuvant treatments and tumor assessment modalities allow a better control of the disease with a higher rate of complete response (cCR). Two different approaches are considered for rectal preservation. A selective approach [2,4] involves identifying suitable patients before any treatment based on favourable tumor characteristics that are likely to lead to a good response to neoadjuvant treatment. An opportunistic approach involves selecting patients after neoadjuvant treatment opportunistically based on a good tumour response which may not have been anticipated. Several studies

* Corresponding author. Department of Colorectal Surgery, Centre Medicochirurgical Magellan, 33600, Pessac, France.
E-mail address: q.denost@bordeaux-colorectal-institute.fr (Q. Denost).

https://doi.org/10.1016/j.ejso.2022.08.031

have demonstrated the feasibility of a watch and wait (W&W) approach [5,6] with organ preservation rates up to 80% reported without a compromise in oncological outcomes.

Assessment of tumor response in LARC is key for a W&W or organ preservation program to be implemented. Tumour response following neoadjuvant therapy using MRI (TRG 1–5, Tumor Regression Grade) is well established [7] as a reliable method of tumour evaluation and accurate diagnosis of complete clinical response (cCR). However, what remains to be determined is the optimum timing of assessment for cCR and subsequently the optimum surveillance intervals if cCR is expected or following cCR confirmation. Recent consensus has suggested evaluation for cCR should be performed between 12 and 24 weeks after commencing neoadjuvant therapy [4,8]. However, many trials have favored to report assessment of cCR from time of completion of neoadjuvant therapy, usually between 6 and 8 weeks following completion. Comparisons of the response assessment time points used to determine cCR in randomized studies of organ preservation strategies indicate substantial variability in terms of the time points selected. A recent international consensus [8] suggested that the optimum time for assessment of complete clinical response after chemoradiotherapy for patients with rectal adenocarcinoma has to be assessed from starting neoadjuvant treatment, and not from completion of it, simila to that recommended for squamous cell carcinoma of the anus [9]. However, with the increasing diversity of neoadjuvant treatment modalities, duration of therapies and increasing utilization of induction chemotherapy, standardizing the timing of cCR assessment from the end of neoadjuvant therapy is more suitable for everyday practice.

The aim of this study was to assess the feasibility and the safety of a defined Response Surveillance Program (RSP) in the standardization of the timing to assess and define complete response.

2. Methods

2.1. Patient identification and recruitment

All patients with non-metastatic low and mid rectal cancer (mrT2-T4, N0/N + M0) treated at CHU Bordeaux from 2016 to 2020 were considered for inclusion in the RSP. Patients enrolled in another organ preservation trial (GRECCAR 12), patients with tumours that were more than hemi-circumferential or patients with a follow-up shorter than 12 months after the end of RSP were not included. RSP was proposed in patients with a good tumor response (TRG1-3) at the first response assessment time, who consented to non-operative management at CHU Bordeaux. All patients gave informed consent for this study.

2.2. Surveillance program protocol

An outline of the departmental Response Surveillance Program (RSP) is summarized in Fig. 1. Timing of evaluation of assessment commenced from the completion date of neoadjuvant chemoradiotherapy (NACRT). Clinical examination (with or without rectoscopy) and MRI evaluation was performed at eight weeks post completion of neoadjuvant therapy and if there were evidence of response (TRG1-3), surveillance was continued to 16 weeks with the same three investigation modalities performed. Again, if evidence of a good response (TRG1-2) was evident, surveillance was continued to 24 weeks at which point clinical examination and MRI evaluation were repeated and a PET-CT performed. If a concordant assessment of complete response (TRG1) was made at this six month mark, the patient entered a long-term active surveillance program of 'watch and wait' (W&W) involving four-monthly clinical examination, endoscopic and MRI evaluation and CT thorax, abdomen and pelvis. If a subcomplete response was identified at six months patients were offered local excision (LE) or TME and if LE was preferred with favorable pathological outcome, patients subsequently entered W&W at this point. If locally recurrent disease was identified during RSP or W&W, treatment in the form of a local therapy or total mesorectal excision (TME) was expedited within two-three weeks.

