The Lancet Regional Health - Western Pacific 6 (2021) 100087

Contents lists available at ScienceDirect

The Lancet Regional Health - Western Pacific

journal homepage: www.elsevier.com/locate/lanwpc

Research paper

Quality of life after sphincter preservation surgery or abdominoperineal resection for low rectal cancer (ASPIRE): A long-term prospective, multicentre, cohort study ☆,☆☆

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ARTICLE INFO

Article history:
Received 23 September 2020
Revised 3 December 2020
Accepted 16 December 2020
Available online 28 December 2020

Keywords:
Quality of life
Rectal cancer
Abdominoperineal resection
Sphincter preservation surgery
Sexual function
Urinary function
Oncological outcome

ABSTRACT

Background: The long-term effects of radical resection on quality of life may influence the treatment selection. The objective of this study was to determine whether abdominoperineal resection has a better effect on the quality of life than sphincter preservation surgery at 3 years after surgery

Methods: This prospective, cohort study included patients who underwent radical resection for low rectal cancer. The primary outcomes were European Organisation for Research and Treatment of Cancer QLQ-C30 and CR38 quality of life scores 3 years after surgery, which were compared with linear generalised estimating equations, after adjustment for baseline values, a time effect, and an interaction effect between time and treatment. The secondary outcomes included sexual-urinary functions and oncological outcomes. The study was registered with ClinicalTrials.gov (NCT01461525).

Findings: Between December 2011 and August 2016, 342 patients were enrolled: 268 (78•4%) underwent sphincter preservation surgery and 74 (21•6%) underwent abdominoperineal resection. The global quality of life scores did not differ between sphincter preservation surgery and abdominoperineal resection groups (adjusted mean difference, 4•2 points on a 100-point scale; 95% confidence interval [CI], −1•3

☆ **Registry URL:** https://clinicaltrials.gov/ct2/show/NCT01461525?term=abdominoperineal+resection&cond=rectal+cancer&draw=2&rank=3
☆☆ **Study Acronym: ASPIRE, A**bdominoperineal resection versus **SP**hincter preservation surgery **I**n low **RE**ctal cancer

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https://doi.org/10.1016/j.lanwpc.2020.100087

to 9•7, $p = 0•1316$). Abdominoperineal resection was associated with a worse body image (9•8 points; 95% CI, 2•9 to 16•6, $p = 0•0052$), micturition symptoms (−8•0 points; 95% CI, -14•1 to −1•8, $p = 0•0108$), male sexual problems (−19•9 points; 95% CI, -33•1 to -6•7, $p = 0•0032$), less confidence in getting and maintaining an erection in males (0•5 points on a 5-point scale; 95% CI, 0•1 to 0•8, $p = 0•0155$), and worse urinary symptoms (−5•4 points on a 35-point scale; 95% CI, −8•0 to −2•7, $p < 0•0001$). The 5-year overall survival was worse with abdominoperineal resection in unadjusted (92•2% vs 80•9%; difference 11•3%, hazard ratio 2•38; 95% CI, 1•27 to 4•46, $p = 0•0052$), but did not differ after adjustment.

Interpretation: In this long-term prospective study, abdominoperineal resection failed to meet the superiority to sphincter preservation surgery in terms of quality of life. Although the global quality of life scores did not differ between groups, this study suggests that sphincter preservation surgery can be an acceptable alternative to abdominoperineal resection for low rectal cancer, offering a better quality of life and sexual-urinary functions, with no increased oncological risk even after 3 years.

Funding: Seoul National University Bundang Hospital, Korea

RESEARCH IN CONTEXT

Evidence before this study

Sphincter preservation and organ integrity restoration have increased in popularity as an alternative to abdominoperineal resection (APR) for low rectal cancer, with the dual goals of optimising the quality of life and curing cancer. However, sphincter preservation surgery (SPS) is not routinely recommended for low rectal cancer because data on the subsequent quality of life (QOL) and its oncological safety are limited. Until recently, no large-scale prospective study has compared QOL after APR or SPS for low rectal cancer, although a permanent stoma after rectal cancer excision is believed to have a detrimental effect on QOL. We searched MEDLINE (via PubMed), the Cochrane Library, and Embase for eligible studies from June 2011 to July 2020. The combinations of keywords and MeSH used were ("Rectal Neoplasms"[MeSH] OR ((rectal OR rectum OR rectums OR Anus OR anal) AND (Tumors OR tumour OR tumour OR tumours OR malignancy OR Neoplasia OR Neoplasm OR cancer OR carcinoma OR adenocarcinoma OR cancers OR malignant OR Neoplasms OR carcinomas OR adenocarcinomas))) AND ((Quality AND life) OR "Quality of Life"[MeSH] OR QOL OR (Patient AND (Preferences OR value))) AND (repair OR Surgery OR Surgical OR Operative OR resection OR (Sphincter AND preservation OR preserve)). Most of the relevant studies concerned rectal cancer rather than low rectal cancer, were retrospective studies or short-term follow-ups or did not consider confounding factors. In a prospective study of patients undergoing treatment for low rectal cancer that only included a few participants ($n = 62$) 1 year after surgery, QOL was similar after APR and SPS. A randomised controlled trial comparing the outcomes of APR and SPS may provide strong support for these surgical strategies for low rectal cancer, but such studies are not feasible because most patients prefer SPS over other methods.

