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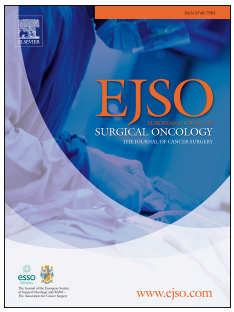

Quality of life after rectal-preserving treatment of rectal cancer

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PII: S0748-7983(20)30645-4

DOI: https://doi.org/10.1016/j.ejso.2020.07.018

Reference: YEJSO 5853

To appear in: *European Journal of Surgical Oncology*

Received Date: 15 May 2020

Revised Date: 25 June 2020

Accepted Date: 15 July 2020

Please cite this article as: Jones HJS, Al-Najami I, Cunningham C, Quality of life after rectal-preserving treatment of rectal cancer, *European Journal of Surgical Oncology* (2020), doi: https://doi.org/10.1016/j.ejso.2020.07.018.

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Quality of life after rectal-preserving treatment of rectal cancer

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There are no conflicts of interest.

Word count: 2,948

Keywords: rectal cancer, organ preservation, quality of life, functional outcomes

ABSTRACT

Aim

Rectal-preserving strategies for managing rectal cancer are becoming more common for selected groups of patients. Oncological outcomes are similar, so long as patients are closely followed, and any local recurrence detected and managed promptly. Functional outcomes are now of increasing importance so patients can be appropriately counselled prior to treatment. We examine functional outcomes in patients managed by multimodal organ-preservation approaches allowing comparison of the full range of strategies.

Materials and methods

Patients attending for surveillance after any of four rectal-preserving treatments for rectal cancer (radiotherapy [RT], local excision [LE], RT then LE or LE then RT) were asked to complete a questionnaire assessing general quality of life and bowel, urinary and sexual function.

Results

100 patients completed questionnaires: 34 managed by neoadjuvant RT followed by 'watch and wait', 40 by LE, and 26 who had composite treatment (18 LE+RT and eight RT+LE). Questionnaires were completed a median of 10 months (IQ range 6-33) following treatment. The LE only group tended to have better bowel function, while the composite groups fared worse; significant differences were noted in LARS and some bowel symptoms scores.

Conclusion

Bowel function appears better after LE alone compared with treatment strategies involving RT, and composite treatments have an additive effect on outcome impairment. Overall quality of life outcomes are good, despite the ongoing requirement for surveillance. As these treatments become more common it is important that patients can be better informed before deciding on a management pathway.

1. INTRODUCTION

Traditional treatment for rectal cancer involves radical surgery, with associated operative morbidity and mortality, as well as longer-term sequelae. Impaired bowel function may result from a stoma or 'low anterior resection syndrome', and pelvic nerve damage may lead to impaired urinary and sexual function [1-3]. As an alternative, organ-preserving treatments are increasingly recognised as feasible in certain situations.

Rectal preservation may be achieved by (chemo-)radiation (RT), local excision (LE) or a combination of the two; each of these options may be suitable to particular patient or tumour characteristics. Patients with more advanced tumours may undergo neoadjuvant RT and achieve (near)complete response, so enter a 'watch and wait' pathway; if there is residual tumour or regrowth, LE may supplement the RT; those with an early cancer may choose primary LE; and if histopathology then shows a more advanced tumour than anticipated adjuvant RT may be preferred to completion radical surgery. Rectal-preserving treatments offer the advantage of avoiding radical surgery in elderly or co-morbid patients, and in those with early screening-detected cancers where radical surgery may be an over-treatment, as well as providing patients who prefer to avoid radical surgery with more choice in their management plan.

Functional outcomes after radical surgery have been studied but there is not much information regarding organ-preserving treatments. A systematic review [4] found little evidence regarding comparative functional outcomes after transanal endoscopic microsurgery (TEM) or total mesorectal excision (TME). In a direct comparison after TEM and TME at a median of 28 months after surgery, overall quality of life scores were similar, but the TEM group showed significantly fewer problems with bowel function and a trend towards better sexual function [5]. In a similar but smaller study of 35 patients [6] impaired function and quality of life were observed in all patients one month after surgery. The impairment persisted at six months in the TME group only, and at 12 months there was no significant difference compared with baseline in either group.

A review of outcomes after chemoradiation (CRT) found 13 articles published over the preceding three years and concluded, unsurprisingly, that the more aggressive the CRT the worse the functional outcome [7]. The studies that included a healthy control group found similar outcomes except for diarrhoea and 'role' and 'social' functioning, that were impaired. They also noted male sexual function was impaired by both surgery and CRT and noted that most studies could not assess female sexual function due to low response rates.