2.3. Tumor response assessment

Within the above defined six-month RSP, interval to tumor response was reported from the beginning of NACRT. A combined assessment of clinical (CR), radiologic (RR) and metabolic (MR) response was performed and concordance required between modalities. CR was measured by digital rectal examination (DRE) with or without rectoscopy at 8, 16 and 24 weeks. RR was assessed using contrast-enhanced rectal MRI, with T2-weighted sequences preferred for assessment of response which was characterized using TRG (Tumor Regression Grade) classification [10,11] as follows: TRG1, complete radiologic response without evidence of tumor; TRG2, good response with dense fibrosis (>75%) with no or minimal residual disease; TRG3, moderate response with >50% fibrosis or mucin and intermediate signal intensity; TRG4, slight response with little areas of fibrosis but mostly tumor; TRG5, no response at all. Metabolic response (MR) was assessed using PET scan at 24 weeks (6 months). This was specifically performed to assess metabolic activity of tumor site and out-rule locoregional or distant disease. If response milestones (as outlined in the RSP protocol, Fig. 1) were not reached at eight, sixteen or twenty-four weeks, patients underwent formal oncological resection in the form of a TME.

2.4. Definitions of complete response

Clinical response to neoadjuvant therapy was considered as 'complete' (cCR) if there was no evidence of a residual or palpable tumour with digital rectal exam (DRE) and RR was TRG1 at 24 weeks. RR that was expected to reach complete response (also described as sub-complete response) was observed if there were obvious downstaging with residual fibrosis and TRG2-3 response at 8 weeks and TRG2 at 16 weeks.

An MR was considered as complete if there was no evidence of FDG-avid locoregional or distant disease on PET-CT performed at 24 weeks following completion of neoadjuvant therapy [6,8].

2.5. Definition of organ preservation

Organ preservation [8] was defined as: avoidance of full rectal excision i.e. radical total mesorectal excision (TME) was not performed, no locoregional regrowth unless amenable to limited, curative (R0) salvage surgery by local excision (LE) and no permanent stoma required (including a never reversed protective stoma, or a stoma owing to toxicities and/or poor functional outcomes).

2.6. Outcome measure

The primary endpoint was to report organ (rectal) preservation rate after a minimum follow up of twelve-months. Secondary endpoints were to report on disease-specific (without local

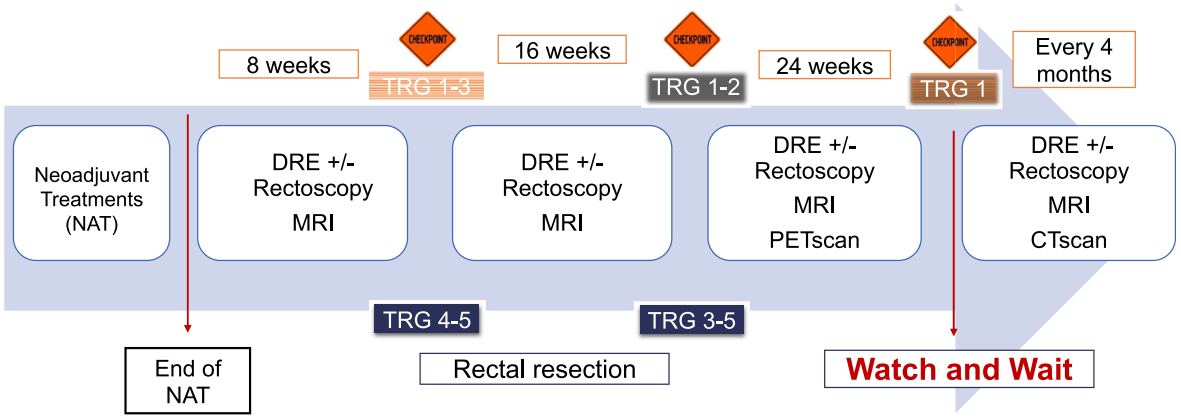

Fig. 1. Outline of defined Response Surveillance Program to monitor for complete clinical response (cCR) following neoadjuvant therapy for rectal cancer.
DRE, digital rectal examination. NAT, neoadjuvant treatments. MRI, magnetic resonance imaging. TEP, positron emission computed tomography. TRG, tumor regression grade.

regrowth) and overall survival at 3 years. Rectal preservation rate was defined as not requiring a formal rectal resection. Reporting of interval to organ preservation, disease free and overall survival was evaluated from the beginning of neoadjuvant treatment and the last follow up. Feasibility was confirmed by enrolling >80% of patients with a complete response and suitable for watch and wait into a watch and wait programme, achieving an organ preservation rate >80% at two years and local recurrence at two years <25%.

2.7. Statistical analysis

Quantitative variables were expressed as median with range and compared using the Mann-Whitney test. Qualitative variables were expressed in proportions and comparisons performed using the Chi-Square test or the Fisher's exact test when appropriate. Survival outcomes i.e. disease-free survival (DFS) and overall survival (OS) were estimated using the Kaplan-Meier method. A p value < 0.05 was considered significant. Statistical analysis was performed using IBM SPSS Statistics, version 20.0.