Added value of this study

This is the first prospective cohort study comparing QOL and the sexual-urinary as well as oncological outcomes after SPS or APR for low rectal cancer during a long-term follow-up of 3 years. Previous studies that compared QOL after these two procedures had limited generalisability, primarily due to a lack of prospective cohort studies, the heterogeneity of tumour locations, the lack of preoperative baseline data, short-term follow-ups, or the failure to consider confounding factors. This results of this low rectal cancer study demonstrate that at 3 years after surgery, global QOL scores did not differ between SPS and APR. In addition, APR was associated with a worse body image, micturition symptoms, male sexual problems, less confidence in getting and maintaining an erection in males, and worse urinary symptoms than was SPS. After adjustment for confounding factors, 5-year overall survival did not differ in patients treated for low rectal cancer with SPS or APR.

Implications of all the available evidence

This study supports that restoration of organ integrity with SPS can be an acceptable alternative to APR for low rectal cancer, with no increased oncological risk after 3 years and better QOL and sexual-urinary functions. In our analysis, the global QOL scale scores were similar between APR and SPS after 3 years follow-up, although SPS fared better on the body image, micturition symptoms, and male sexual problems scales. To our knowledge, this is the first large-scale long-term, prospective, multicentre study showing that APR failed to meet the superiority to SPS based on the QOL assessment. Patients with low rectal cancer should receive comprehensive information about the possible impact of radical surgery on their QOL and postoperative functions to allow them to make informed shared decisions.

1. Introduction

Sphincter preservation and the restoration of organ integrity have increased in popularity [1–3] as an alternative to abdominoperineal resection (APR) for low rectal cancer [4], with the dual goals of optimising patient quality of life (QOL) and curing cancer [1]. The current preoperative chemoradiotherapy for rectal cancer increases the stoma-free rate [5], improves therapeutic compliance, and reduces local recurrence [6]. However, sphincter preservation surgery (SPS) is not routinely recommended for low rectal cancer owing to limited QOL and oncological safety evidence. Furthermore, up to 80% of patients who undergo SPS experience low anterior resection syndrome (LARS), with symptoms ranging from changes in bowel frequency to faecal incontinence [7,8], and 19% of patients require a permanent stoma [9].

Until recently, no large-scale prospective study has compared QOL after APR or SPS for low rectal cancer, although a permanent stoma following rectal cancer excision is believed to have a detrimental effect on QOL [10,11]. A prospective study of 62 patients 1 year after surgical treatment for low rectal cancer showed that QOL was similar after APR and SPS [12]. However, previous studies that compared QOL after these two procedures had limited generalisability, primarily due to a lack of prospective cohort studies, the heterogeneity of tumour locations, the lack of preopera-

tive baseline data, short-term follow-ups, or the failure to consider confounding factors [10–14]. A randomised controlled trial comparing the outcomes of APR and SPS should provide strong support for these surgical strategies for low rectal cancer, but such studies are not feasible because most patients prefer SPS to other methods. A prospective observational study may be sufficient if a randomised controlled trial comparing the outcomes of APR and SPS is unethical or impractical. Incorporating high-quality methodologies, including blinding for assessment, an intention-to-treat (ITT) analysis, and complete follow-up, as used in randomised controlled trials, can improve the quality of observational studies. In this context, the ASPIRE prospective cohort study was designed to compare QOL, including sexual-urinary functions and oncological outcomes, between APR and SPS for low rectal cancer. The objective of the study was to test the hypothesis whether APR has a better effect on QOL than SPS at 3 years after surgery, based on a previous study in which APR provided better QOL in long-term survivors [13].