Several studies have looked at patients who have LE after neoadjuvant RT as part of an organ-preserving approach and have generally found little difference in the long term [8-10]. Very few

studies have compared RT alone with RT then LE [11]. No studies were found that report functional outcomes for patients having TEM then adjuvant radiotherapy. Anecdotally, our impression from our own population is that the outcomes from this regime are good, but evidence is needed to inform patients embarking on this pathway.

To make an informed decision about treatment options, patients with rectal cancer need to be made aware of possible outcomes. Oncological outcomes are important, but the expected longer-term quality of life and functional outcomes are an important factor and may play a greater role in the decision-making of certain patient groups. If we are unable to demonstrate an improved quality of life, the argument for organ-preserving approach is less potent. In this paper we seek to increase the information available to inform patients' decision-making by reporting on functional outcomes and quality of life in patients who have undergone any of four rectal-preserving pathways: neoadjuvant RT alone, RT followed by TEM, TEM alone, and TEM followed by adjuvant radiotherapy. Our goal is to describe the impacts that these organ-preserving approaches have, recognising that they are not equivalent alternatives to choose between at the start of treatment, to be directly compared; rather, they may become suitable for a particular patient at a particular time during their treatment pathway.

2. MATERIALS AND METHODS

Patients attending for surveillance following rectal-preserving treatment for rectal cancer at one institution between April 2017 and April 2019 were asked to complete a questionnaire at their follow-up visit. Patients had completed treatment within the previous five years and at least four months had passed since completing the last treatment, be this surgery or radiotherapy. All were disease-free at the time of evaluation. Patients who had undergone radical surgery were not included. The questionnaires were collected at a range of time points following treatment determined by logistical considerations. This approach was adopted because an earlier attempt at a more structured postal survey had a very low response rate.

The three groups assessed were: 1) RT alone: these patients had neoadjuvant CRT and were then managed by 'watch and wait'; 2) TEM alone: these underwent LE by TEM; 3) Composite, including i) RT followed by TEM because of residual tumour or regrowth and ii) TEM followed by adjuvant RT because of high-risk histopathological features.

Radiation, whether neo-adjuvant or adjuvant, involved CRT (45 – 50.4 Gy in 25 or 28 fractions with oral capecitabine). All groups were followed up on the standard surveillance schedule with CEA

(carcinoembryonic antigen), endoscopy and pelvic MRI every 3-4 months for the first 2 years, then 6-12 monthly until 5 years. CT chest-abdomen-pelvis was performed yearly up to 3 years.

For patients having composite treatment time till questionnaire completion was calculated from the date of the last treatment. Incomplete questionnaires were included if most items had been answered. If a response was missing to an item, or to one or more items that contributed to a summary score, that item or score was not included in the relevant analysis.

2.1 Questionnaire

The questionnaire is a composite of several validated questionnaires looking at general measures and specifically at bowel, urinary and sexual function: EuroQol EQ-5D-3L, EORTC QLQ-C30 (European organisation for research and treatment of cancer), EORTC QLQ-CR29 (colorectal supplement), LARS (low anterior resection syndrome, for bowel symptoms), Vaizey (for bowel incontinence), IPSS (international prostate symptom score for urinary function), IIEF-5 (international index of erectile function, men only) and the MFSQ-9 (McCoy female sexuality questionnaire, women only).

The EuroQol EQ-5D-3L comprises an index score based on five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and a visual analogue scale (EQ-VAS) showing the patient self-rated health [12]. The EORTC QLQ-C30 was developed to assess the quality of life in cancer patients [13]. It contains 30 items, which are tallied to give a global health and quality of life scale, five functional scales: physical, role, cognitive, emotional and social, and a number of symptom scales. Scores were generated according to the EORTC scoring guidelines. The EORTC QLQ-CR29 was designed to evaluate colorectal cancer therapy from a patient's perspective [14] and comprises 29 items including ano-rectal, urinary and sexual functioning, with separate questions for patients with a stoma. Ano-rectal function was additionally assessed using the LARS and Vaizey scoring system. The LARS system comprises five items and gives a total score between 0 (no LARS) and 42 (major LARS) [15]. It was developed for use after low anterior resection but has also been shown of value in more general patient populations [16]. The Vaizey score [17] has seven items and gives a total between 0 (perfect continence) and 24 (totally incontinent).

The IPSS [18] assesses urinary function. It was developed for men but has also been shown suitable for women [19]. It comprises seven questions on specific symptoms and an overall quality of life due to urinary symptoms item. The IPSS score ranges from 0 (asymptomatic) to 35 (severely symptomatic). Male sexual function was assessed with the IIEF-5 score [20], which contains five items and gives a total from 5 (severe dysfunction) to 25 (no dysfunction). Female sexual function was assessed with the MFSQ-9 [21] which is composed of nine items assessing four dimensions, giving a total ranging from 9 (less function) to 63 (higher function).