3. Results

3.1. Demographic and clinical characteristics

A total of 314 patients who underwent neoadjuvant treatment for locally advanced low and mid rectal adenocarcinoma and were eligible for enrollment in the Response Surveillance Program (RSP). At eight weeks after the completion date of NACRT (first post-treatment assessment), 197 patients underwent total mesorectal excision (TME), 31 abdominoperineal resection (APR) and 26 pelvic exenteration (PE) for TRG4-5 response and 19.1% (n = 60) continued in the RSP. At 16 weeks after the end of NACRT (second assessment), two patients underwent LE and one TME for TRG 3–4 tumours, one patient refused any surgical management despite an incomplete response and was followed up outside RSP and 17.8% (n = 56) continued in the RSP. At 24 weeks after the end of NACRT (final assessment), five patients underwent LE for TRG2 response and one TME for TRG3 response. A total of fifty patients completed the Response Surveillance Program (RSP) and began Watch and Wait (W&W) as summarized in Figs. 2 and 3.

All patients were diagnosed between January 2016 and December 2020. The median follow-up period was 32.4 months (range 12.7–62.0) from the start of NAT. The median age was 67 years old (37–87). 62% (n = 31) of patients were male and 38% (n = 19) female. At diagnosis, median tumor size was 4 cm (range 2–7 cm) and the

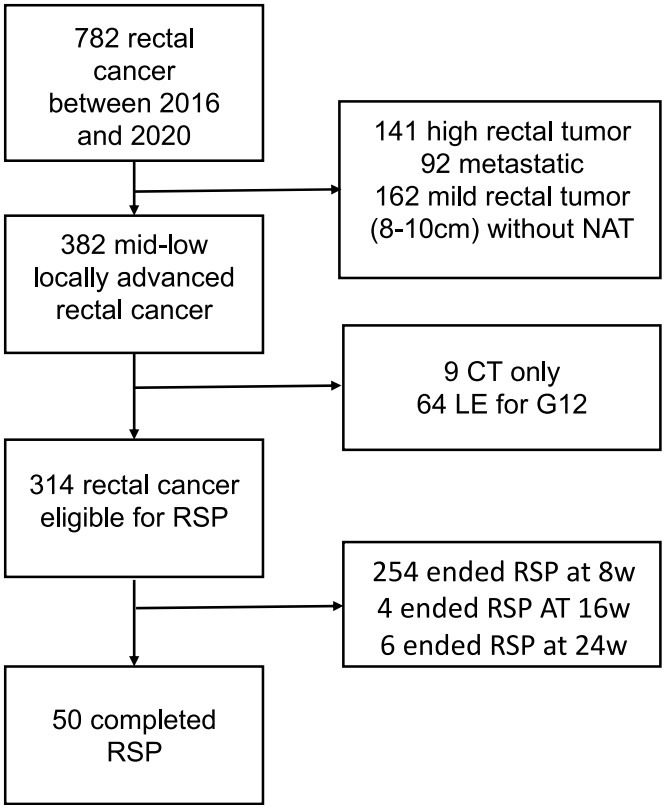

Fig. 2. Flow chart of patient selection for inclusion in feasibility study of Response Surveillance Program between January 2016 and December 2020.
CT, chemotherapy. LE, local excision. NAT, neoadjuvant therapy. RSP, Response Surveillance Program.

median distance from anal margin was 3.5 cm (range 1–9 cm). Nine (18%) patients were tumour stage T4, 27 (54%) stage T3 and 14 (28%) stage T2. In four cases, T4 tumours invaded the prostate (T4b) and in five cases the levator ani muscles. Node negative disease at diagnosis was identified in in 48% (n = 24), 48% (n = 24) N1 and 4% (n = 2) N2. Patients' characteristics are summarized in Table 1.

3.2. Neoadjuvant therapy

The majority, 50% (n = 25) received standard long course chemo-radiotherapy (RTCT) with 50Gy external beam radiotherapy in 25 sessions over 5 weeks with radiosensitising chemotherapy in the form