2. Methods

ASPIRE was a prospective, non-randomised study approved by the Institutional Review Boards of six clinical recruiting sites (Seoul National University Bundang Hospital, B-1105/127-010; National Cancer Centre, NCCTS-11-577; Seoul National University Hospital, H-1108-066-373; Hallym University Hospital, 2012-i048; Seoul Metropolitan Government Seoul National University Boramae Medical Centre, 06-2012-121; Daehang Hospital, DH12-0007), which are listed together with the study protocol and the statistical analysis plan in Supplement 1. All study-related information was stored securely at each site to protect the participants' privacy and leakage of information. All laboratory specimens, reports, data collection, process, and administrative forms were identified using the identification number to maintain confidentiality. All records contained names or other personal identifiers, such as locator forms and informed consent forms, were stored separately from the study records identified with a code number. All local databases were secured using password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant identification numbers to other identifying information were stored in a separate, locked file in an area with limited access. The study was registered at ClinicalTrials.gov (NCT01461525). This study enrolled participants for over 5 years between December 6, 2011, and August 12, 2016, to meet the sample requirements, with a follow-up period of 3 years. All participants signed informed consent forms. Patients aged 20–80 years with low rectal adenocarcinoma with an inferior margin $\leq$5 cm from the anal verge, determined with a digital rectal examination or rigid proctoscopy, were eligible if they required radical resection, with no restriction on whether preoperative chemoradiotherapy was necessary. The inclusion criterion was the availability of abdominal, pelvic, and chest computed tomography (CT) scans and anorectal magnetic resonance imaging (MRI) for American Joint Committee on Cancer staging [15]. The exclusion criteria included metastatic lesions and prostate or bladder invasion requiring extended total mesorectal excision (TME).

2.1. Outcomes

The primary outcomes were QOL scores measured 3 years after surgery using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30 (QLQ-C30) and EORTC QLQ-CR38. These scores were compared using linear generalised estimating equations (GEEs), adjusted for baseline values, a time effect, and an interaction effect between time and treatment. The working covariance matrix was set as an independent structure. The secondary outcomes were sexual-urinary functions at 3 years after surgery, measured with the International Index of Erectile Function 5 (IIEF-5), the Female Sexual Function Index (FSFI), and the International Prostate Symptom Score (IPSS), and oncological outcomes, including the disease-free survival, relapse-free survival, and overall survival rates [16]. The survival status of all eligible patients was confirmed based on the status of each patient's resident registration number with Statistics Korea (*KOSTAT, mdis.kostat.go.kr*). In QLQ-C30 and QLQ-CR38, the global QOL status, function, and symptom scale scores are reported on scales ranging from 0 to 100. The IIEF-5 score ranges from 5 to 25, the FSFI score ranges from 2 to 36, and the IPSS score ranges from 0 to 35. Higher scores indicate better function on function scales and more-severe symptoms on symptom scales. Morbidity and 30-day mortality were also monitored.

2.2. Interventions

All surgical procedures were performed by surgeons experienced in open and laparoscopic or robotic TME for low rectal cancer. Only surgeons who had previously performed $\geq$50 radical proctectomies for rectal cancer, including $\geq$20 cases each of APR and SPS, were invited to participate. The Seoul Colorectal Research Group (SECOG), including the surgeons participating in this study, attended biweekly online teleconferences and monthly face-to-face meetings. In all patients, the decision to perform preoperative chemoradiotherapy was based on local policies. Patients with T3, T4, or positive nodes without distant metastasis received preoperative chemoradiotherapy, as in our previous study [17], as did those with T2 low rectal cancer scheduled to undergo sphincter preservation [5]. Short-course radiotherapy was permitted at the discretion of the multi-department team [18].

The surgical treatment was selected with an informed shared decision after the patient was given sufficient information about APR or SPS to reduce any potential bias or preference risk for the surgical method. During an interview, the treatment protocol, risks, benefits, and long-term outcomes associated with APR and SPS were described to the patients and their families. APR was strongly recommended for participants in whom margin-negative resection would result in the loss of anal sphincter function and incontinence, or if the tumour directly involved the anal sphincter or the levator ani muscles, as indicated by MRI or a digital rectal examination [1], even if the patient had a strong preference for avoiding a stoma, and was willing to accept a higher oncological risk to undergo SPS. SPS involved TME with the preservation of the autonomic nerves [19,20]. Intersphincteric dissection through a perineal approach was performed selectively to provide an adequate distal margin [2]. Protective loop ileostomy was recommended for all patients undergoing SPS. Intestinal continuity was re-established after postoperative adjuvant therapy was completed or at 3 months. APR was performed with similar preservation of the autonomic nerves as achieved with SPS. Extralevator APR was permitted [21].

The pathological examination included an assessment of the involvement of the circumferential resection margin or the distal and proximal margins of the tumour. The patients were followed-up every 3 or 6 months for 2 years and then every 6 months for up to 5 years. The follow-ups included a physical examination and laboratory tests; abdominal, pelvic, and chest CT every 6 months; and colonoscopy 1 year after surgery and every 2 years thereafter.