2.2 Statistical analysis

Data were collated and descriptive statistics obtained in Excel. R statistical software (www.r-project.org) was used for analysis. Data are presented as median and interquartile range (IQR) or mean and standard deviation (sd). For comparison of the three treatment groups Kruskal-Wallis test was used. Chi-square or Fisher's exact test were used for categorical variables. ANCOVA (analysis of covariance) was used to check for potential confounding effects on the outcomes across groups. A p-value ≤0.05 was considered statistically significant.

3. RESULTS

Questionnaires were completed by 100 of 106 patients who were approached (94%). These included 34 patients managed by RT alone, 40 managed by TEM alone, and 26 who had composite treatment comprising RT then TEM in eight and TEM then RT in 18 patients. Two patients (2%) had stomas (one in TEM and one in RT group). Most patients fully completed the questionnaire. Some patients missed segments, most commonly the sexual function parts, and occasionally single items were missed. The median time between treatment and questionnaire completion was 10 months, IQR 6-33 months. The groups were similar in terms of age, sex, and follow-up period. Table 1 shows demographic details for each group and summarises all scores.

3.1 Overall quality of life

Both the EQ-5D index and the visual analogue score (VAS) were similar between the groups. The average EQ-5D index was above 0.8 in all groups and the average VAS over 75, indicating fairly good overall quality of life.

3.2 EORTC scores

There were no significant differences in the functional scales (Figures 1) nor in the global health status score and QLQ-C30 summary score.

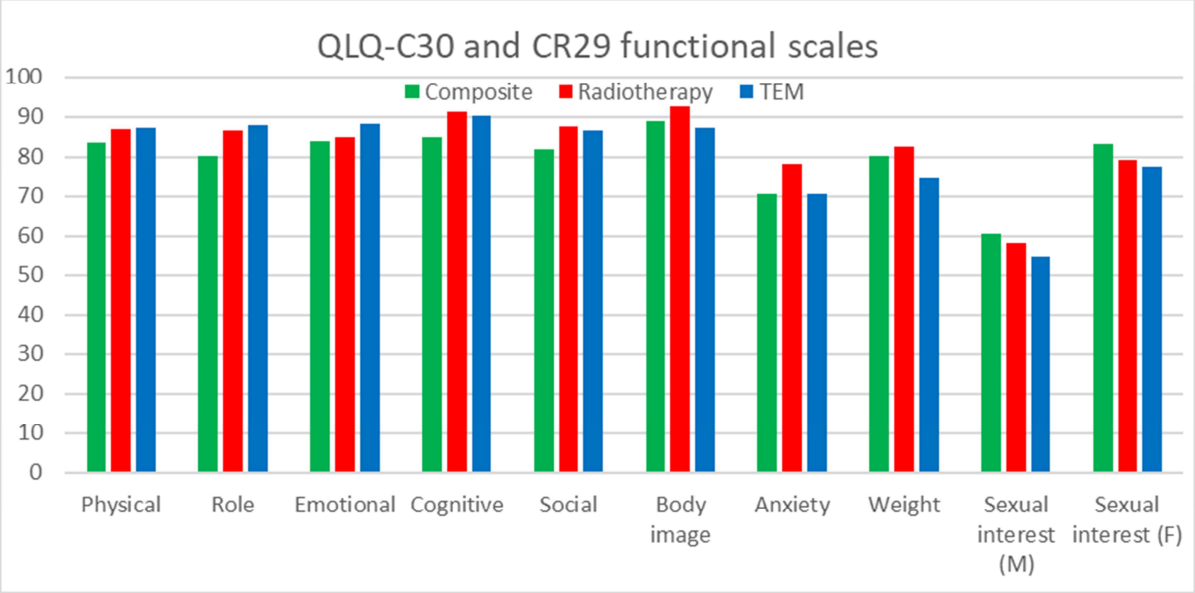

Figure 1: EORTC QLQ-C30 and CR29 functional scales, showing mean score for each treatment group

3.3 Ano-rectal function

The LARS score was significantly different between groups, lowest (better) in the TEM group and highest in the composite group. The mean LARS score for the TEM only group was 17, in the 'no LARS' range (0-20), while for the other groups the median score was in the 'minor LARS' range (21-29). Over 40% (11/26) in the composite group had 'major LARS' (score $\geq$30) compared to a quarter in the TEM (10/39) and RT (8/34) groups. Figure 2 shows the LARS severity for each treatment. The Vaisey score tended to be higher in the composite group, but this was not significant. Figure 3 shows the median LARS and Vaisey score for each treatment group. ANCOVA demonstrated the LARS score increased with age in each group.