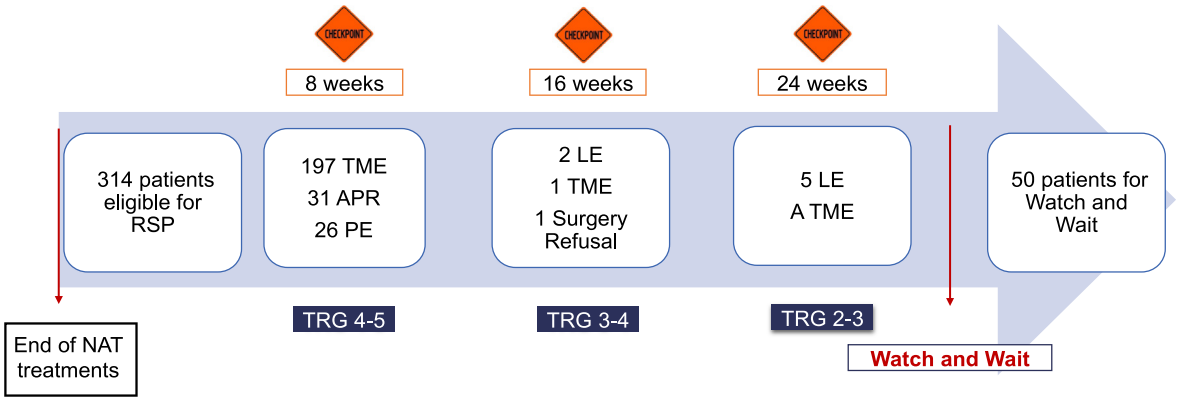

Fig. 3. Flow chart of patient followed during Response Surveillance program after NAT.
APR, abdominoperineal resection. LE, local excision. NAT, neoadjuvant. PE, pelvic exenteration. TME, total mesorectal excision. TRG, tumor regression grade. RSP, Response Surveillance Program.

Table 1
Patient and tumour characteristics and neoadjuvant treatment regimes.

	N (%)
Age (years)*	67 (37–87)
Sex Ratio M/F	31/19
BMI (kg/m^2)*	26.0 (18.2–37.6)
Tumor size (cm)*	4 (2–7)
Distance from anal verge (cm)*	3.5 (1–9)
Tumor stage	
mrT2	14 (28%)
mrT3	27 (54%)
mrT4	9 (18%)
Nodal Stage	
mrN0	24 (48%)
mrN1	24 (48%)
mrN2	2 (4%)
Neoadjuvant Treatment	
RTCT	25 (50%)
CT + RTCT	18 (36%)
CT + RTCT + CT	4 (8%)
ShortRT + CT	3 (6%)

BMI, body mass index. CT, chemotherapy. mrN, clinical nodal stage (MRI). mrT, clinical tumor stage (MRI). RTCT, radiochemotherapy.
* median (range).

of oral 5-FU (Capecitabine). Twenty-two (40%) patients received induction chemotherapy with 4–6 cycles of FOLFIRINOX following by standard RTCT (CT + RTCT). Three (6%) patients received short course chemoradiotherapy with 25Gy delivered in 5 sessions followed by 4–6 cycles of FOLFIRINOX (shortRT + CT). Four (8%) patients received CT + RTCT upfront followed by 4–6 cycles of FOLFOX (CT + RTCT + CT).

3.3. Feasiblity outcomes

All 50 patients who achieved cCR within the RSP programme were successfully enrolled into W&W (100% enrollment) following completion of RSP plus seven patients with sub-complete response who underwent a local excision also entered W&W. During the overall follow-up period an 88% (n = 50) organ (rectal) preservation rate was achieved as seven patients in the entire patient group required savage TME or APR following W&W (± LE for subcomplete responders) during this follow-up period. Local recurrence occurred in 20% (n = 10) of patients at two years and 22% (n = 11) of patients by three years.

Table 2
Overview of locoregional regrowth patterns, interval to regrowth and management.

Site	T	N	Time to recurrence (months)	NAT	Treatment
Local					
1	T2	N1	15	RTCT	APR
2	T3	N0	22	RTCT	TME
3	T2	N0	23	CT-RTCT	LE
4	T3	N0	14	RTCT	LE-TME
5	T3	N0	11	CT-RTCT	LE
6	T2	N1	29	RTCT	TME
7	T3	N1	21	RTCT	TME
8	T2	N1	14	RTCT	RTE
9	T4	N1	19	CT-RTCT	LE
10	T3	N0	12	RTCT	TME
11	T4	N1	13	CT-RTCT-CT	APR

APR, abdominoperineal resection. CT, chemotherapy. LE, local excision. RTCT, radiochemotherapy. TME, total mesorectal excision.