2.3. Statistical analysis

The sample size was estimated by taking the mean difference in the global QOL of QLQ-C30 (10 points) as the thresh-

old for a clinically relevant difference between the two groups, with a standard deviation of 25, based on the recommendations of a previous study [22]. The patients were predicted to undergo APR or SPS in a ratio of 1:3 based on the rate of APR for rectal cancer reported in a previous study [3]. Assuming a statistical power of 80% and a two-sided type I error rate of 0•05, 66 patients were required to undergo APR. With an expected dropout rate of 10%, the target sample size was 294, including 74 patients undergoing APR and 220 patients undergoing SPS. Enrolment was continued until the sample requirements were met.

Statistical analyses were performed with an observational analogue (OA) of ITT, including SPS or APR with colostomy at the initial surgery, and the OA of per-protocol population, excluding patients who were converted to permanent stoma in the SPS group, as used in a previous study [23]. The baseline characteristics were compared with the χ^2 test or Fisher's exact test for categorical variables or with Student's *t*-test for continuous variables. The QOL and functional scales, as primary and secondary outcomes, respectively, were compared with linear GEE models, adjusted for baseline values, a time effect, and an interaction effect between time and treatment. In the multivariable GEE analysis, the potential covariates included age, sex, body mass index, tumour size, operation time, preoperative chemoradiotherapy, morbidity, approach method, and pathological stage [1,6,9–14,17–20,24,25]. The QOL and functional scales in both groups and the two-sided 95% CI of the differences were calculated. To determine the robustness of the findings of the primary analysis, additional full OA-ITT analyses were conducted with multiple imputed outcomes [26], and sensitivity analyses were performed after excluding deceased patients, apart from those included in the primary analysis. The clustering effect at surgeon-level was quantified through the intraclass correlation coefficient (ICC). To address important differences in the potential confounders between the two groups, we estimated the propensity score, which is the probability of treatment group assignment. The propensity score model included pre-treatment variables: age, sex, body mass index, tumour distance from the anal verge, preoperative chemoradiotherapy, and initial clinical stage. At most, three patients in the SPS group were matched to each patient in the APR group based on the nearest propensity score with a caliper width of 0•2. The standardised mean differences were calculated to assess the comparability of the treatment groups. Prespecified subgroup analyses were conducted in patients with very low rectal cancer, defined as ≤3 cm from the anal verge. There was no allowance for multiplicity.

The probabilities of survival were estimated with the Kaplan-Meier technique, and compared with log-rank tests. A multivariable Cox regression hazard model was used to identify the factors that were independently associated with survival. All statistical tests were two-sided, and values of $p < 0•05$ were considered statistically significant. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC, USA) or Stata version 15.0 (StataCorp LLC, College Station, TX, USA).

2.4. Role of the funding source

This work was supported by a grant from Seoul National University Bundang Hospital (Grant no. 03-2011-001). The funders were not involved in study design, data collection, data analysis, interpretation, writing of the report, the preparation, review, approval of the manuscript, or in the decision to submit the manuscript for publication. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit the paper.

3. Results

3.1. Study population

Between December 2011 and August 2016, 1043 patients with low rectal cancer were assessed for eligibility, and 701 patients were excluded: 504 did not meet the eligibility criteria due to the following reasons: age below 20 years ($n = 13$) or more than 80 years ($n = 77$); metastasis ($n = 121$); invasion of prostate ($n = 32$), bladder ($n = 24$), vagina ($n = 37$), and uterus ($n = 5$); local excision after concurrent chemoradiotherapy ($n = 152$); and emergency operation ($n = 43$). Additionally, 197 patients refused to participate (Fig. 1).

The participation rate for patients within the inclusion criteria was 63.5% (342/539). A total of 342 patients (mean [standard deviation] age 59•4 [11•0] years) were enrolled, 268 (78•4%) of whom underwent SPS and 74 (21•6%) underwent APR. Of these 268 SPS patients, 22 were converted to permanent stoma: APR ($n = 11$), due to anastomosis leakage ($n = 3$), pelvic abscess formation ($n = 1$), faecal incontinence ($n = 1$), persistent fistula formation ($n = 2$) or local recurrence ($n = 4$); T-colostomy ($n = 9$) due to anastomosis leakage ($n = 3$) and pelvic abscess formation ($n = 1$), faecal incontinence ($n = 2$) or fistula formation ($n = 3$); and Hartmann procedure ($n = 2$) due to anastomosis leakage ($n = 1$) or persistent fistula formation ($n = 1$). From the remaining 261 SPS patients in whom a protective ileostomy was created, stoma repair was not performed in eight patients due to the following reasons: died ($n = 2$), failed to follow-up ($n = 2$), suffered metastases ($n = 3$), experienced reduced anal sphincter function ($n = 1$). In the end, 30 patients (11.2%) in the SPS group had a permanent stoma. The baseline characteristics are shown in Table 1 and in Appendix p 2. Age, sex, body mass index, and the rate of preoperative chemoradiotherapy were similar in both groups. The tumours were closer to the anal verge in the APR group. The tumours were larger, and the pathological T classification was more advanced in the APR group. There were more postoperative complications in the APR group than in the SPS group, particularly pelvic abscess, wound problems, and acute voiding difficulty (Table 2). There were no deaths within 30 days of surgery.