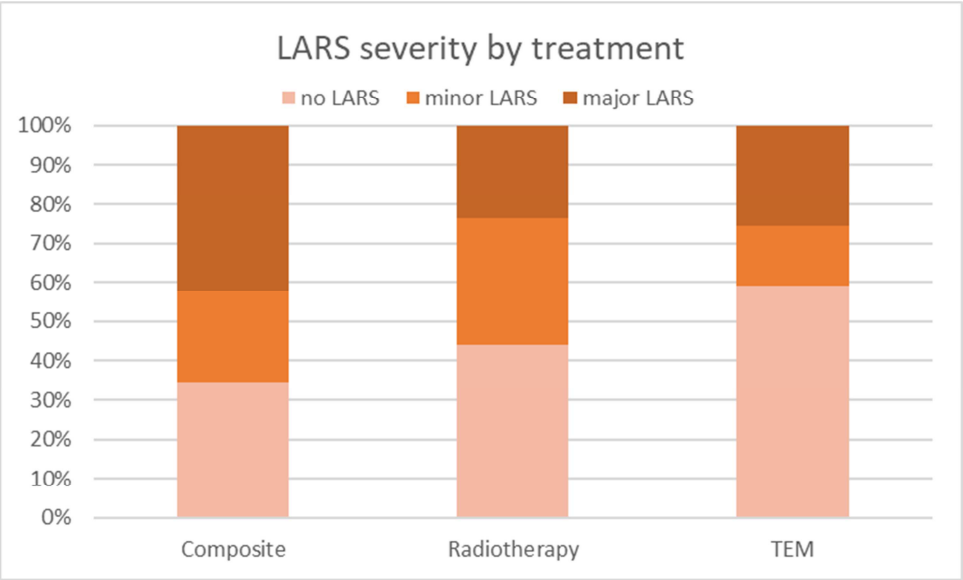

Figure 2: LARS score severity in each treatment group

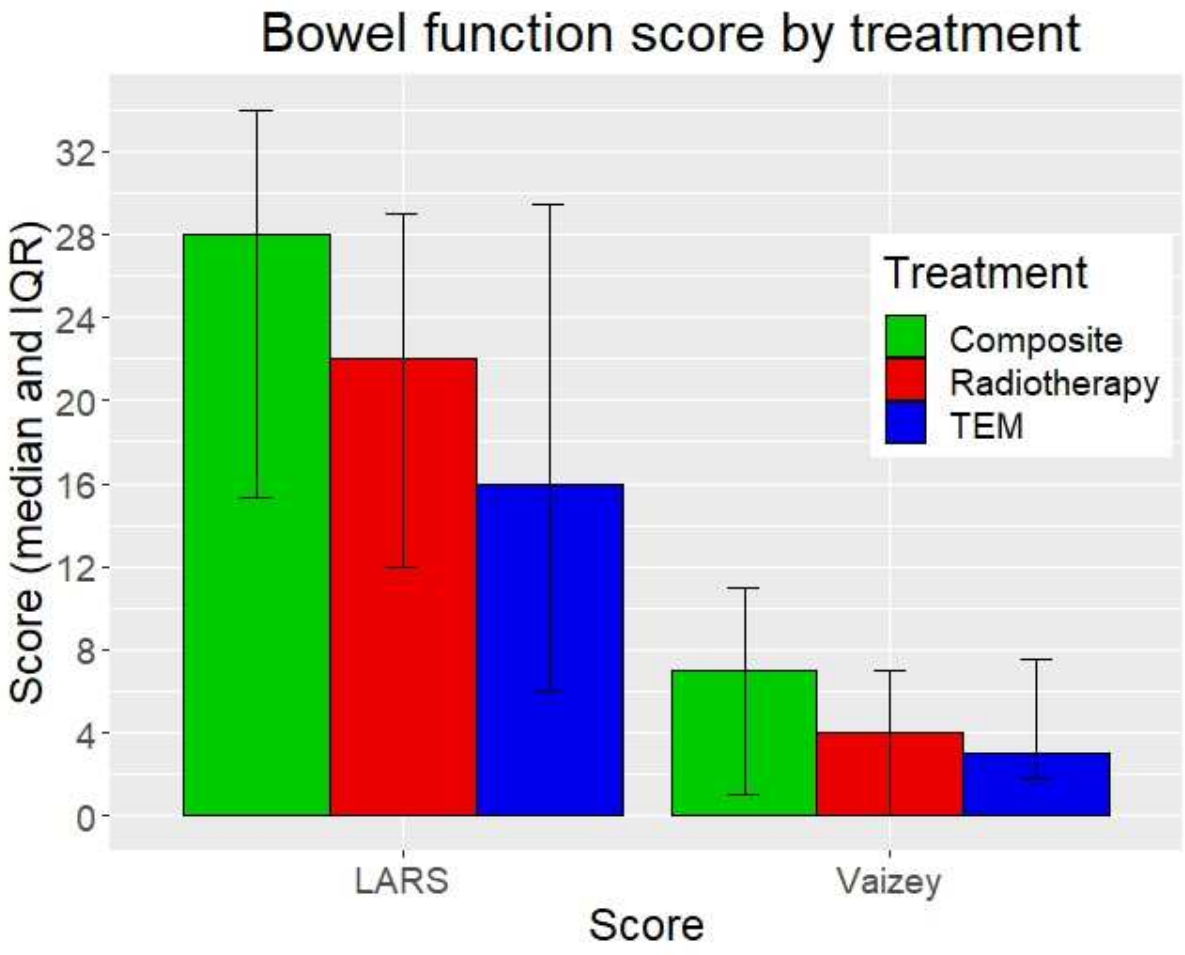

Figure 3: LARS and Vaisey scores by treatment group showing median, error bars indicate interquartile range.

The QLQ-C30 includes symptom scores for constipation and diarrhoea and the QLQ-CR29 includes six bowel-related symptom scores. There were significant differences between groups for blood and mucus in the stool and embarrassment due to bowel function. Figure 4 is a radar chart showing the mean value of the symptom score in each group, indicating higher symptom load in the composite group.