3.4. Identification of recurrent disease and survival outcomes

Table 2 summarizes clinical characteristics and outcomes for patients who developed locoregional recurrence. Following completion of RSP and commencement of W&W, recurrent disease was identified in 28% (n = 14). Recurrence patterns were as follows: 22% (n = 11) local regrowth, 2% (n = 1) mesorectal lymph node regrowth and 4% (n = 2) metastatic recurrence. Median time to recurrence from the end of the six month RSP was 15 months (rage 11–29 months). Four local recurrences were suitable for local therapy (n = 3 local excision and n = 1 brachytherapy). The other seven patients with local recurrence were treated by rectal excision (n = 5 TME, n = 2 abdominoperineal resection), and a clear R0 resection margin was achieved in all cases.

Two patients died during follow up, resulting in an overall survival rate at 3 years of 98% and disease-free survival of 67%. One mortality occurred due to complications from metastatic disease and one non-cancer related mortality occurred. Overall and disease-free survival of patients enrolled in Response Surveillance Program feasibility study are illustrated in Fig. 4.

4. Discussion

In this feasibility study, we identified a high organ preservation rate and favorable cancer outcomes following a defined Response Surveillance Program (RSP) which facilitates a defined pathway to monitor for complete clinical response (cCR) following neoadjuvant

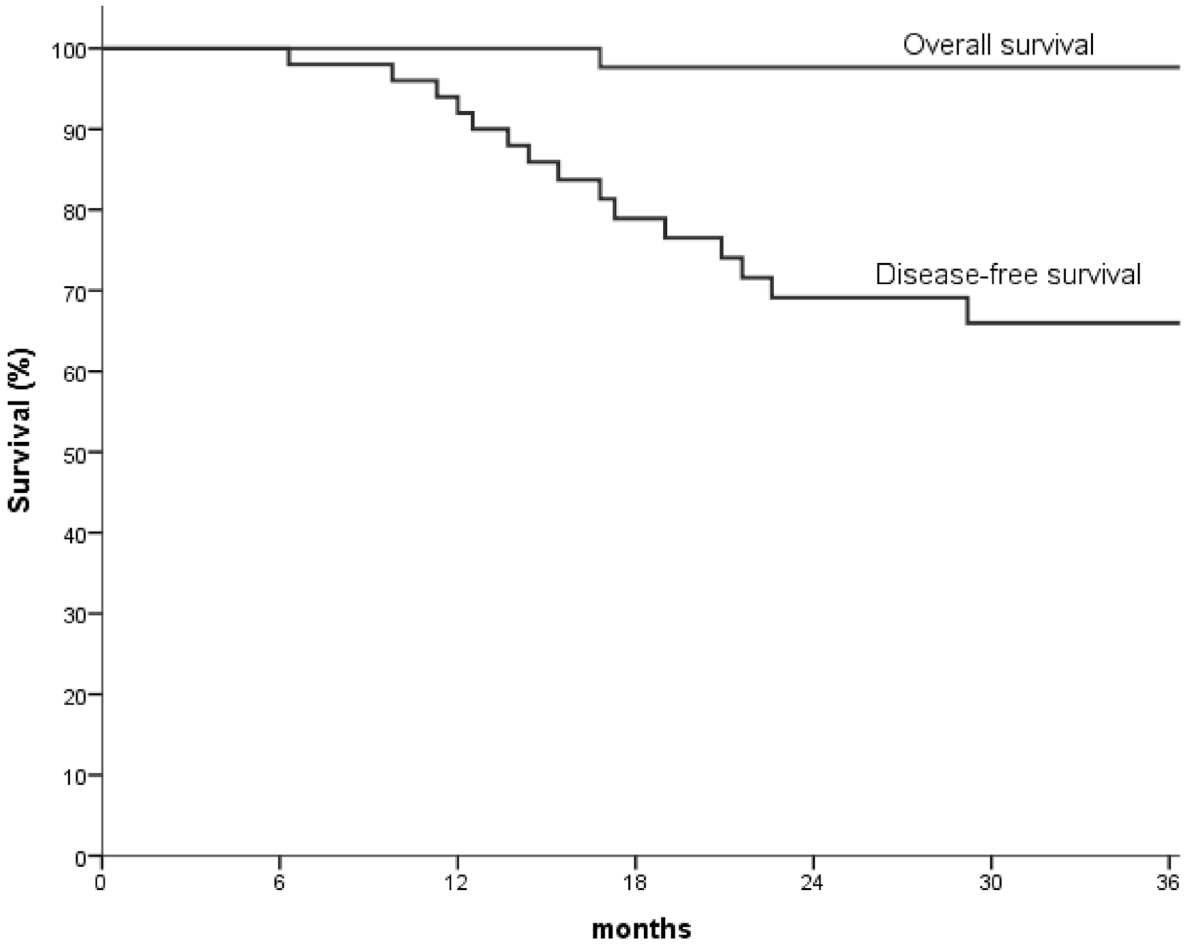

Fig. 4. Overall and disease-free survival of patients enrolled in Response Surveillance Program feasibility study.

therapy for rectal cancer. Organ preservation in rectal cancer is an opportunity to individualize patient treatment, avoid the morbidity of total mesorectal excision (TME) and the long-term sequelae of surgery for patients who achieve a complete clinical response (ycCR) [12–15]. The principle of organ preservation has already proven its feasibility but the optimum timing interval and method for assessing tumor response and selecting patients in complete response is not agreed.