Overall, 100% of patients at baseline, 90% at 1 year, 82% at 2 years, and 78% at 3 years completed the questionnaires (Appendix p 3). The response rates for each scale were similar in both groups.

3.2. Primary outcomes

In the OA-ITT analysis, the global QOL scores in QLQ-C30 at 3 years did not differ between the SPS and APR groups in the multivariable GEE analysis (adjusted mean difference 4•2 points on a 100-point scale; 95% CI, −1•3 to 9•7, $p = 0•1316$) (Table 3 and Appendix p 4). Only the diarrhoea score was better in the APR group than in the SPS group (7•8 points; 95% CI, 2•2 to 13•5, $p = 0•0067$). On QLQ-CR38, body image (9•8 points; 95% CI, 2•9 to 16•6, $p = 0•0052$), micturition symptoms (−8•0 points; 95% CI, −14•1 to −1•8, $p = 0•0108$), and male sexual problems (−19•9; 95% CI, −33•1 to −6•7, $p = 0•0032$) were better in the SPS group than in the APR group (Table 4). The QLQ-C30 and QLQ-CR38 scores showed similar patterns in the analyses with imputed outcomes using the multiple imputation method (Appendix p 5) and in the sensitivity analysis after deceased patients were excluded (Appendix p 6). The level-3 ICC of EORTC C30 and CR38 scores among surgeons ranged from less than 0•001 for sexual function to 0•223 for fatigue (Appendix p7).

After the propensity score was estimated, a total of 131 patients were matched. In the propensity-score-matched analysis, body image and micturition problems still showed patterns similar to those in the OA-ITT analysis (Appendix p 8).

Table 1
Baseline characteristics of the intention-to-treat population.

	SPS (n = 268)*	APR (n = 74)
Age, years, median (IQR)	59•0 (52•0–68•0)	61•5 (53•0–68•0)
Sex		
Male	174 (65%)	56 (76%)
Female	94 (35%)	18 (24%)
body mass index, (kg/m^2)	24•1 (22•3–26•0)	22•3 (19•9–26•7)
enrollment according to centers		
Seoul National University Bundang Hospital	140 (52%)	27 (37%)
Seoul National University Hospital	58 (22%)	38 (51%)
National Cancer Center, Korea	48 (18%)	3 (4%)
Hallym University Hospital	10 (4%)	••
Daehang Hospital	7 (3%)	3 (4%)
Boramae Medical Center	5 (2%)	3 (4%)
EORTC QLQ-C30 scores at baseline†		
Global QOL	64•2 (21•6)	48•5 (22•7)
Functional scales		
Physical functioning	86•6 (15•1)	79•1 (19•2)
Role functioning	88•0 (17•8)	78•6 (27•0)
Emotional functioning	79•3 (20•7)	69•0 (23•9)
Social functioning	73•9 (25•9)	65•5 (28•5)
Cognitive functioning	86•5 (15•7)	84•0 (17•1)
Symptom scales		
Pain	10•8 (18•8)	23•4 (28•3)
Fatigue	21•5 (19•3)	31•5 (24•1)
Nausea and vomiting	3•6 (8•7)	1•8 (5•9)
Appetite loss	10•2 (21•1)	18•9 (25•3)
Constipation	11•5 (24•1)	18•5 (27•1)
Diarrhoea	13•3 (21•3)	17•6 (26•6)
Dyspnoea	7•4 (16•1)	10•4 (20•6)
Insomnia	16•3 (24•4)	25•7 (29•0)
Financial difficulties	27•4 (28•9)	35•1 (30•2)
EORTC QLQ-CR38 scores at baseline†		
Function scales		
Body image	79•3 (20•2)	65•6 (27•6)
Sexual functioning	18•4 (23•9)	16•2 (22•1)
Future perspective	55•3 (27•7)	39•6 (26•9)
Sexual enjoyment	29•9 (28•0)	22•8 (26•3)
Symptom scales		
Micturition problem	17•6 (17•4)	26•7 (22•1)
Chemotherapy side-effects	12•7 (15•4)	18•8 (18•6)
GI symptoms	13•2 (14•8)	20•2 (19•6)
Male sexual problems	25•6 (27•6)	38•6 (31•2)
Female sexual problems	21•3 (23•4)	18•8 (24•3)
Weight loss	12•2 (22•4)	19•8 (27•5)
Tumour distance from anal verge (cm)‡	4•0 (3•0–5•0)	1•5 (0•0–2•5)
Preoperative chemoradiotherapy§		
No	75 (28%)	23 (31%)
Yes	193 (72%)	51 (69%)
Preoperative faecal incontinence		
No	199 (74%)	33 (45%)
Yes	67 (25%)	40 (54%)
Missing value	2 (1%)	1 (1%)
Initial clinical T stage		
1	6 (2%)	3 (4%)
2	41 (15%)	5 (7%)
3	206 (77%)	57 (77%)
4a	8 (3%)	5 (7%)
4b	7 (3%)	4 (5%)
Initial clinical stage (cTNM)		
1	27 (10%)	7 (10%)
2	63 (24%)	24 (32%)
3	178 (66%)	43 (58%)
Restaging after preoperative chemoradiotherapy (ycTNM)‖		
0	5 (2%)	2 (4%)
1	46 (25%)	12 (24%)
2	49 (27%)	17 (35%)
3	85 (46%)	18 (37%)
Operative time (min)	235 (178–300)	210 (165–250)
Approach method¶		
Open surgery	50 (19%)	24 (32%)
Minimally invasive surgery	218 (81%)	50 (68%)
Laparoscopy	190 (71%)	47 (64%)
Open conversion	5 (2%)	3 (4%)
Robotic	23 (8%)	••