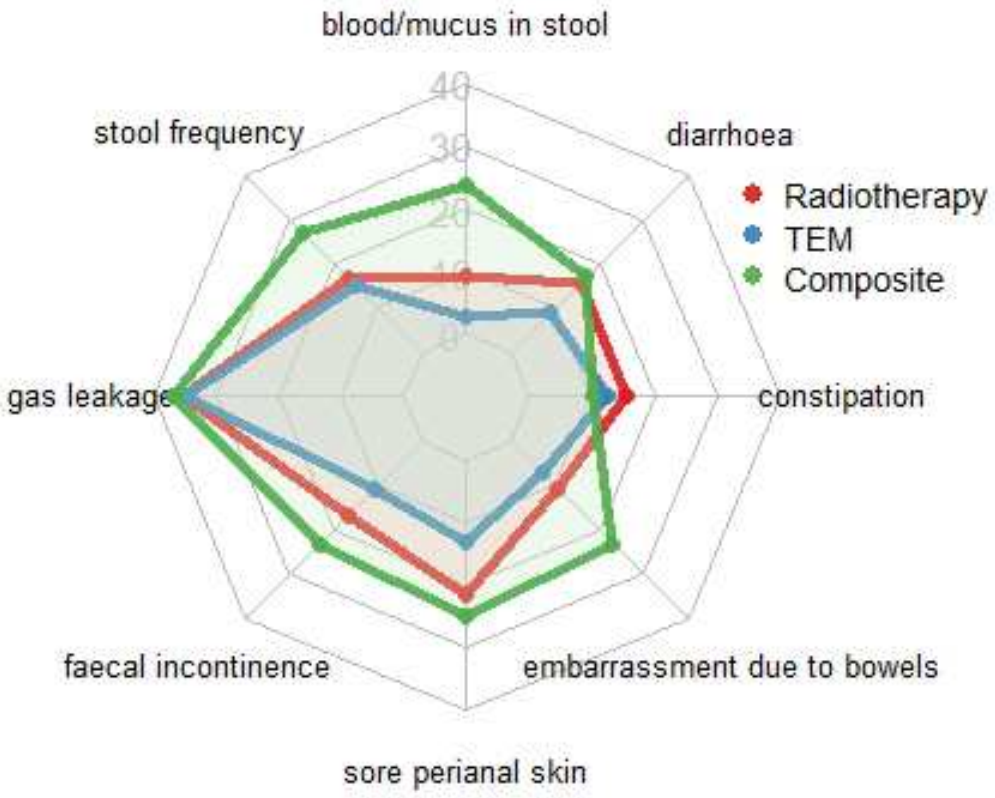

Figure 4: Radar chart showing mean symptom score for eight bowel-related symptoms in the QLQ-C30 and CR29 scales.

3.4 Urinary function

Table 1 shows results for IPSS scores for urinary function and the three QLQ-CR29 urinary-related symptom scores. There were no significant differences between groups; most patients in all groups were mildly symptomatic according to the IPSS score, and were delighted, pleased or mostly satisfied with their quality of life due to urinary symptoms.