Habr Gama et al. [16], a leading group exploring the benefits and feasibility of 'Watch and Wait' (W&W) and organ preservation in rectal cancer in 2004 reported a rectal preservation rate of 93% for 71 patients during a mean follow-up period of 57 months. In 2016, *Martens* et al. [17] reported a rectal preservation of 87% for 100 patients during a median follow-up period of 41 months. Subsequent studies have confirmed similar organ preservation and survivals rates despite heterogeneity in patient selection, tumor and nodal stage at diagnosis and neoadjuvant therapy. Three clinical trials have also demonstrated that organ preservation can be achieved and maintained with local excision (LE) of small remnant tumours or areas of subcomplete response with subsequent successful W&W management [2,4,18].

To maximize the potential for organ preservation in clinical practice it is key that we identify a combination of investigations that most accurately identify cCR and that sufficient time is allowed following neoadjuvant therapy for cCR to develop. Digital rectal examination (DRE) is an easily reproducible test to assess clinical response and can provide useful prognostic information including tumour fixation. Serial DRE during neoadjuvant therapy can identify refractory cases in which preoperative therapy may be altered in an attempt to improve tumor response. Serial examination is important as an isolated DRE clinical exam could underestimate tumor response in up to 78% of patients [19], therefore it's important that it be repeated several times, by an experienced physician and findings considered with other examinations.

MRI is a key investigation in organ preservation and particularly in our proposed RSP protocol because of its effectiveness to assess tumor response without surgery. The correlation between TRG response and oncological outcome has already been demonstrated in several studies [20,21]. Furthermore, the MERCURY trial [10] and TRIGGER [7] trial have highlighted correlation between ymrT stage or TRG response and ypT stage after surgery. It appears that the degree of tumor replacement by fibrosis (TRG response) correlates with tumor response and survival at a greater statistical significance than ymrT stage does. It was therefore important to use TRG classification, performed by specialtytrained radiologists in order to predict tumor response [22].

$^{(18)}$F-FDG PET has been criticized for its limited ability to accurately quantify tumour and nodal response following neoadjuvant therapy for rectal cancer [23] compared to other examination like MRI which is considered the gold standard investigation for evaluating response. The real value in PET CT imaging is to identify locoregional disease or sites of distant metastases as opposed to quantification of tumour response. PET-CT is accurate in this regard with sensitivity and specificity of 100% (CT 54% MRI 67%) and 60%

(CT 80%, MRT 67%). Positive and negative predictive values were 77% (CT 78%, MRI 83%) and 100% (CT 57%, MRI 50%) [24]. Therefore, presence or lack of hypermetabolism on PET-CT imaging at 6 months following completion of neoadjuvant therapy, that is at the end of RSP, can influence the decision to proceed with resectional TME or continue to strive for organ preservation with watch and wait.

Timing of assessment is also important to optimize potential for cCR. The Brazilian study group [5] demonstrated that the majority of cCR can occur after 16 weeks (62% of patients in complete response), and standard response assessment at 8–12 weeks may miss the opportunity to achieve complete response. Therefore, it is necessary to consider patients in near complete or subcomplete response (nCR) defined by minor irregularities on DRE or TRG 1–2 response with additional assessment every 6–8 weeks instead of immediate rectal excision. This is consistent with recent studies [25,26] which revealed that majority of nCR patients at first assessment finally achieved complete response and delayed or salvage rectal excision for incomplete response despite initial hope of complete response do not affect oncological outcomes. However, it is important to continue to formally monitor response to ensure that the appropriate progress is being made.