(*continued on next page*)

Table 1 (*continued*)

	SPS (n = 268)*	APR (n = 74)
Tumour size (cm)**	2•5 (1•6–3•6)	3•0 (2•4–4•5)
Pathologic T classification		
0, Tis	35 (13%)	4 (5%)
1	32 (12%)	7 (9%)
2	92 (34%)	22 (30%)
3	108 (40%)	39 (53%)
4	1 (1%)	2 (3%)
Pathologic N classification		
0	187 (70%)	52 (70%)
1	60 (22%)	18 (25%)
2	21 (8%)	4 (5%)
Distal resection margin (cm)**	1•0 (0•5–1•5)	4•0 (2•2–5•0)
Radial resection margin (mm)**	7•0 (4•0–12•0)	5•0 (2•0–10•0)
Circumferential resection margin		
Negative (> 1 mm)	211 (79%)	55 (74%)
Positive (≤ 1 mm)	19 (7%)	9 (12%)
Missing value	38 (14%)	10 (14%)
Time to pass first flatus (days)	2•0 (1•0–2•0)	3•0 (2•0–3•0)
Postoperative hospital stay (days)	8•0 (6•0–10•0)	8•0 (7•0–11•0)
Postoperative adjuvant chemotherapy		
No	73 (27%)	22 (28%)
Yes	195 (73%)	52 (72%)

Values are medians (interquartile ranges) or numbers (%). APR=abdominoperineal resection; SPS=sphincter preservation surgery.

* Ileostomies were created in 261 patients (97•4%) at the time of SPS.

† Values are mean (standard deviation). The EORTC QLQ-C30 and CR38 scores are reported on a scale ranging from 0 to 100. Higher scores indicate better function on function scales and more-severe symptoms on symptom scales.

‡ Defined as the distance between the lower border of the tumour and the anal verge, determined with digital rectal examination or proctoscopy.

§ Short-course radiotherapy was administered to four patients in the SPS group and one patient in the APR group.

‖ MRI data were missing at restaging after chemoradiotherapy for eight patients in the SPS group and two patients in the APR group.

¶ Intersphincteric dissection through a perineal approach was performed in 123 patients (45•9%) in the SPS group and extralevator APR was not performed.

** Tumour size, distal resection margin, or radial resection margin were not determined in 28 patients in the SPS group and four patients in the APR group with pathological complete remission.

Table 2
Perioperative complications and events within postoperative 30th days.