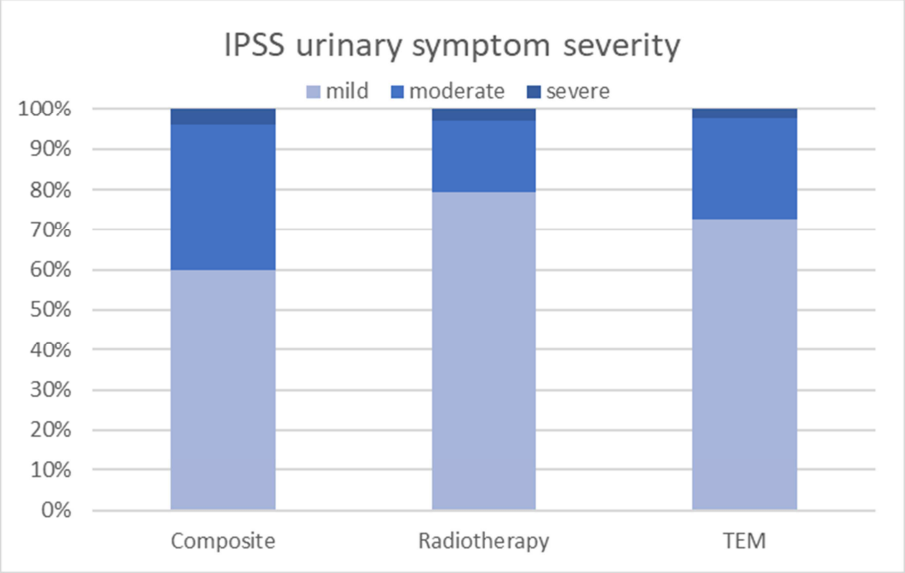

Figure 5: Severity of IPSS urinary symptoms for the treatment groups.

3.5 Sexual function

Only 29% (24/82) of patients indicated that they were sexually active; the median age for these patients was 65, compared with 73 overall, and the rate was higher for men (36%) than women (17%). Although the questionnaire did not ask for further details, many patients volunteered that the reason was age or lack of spouse/ partner. The QLQ-CR29 includes questions on interest in sex, impotence and dyspareunia. Most patients indicated a moderate interest in sex, and this was higher in women than men. There was a moderate level of impotence in all groups, while dyspareunia was rarely reported. There were no significant differences between groups. The IIEF questionnaire was completed by 35 of 64 men (55%) and showed a trend for less severe erectile dysfunction in the TEM group and more severe in the composite group. Only 6 of 36 women (17%) fully completed the MFSQ questionnaire. This showed a moderate level of sexual function, with no difference between groups.

4. DISCUSSION AND CONCLUSIONS

Managing rectal cancer with an organ preserving strategy is gaining traction in specialist rectal cancer practice. There is an obvious role in those who are unfit for radical surgery, but increasingly, patients and clinicians are considering this a viable option in those fit for traditional treatments. Rectal preserving strategies have the advantage of avoiding radical surgery and particularly stoma formation, but there is uncertainty about whether the benefit in quality of life that can be expected from organ preservation persists as the boundaries are stretched by combining local excision and

radiotherapy. This study describes the functional outcome in three streams of patients treated with an organ-preserving strategy and will be valuable in understanding the impact of these treatments on functional outcome and quality of life so as to inform patients and aid healthcare professionals in navigating these difficult treatment decisions. This is a pragmatic study, collecting information from patients at a time when they were generally able and willing to complete a long and detailed questionnaire. We did not collect baseline questionnaires for practical reasons, and because it is known that the presence of a rectal tumour has a negative impact on quality of life. The interval between treatment and data collection was also determined by practical considerations. We aimed to collect snapshot assessments, rather than a series from each patient at fixed times, which would have diminishing returns as response rate is known to drop over time with sequential questionnaires [22].

This study had adequate patients having single treatment with either neoadjuvant RT (34) or TEM 40), but only 18 in the TEM+RT group and just eight in the RT+TEM group, which were combined into a composite group. All patients were disease-free at the time of completing the questionnaire, so although they were undergoing surveillance and living with the inherent uncertainty, they may have experienced the 'rejoice' effect of having overcome cancer, which Nord [23] noted has an important impact on perceived quality of life. Most patients reported a good quality of life, with a mean EQ-5D index of 0.87 and mean VAS score of 80. The figures are a little better than those obtained by Doornebosch [5] in three groups: 31 patients who had TEM, 31 who had TME, and 31 healthy people. Mean EQ-5D in their TEM group a median of 28 months after surgery was 0.81, compared with 0.76 in both TME and 'healthy' groups. The mean EQ-VAS in their TEM group was 76, the same as for the healthy group, and better than 70 for the TME group.

There were few significant differences between groups, indicating that the treatment modalities are equivalent in terms of impact on quality of life, apart from some areas of ano-rectal function. The TEM group reported significantly lower LARS scores compared with the composite group (26% major LARS vs 42%) and fewer symptoms of blood and mucus (mean score 2 vs 18) and embarrassment due to bowel function (mean score 5 vs 17). Although developed for anterior resection patients, the LARS score has found wider application; recent studies in the general population in the Netherlands [24] and Denmark [25] found major LARS is common, reported by 19% of women and 10% of men aged over 50. Our results confirm an increase of LARS score with age regardless of treatment group.