In the Response Surveillance Program (RSP) suggested by the authors formal assessment of response is performed at regular intervals up to the final time point of 24 weeks (6 months) following completion of NACRT. The authors suggest that monitoring and reporting of interval to cCR should commence following completion of neoadjuvant therapy. This is in contrast to a recent large review where the interval to cCR was reported for each study from the start of neoadjuvant therapy [8]. The reason for this is that there was only one neoadjuvant treatment plan for each study, but this is not reproducible in everyday clinical practice where patients in different centers may have different and evolving treatments over time. The variety of emerging total neoadjuvant therapy (TNT) strategies (*RAPIDO, PRODIGE23, OPRA*) [1,27,28] also need to be considered. All have varying regimen and duration of therapies thus it is most appropriate to continue to report on oncological outcomes (overall and disease-free survival and local recurrence) at an interval beginning from the commencement of neoadjuvant therapy. However, when it comes to reporting response rate the authors propose that reporting the interval to cCR, particularly within an RSP, should be performed from completion of neoadjuvant therapy and in particular NACRT for standardization of reporting as a reference point from which response can be expected needs to be defined. This differs slightly to a recent international consensus [8], where follow up time was calculated from start of neoadjuvant therapies.

There are a number of limitations to this study. This is a small single-center feasibility study however it is an ultra-high volume rectal cancer center. All patients were included and followed in Bordeaux University Hospital by trained surgeons and radiologists with a special interest in treatment of rectal cancer surveillance and organ preservation. As a feasibility study, it does not include a comparative control arm. The Response Surveillance Program is designed to be as objective and reproductible as possible and could be considered in high-volume centers where a formal organ preservation program is considered. It is not part of our standard practice to utilize endoscopy for tumour response assessment however we have included the option of rectoscopy at each stage for those whom it is standard practice with clear criteria for response classification [6,8]. We also did not record the patient experience of the RSP or organ preservation in the cohort included in this study but it is now an important focus of our practice following completion of this feasibility study.

In conclusion, this feasibility study confirms that a defined Response Surveillance Program to facilitate increased time for development of complete clinical response following neoadjuvant therapy for rectal cancer with regular clinical and radiological surveillance results in favorable organ preservation rates and acceptable oncological outcomes. The authors recommend that this program commence following completion of neoadjuvant therapy and can continue up to 24 weeks with a mechanism to transition to watch and wait or surgery as required.

Conflict of interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

Mehdi Boubaddi: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Christina Fleming:** Methodology, Project administration, Writing – original draft, Writing – review & editing, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Nora Frulio:** Data curation. **Cécile Salut:** Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Eric Rullier:** Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Quentin Denost:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

References

[1] Conroy T, Bosset J-F, Etienne P-L, Rio E, Francois E, Mesgouez-Nebout N, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:702–15.

[2] Rullier E, Rouanet P, Tuech J-J, Valverde A, Lelong B, Rivoire M, et al. Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial. Lancet 2017;390:469–79.

[3] Martin ST, Heneghan HM, Winter DC. Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. Br J Surg 2012;99:918–28.

[4] Garcia-Aguilar J, Renfro LA, Chow OS, Shi Q, Carrero XW, Lynn PB, et al. Organ preservation for clinical T2N0 distal rectal cancer using neoadjuvant chemoradiotherapy and local excision (ACOSOG Z6041): results of an open-label, single-arm, multi-institutional, phase 2 trial. Lancet Oncol 2015;16:1537–46.

[5] Habr-Gama A, São Julião GP, Fernandez LM, Vailati BB, Andrade A, Araújo SE, et al. Achieving a complete clinical response after neoadjuvant chemoradiation that does not require surgical resection: it may take longer than you think. Dis Colon Rectum 2019;62:802–8.

[6] Maas M, Beets-Tan RGH, Lambregts DMJ, Lammering G, Nelemans PJ, Engelen SME, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol 2011;29:4633–40.

[7] Battersby NJ, Dattani M, Rao S, Cunningham D, Tait D, Adams R, et al. A rectal cancer feasibility study with an embedded phase III trial design assessing magnetic resonance tumour regression grade (mrTRG) as a novel biomarker to stratify management by good and poor response to chemoradiotherapy (TRIGGER): study protocol for a randomised controlled trial. Trials 2017;18:394.

[8] Fokas E, Appelt A, Glynne-Jones R, Beets G, Perez R, Garcia-Aguilar J, et al. International consensus recommendations on key outcome measures for organ preservation after (chemo)radiotherapy in patients with rectal cancer. Nat Rev Clin Oncol 2021;18:805–16.

[9] James RD, Glynne-Jones R, Meadows HM, Cunningham D, Sun Myint A, Saunders MP, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2×2 factorial trial. Lancet Oncol 2013;14:516–24.

[10] Patel UB, Taylor F, Blomqvist L, George C, Evans H, Tekkis P, et al. Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience. J Clin Oncol 2011;29:3753–60.