	SPS (n = 268)	APR (n = 74)	Difference (95% CI)*
Perioperative complications within 30 days, total	71 (26%)	29 (39%)	−13% (−26% – 0%)
Anastomotic leakage	15 (6%) †	••	
Pelvic abscess	2 (1%)	5 (7%)	−6% (−15% – −1%)
Ileus	35 (13%)	10 (14%)	0% (−11% – 8%)
Wound problem	8 (3%)	10 (14%)	−11% (−21% – −3%)
Acute voiding difficulty	11 (4%)	8 (11%)	−7% (−17% – 0%)
Bleeding	1 (<1%)	1 (1%)	−1% (−8% – 1%)
Deep vein thrombosis	2 (1%)	••	
Pulmonary problem	3 (1%)	1 (1%)	0% (−7% – 2%)
Others	6 (2%)‡	4 (5%)§	−3% (−12% – 1%)
Reoperation			
No	254 (95%)	70 (9%)	0% (−5% – 9%)
Yes	14 (5%)‖	4 (5%)¶	0% (−9% – 5%)
Readmission	32 (12%)**	12 (16%)††	−4% (−16% – 4%)
30-day mortality	••	••	0% (−6% – 2%)

Values are numbers (%). APR=abdominoperineal resection; SPS=sphincter preservation surgery; CI=confidence interval.

* The CI was estimated from Wilson CI.

† included the anastomotic leakage occurred within 30th days postoperatively (n = 7), and silent leakage within 30 days postoperatively but delayed anastomotic problem such as pelvic abscess or persistent fistula (n = 8).

‡ Bowel ischaemia (n = 1), ileal perforation (n = 1), parastomal hernia (n = 1), perianal abscess (n = 1), phlebitis (n = 1), rectovaginal fistula (n = 1).

§ Lymphocele (n = 1), pelvic inflammatory disease (n = 1), phlebitis (n = 1), rectourethral fistula (n = 1).

‖ Prolonged ileus (n = 1), anastomotic leakage (n = 7), rectovaginal fistula (n = 1), ileal perforation (n = 1), voiding difficulty (n = 1), wound problem (n = 3).

¶ Prolonged ileus (n = 2), wound problem (n = 2).

** Adhesive ileus (n = 17), anastomotic leakage (n = 3), hematoma (n = 1), parastomal hernia (n = 1), rectovaginal fistula (n = 1), voiding difficulty (n = 2), wound problem (n = 7).

†† Adhesive ileus (n = 5), pelvic inflammatory disease (n = 1), rectourethral fistula (n = 1), voiding difficulty (n = 1), wound problem (n = 4).