Several studies have used these or similar questionnaires before and after TEM as there was initial concern that the large diameter of the TEM scope may cause sphincter dysfunction. A number of studies showed that ano-rectal function may temporarily deteriorate in the weeks following surgery

but recovers over months to levels comparable with healthy population controls [22,26,27]. Allaix [28] also measured ano-rectal function with manometry. Compared to pre-TEM measures, manometry deteriorated initially but returned to baseline by 12 months. Verseveld [29] looked at TAMIS (transanal minimally invasive surgery), which has gained popularity as a technique for LE, and also found no significant difference in bowel function at six months post-surgery compared to before surgery, while overall quality of life on EQ-VAS improved after treatment.

Comparing neoadjuvant RT with other options, a matched-control study [30] compared RT alone with RT then TME, with 41 patients in each group. Both groups reported defaecation problems and impaired health-related quality of life, but outcomes for the RT alone group were substantially better in several functional domains. The CARTS study [31] assessed QLQ-30 up to three years, and LARS at least four years after treatment in 43 patients who had CRT then either TEM or TME. They noted slightly better outcomes in the TEM group, although 50% (16/32) reported major LARS in the long-term.

Coco [9] compared RT+TEM with TEM alone in a total of 47 patients and found no significant differences in ano-rectal function at one year. Martens [11] assessed the Vaisey score at least three years after treatment in 22 patients having RT alone and 7 with RT+TEM, and found outcomes were good in the RT group and moderate in the RT+TEM group, while 43% of RT+TEM patients reported major incontinence, similar to our findings.

No studies were found that reported functional outcomes for patients having TEM then adjuvant radiotherapy. Of the two composite pathways, the investigators had the impression that RT after TEM has less impact on ano-rectal function than neo-adjuvant RT, but numbers in these groups are too small to reach a conclusion.

Limitations of this study include a relatively small sample size and variable interval between treatment and questionnaire. The groups are not homogenous as certain tumour and patient factors favour certain treatment pathways. Our aim is to understand the functional effects of different treatments rather than compare options for a certain tumour or patient type. The design is necessarily pragmatic to maximise response rate so snapshot assessments were obtained at a convenient time when the patient attended for surveillance rather than a more structured postal approach that would yield a much smaller sample.

Any rectal-preserving strategy commits the patient to a prolonged period of intense surveillance so local recurrence can be promptly detected and treated. This surveillance may itself be a source of anxiety to patients. There is a need for further detailed qualitative studies to address this.

Overall, our study suggests that patients undergoing TEM alone have better ano-rectal function than those having radiotherapy, and composite treatment has an additive effect on bowel function. Significant differences were observed in the LARS score and symptoms of blood and mucus in the stool and embarrassment due to bowels. In all treatment groups, overall quality of life scores were comparable with published reports for healthy controls, so the surveillance regime per se does not appear to have a significant negative impact.

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TABLE

Table 1: Demographic details, Euroqol EQ-5D index and VAS scores, EORTC QLQ-C30 and CR29 scores and scores for ano-rectal, urinary, and sexual function by treatment group, showing mean and standard deviation unless otherwise indicated. Details of scores are found in the Methods section.