[11] Patel UB, Brown G, Rutten H, West N, Sebag-Montefiore D, Glynne-Jones R, et al. Comparison of magnetic resonance imaging and histopathological response to chemoradiotherapy in locally advanced rectal cancer. Ann Surg

Oncol 2012;19:2842–52.
[12] Rouanet P, Bertrand MM, Jarlier M, Mourregot A, Traore D, Taoum C, et al. Robotic versus laparoscopic total mesorectal excision for sphincter-saving surgery: results of a single-center series of 400 consecutive patients and perspectives. Ann Surg Oncol 2018;25:3572–9.
[13] Dames NB, Squire SE, Devlin AB, Fish R, Bisset CN, Tozer P, et al. Let's talk about sex": a patient-led survey on sexual function after colorectal and pelvic floor surgery. Colorectal Dis 2021;23:1524–51.
[14] Shiraishi T, Ito M, Sasaki T, Nishizawa Y, Tsukada Y, Ikeda K. Association between urinary function and resected pattern of the autonomic nerve system after transanal total mesorectal excision for rectal cancer. Colorectal Dis 2021;23:405–14.
[15] Lemini R, Jabbal IS, Stanek K, Borkar SR, Spaulding AC, Kelley SR, et al. Permanent stoma: a quality outcome in treatment of rectal cancer and its impact on length of stay. BMC Surg 2021;21:163.
[16] Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro Jr U, Silva e Sousa Jr AH, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 2004;240:711–7. ; discussion 717-718.
[17] Martens MH, Maas M, Heijnen LA, Lambregts DMJ, Leijtens JWA, Stassen LPS, et al. Long-term outcome of an organ preservation program after neoadjuvant treatment for rectal cancer. J Natl Cancer Inst 2016;108:djw171.
[18] Rombouts AJM, Al-Najami I, Abbott NL, Appelt A, Baatrup G, Bach S, et al. Can we Save the rectum by watchful waiting or TransAnal microsurgery following (chemo) Radiotherapy versus Total mesorectal excision for early REctal Cancer (STAR-TREC study)?: protocol for a multicentre, randomised feasibility study. BMJ Open 2017;7:e019474.
[19] Guillem JG, Chessin DB, Shia J, Moore HG, Mazumdar M, Bernard B, et al. Clinical examination following preoperative chemoradiation for rectal cancer is not a reliable surrogate end point. J Clin Oncol 2005;23:3475–9.
[20] Barbaro B, Fiorucci C, Tebala C, Valentini V, Gambacorta MA, Vecchio FM, et al. Locally advanced rectal cancer: MR imaging in prediction of response after preoperative chemotherapy and radiation therapy. Radiology 2009;250:730–9.
[21] Rödel C, Martus P, Papadoupolos T, Füzesi L, Klimpfinger M, Fietkau R, et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. J Clin Oncol 2005;23:8688–96.
[22] Siddiqui MRS, Bhoday J, Battersby NJ, Chand M, West NP, Abulafi AM, et al. Defining response to radiotherapy in rectal cancer using magnetic resonance imaging and histopathological scales. World J Gastroenterol 2016;22:8414–34.
[23] Joye I, Deroose CM, Vandecaveye V, Haustermans K. The role of diffusion-weighted MRI and (18)F-FDG PET/CT in the prediction of pathologic complete response after radiochemotherapy for rectal cancer: a systematic review. Radiother Oncol 2014;113:158–65.
[24] Denecke T, Rau B, Hoffmann K-T, Hildebrandt B, Ruf J, Gutberlet M, et al. Comparison of CT, MRI and FDG-PET in response prediction of patients with locally advanced rectal cancer after multimodal preoperative therapy: is there a benefit in using functional imaging? Eur Radiol 2005;15:1658–66.
[25] Hupkens BJP, Maas M, Martens MH, van der Sande ME, Lambregts DMJ, Breukink SO, et al. Organ preservation in rectal cancer after chemoradiation: should we extend the observation period in patients with a clinical near-complete response? Ann Surg Oncol 2018;25:197–203.
[26] van der Valk MJM, Hilling DE, Bastiaannet E, Meershoek-Klein Kranenbarg E, Beets GL, Figueiredo NL, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. Lancet 2018;391:2537–45.
[27] Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CAM, Putter H, Meershoek-Klein Kranenbarg E, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:29–42.
[28] Garcia-Aguilar J, Patil S, Kim JK, Yuval JB, Thompson H, Verheij F, et al. Preliminary results of the organ preservation of rectal adenocarcinoma (OPRA) trial. J Clin Oncology 2020;38:4008. –4008.