	RT alone n=34	TEM alone n=40	Composite n=26	p value
Demographics				
Male n (%)	24 (71%)	21 (53%)	19 (73%)	0.15
Age (median, IQR)	76 (70-80)	74 (67-80)	70 (66-77)	0.17
Time till questionnaire, months (median, IQR)	9 (6-25)	8 (6-30)	19 (8-34)	0.56
EQ overall quality of life measures				
EQ-5D index	0.83 (0.25)	0.87 (0.14)	0.90 (0.15)	0.47
EQ VAS	78 (15)	84 (11)	79 (14)	0.15
EORTC QLQ-30				
Physical functioning	83.7 (21.7)	87.0 (14.7)	87.2 (15.3)	0.94
Role functioning	80.4 (29.7)	86.8 (20.7)	87.8 (18.0)	0.86
Emotional functioning	84.1 (23.0)	85.0 (20.0)	88.1 (16.5)	0.86
Cognitive functioning	84.8 (22.2)	91.5 (12.6)	90.4 (15.0)	0.41
Social functioning	81.9 (26.7)	87.6 (21.5)	86.5 (18.9)	0.66
SYMPTOM SCORES				
Fatigue	20.3 (24.5)	17.4 (19.4)	20.5 (20.0)	0.81
Nausea/ vomiting	7.4 (18.9)	4.3 (17.0)	0.0 (0.0)	0.022*
Pain	14.2 (27.3)	8.1 (16.2)	9.0 (17.8)	0.74
Dyspnoea	10.8 (24.2)	10.3 (19.0)	12.8 (21.2)	0.74
Insomnia	23.5 (34.4)	23.1 (24.4)	21.8 (24.8)	0.81
Appetite loss	12.7 (28.4)	6.8 (20.5)	7.7 (19.6)	0.63
Constipation	11.8 (23.0)	9.4 (21.6)	7.7 (14.3)	0.83
Diarrhoea	11.8 (23.0)	6.8 (17.4)	12.8 (23.2)	0.42
Financial impact	4.9 (18.6)	3.4 (10.2)	2.6 (9.1)	0.94
OVERALL SCORES				
Global health status	79.7 (18.0)	77.1 (19.0)	76.6 (19.9)	0.76
Summary score	84.8 (18.4)	88.6 (13.0)	88.3 (10.6)	0.87
EORTC QLQ-CR29				
Body image	88.9 (20.7)	92.8 (10.5)	87.3 (14.2)	0.36
Anxiety	70.6 (28.1)	78.3 (24.5)	70.5 (25.5)	0.32
Weight	80.4 (30.8)	82.5 (28.2)	74.6 (31.5)	0.56
Sexual interest (Male)	60.6 (28.4) n=22	58.3 (34.0) n=20	54.8 (28.1) n=14	0.26
Sexual interest (Female)	83.3 (25.2) n=8	79.2 (29.5) n=16	77.8 (27.2) n=6	0.15
SYMPTOM SCORES				
Urinary frequency	30.729.4 (22.5)	32.5 (27.2)	33.3 (23.6)	0.76
Urinary incontinence	12.7 (23.2)	10.8 (20.5)	12.8 (19.0)	0.83
Dysuria	0 (0)	4.2 (11.2)	2.6 (9.1)	0.11
Blood/ mucus in stools	6.9 (11.7)	2.1 (6.7)	17.9 (16.9)	0.000008*
Stool frequency	12.6 (13.8)	11.3 (15.2)	20.3 (19.4)	0.16

Flatulence	26.4 (25.8)	26.1 (27.4)	27.5 (25.9)	0.95
Faecal incontinence	12.6 (22.6)	8.1 (16.5)	17.4 (22.2)	0.19
Sore perianal skin†	16.1 (26.2)	9.9 (20.6)	18.8 (24.3)	0.25
Embarrassment due to bowels	8.0 (17.0)	5.4 (12.5)	17.4 (22.2)	0.040*
Abdominal pain	2.9 (12.6)	5.8 (14.9)	1.3 (6.5)	0.23
Buttock pain	5.9 (15.3)	6.7 (15.5)	10.3 (18.3)	0.48
Bloating	7.8 (18.5)	10.8 (20.5)	12.8 (21.2)	0.52
Dry mouth	16.7 (27.5)	13.3 (18.2)	16.7 (25.4)	0.99
Hair loss	4.9 (12.0)	0.8 (5.3)	2.6 (9.1)	0.16
Taste	12.7 (27.2)	2.5 (11.7)	7.7 (21.7)	0.073
Impotence	40.9 (38.4), n=22	42.9 (42.4), n=21	61.9 (36.6), n=14	0.21
Dyspareunia	4.8 (12.6), n=7	4.2 (11.4), n=16	5.6 (13.6), n=6	0.18
Ano-rectal function				
LARS score	20.8 (11.8)	17.1 (12.9)	25.1 (11.2)	0.047*
Vaizey score	4.8 (5.2)	4.8 (4.8)	7.4 (5.9)	0.17
Urinary function				
IPSS score	4.9 (4.1)	5.8 (4.7)	7.4 (5.9)	0.34
IPSS QOL score	1.0 (0.8)	1.6 (1.5)	1.8 (1.4)	0.10
Sexual function: male				
Sexually active?	6/22 (27%)	9/19 (47%)	4/12 (33%)	0.40
IIEF-5 score **Sexually active only**	15.7 (6.5) 19.0 (4.3)	15.2 (8.7) 19.7 (6.5)	13.6 (8.5) 20.7 (4.0)	0.071
Sexual function: female				
Sexually active?	0/9 (0%)	4/15 (27%)	1/5 (20%)	0.24
MFSQ global score	32.0 (n/a), n=1	24.8 (7.1), n=4	28.0 (n/a), n=1	0.19

*Indicates statistical significance i.e. p<0.05, † or peristomal skin for those with stoma

FIGURES LEGENDS

Figure 1: EORTC QLQ-C30 and CR29 functional scales, showing mean score for each treatment group

Figure 2: LARS score severity in each treatment group

Figure 3: LARS and Vaisey scores by treatment group showing median, error bars indicate interquartile range

Figure 4: Radar chart showing mean symptom score for eight bowel-related symptoms in the QLQ-C30 and CR29 scales.

Figure 5: Severity of IPSS urinary symptoms for the treatment groups

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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15 May 2020