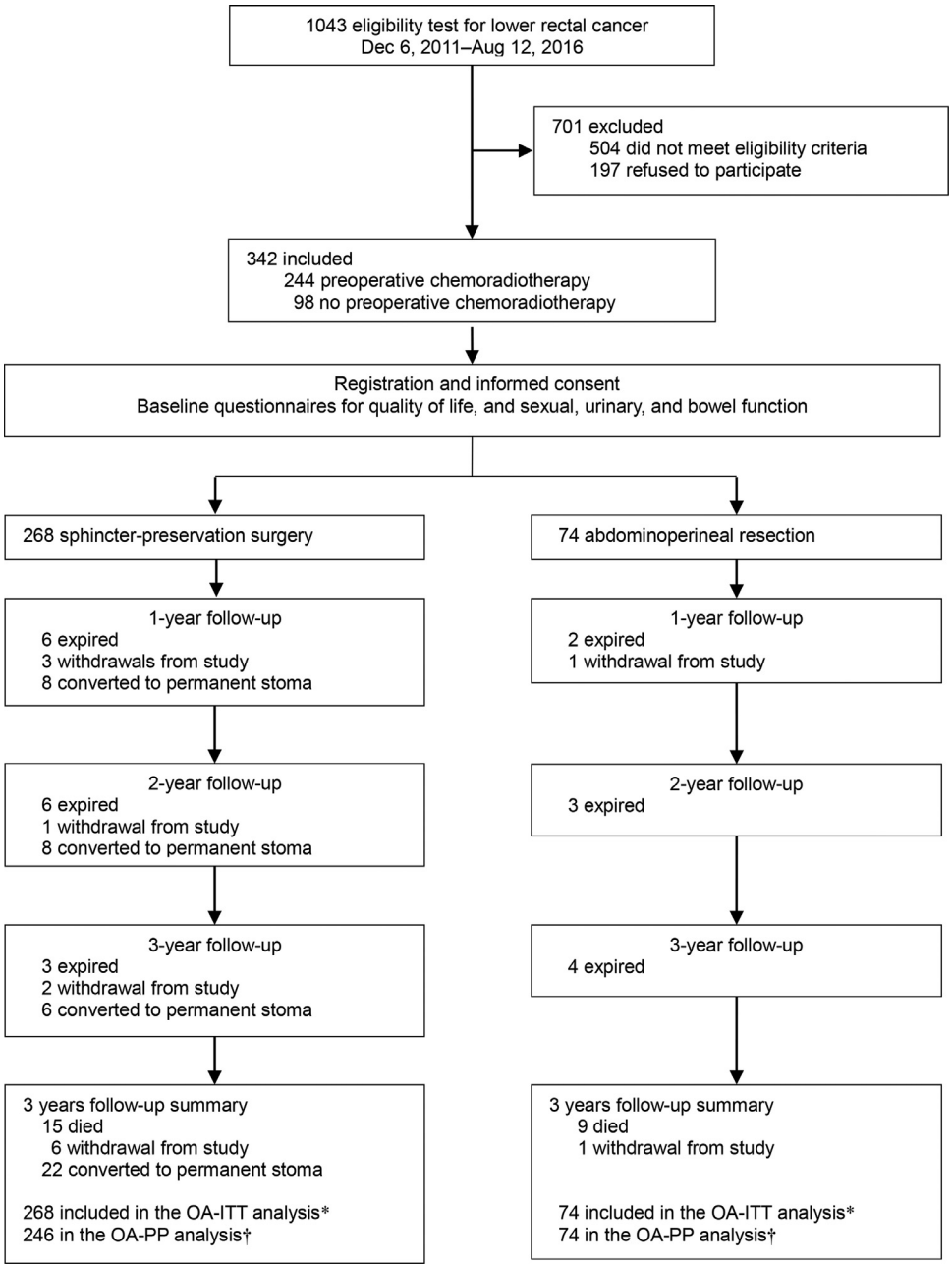

Fig. 1. Flow of participants in the ASPIRE study.
*All participants enroled for treatment. The intention-to-treat population was the primary analysis set for all primary and secondary efficacy endpoints. †Patients who completed the study without any major protocol violations, including conversion to permanent stoma in the sphincter preservation surgery group. OA-ITT= observational analogues of intention-to-treat; OA-PP= observational analogues of per protocol.

3.3. Secondary outcomes

The IIEF-5 and FSFI scores did not differ between the SPS and APR groups, except for the confidence to get and maintain an erection (questionnaire item 1), which was better in the SPS group (adjusted mean score difference, 0•5 points on a 5-point scale; 95% CI, 0•1 to 0•8, $p = 0•0155$) (Fig. 2; Appendix p 9). The urinary function was better in the SPS group on all scales, except for nocturia, which was similar in both groups. The total IPSS score at 3 years was better in the SPS group than in the APR group (−5•4 on a 35-point scale; 95% CI, −8•0 to −2•7, $p < 0•0001$).

At final database lock on September 4, 2019, 42 patients had died (26 in the SPS group and 16 in the APR group). Over a median follow-up period of 63•9 months (interquartile range, 49•2–76•8 months), the rates of systemic and local recurrence did not differ between the two groups (Appendix p 11). In unadjusted analysis, the estimated 3-year disease-free survival and 3-year relapse-free survival rates were not significantly different between SPS and APR, but the 3- and 5-year overall survival rates were greater with SPS (3 years: 94•4% [95% CI, 91•7%–97•1%] and 89•2% [95% CI, 82•1%–96•3%]; 5 years: 92•2% [95% CI, 88•9%–95•5%] and 80•9% [95% CI, 71•4%–90•4%], respectively; log-rank $p = 0•0052$) (Fig. 3). Overall survival in patients with stage 0–1 low rectal cancer was similar in both groups, but overall survival in patients with stage 2–3 low rectal cancer was significantly different. There were no differences between APR and SPS in the survival outcomes in the Cox regression models adjusted for the pre-specified covariates (Appendix p 12).

Table 3
EORTC QLQ-C30 scores over 3 years according to treatment group.

	1 year SPS Mean (SD)	APR Mean (SD)	2 years SPS Mean (SD)	APR Mean (SD)	3 years SPS Mean (SD)	APR Mean (SD)	Difference (SPS-APR) at 3 years Multivariable GEE* Mean (95% CI)	p value
Global QOL	62·0 (19·2)	58·7 (19·6)	65·5 (18·1)	60·6 (19·6)	64·2 (18·0)	57·7 (17·4)	4·2 (−1·3 to 9·7)	0·1316
Functional scales								
Physical functioning	91·1 (11·8)	84·2 (14·5)	90·9 (12·5)	84·1 (15·0)	90·2 (14·0)	83·7 (18·3)	3·8 (−1·6 to 9·2)	0·1707
Role functioning	88·0 (19·9)	79·0 (23·4)	86·8 (19·3)	79·5 (24·6)	85·9 (19·7)	79·3 (23·3)	2·8 (−3·9 to 9·6)	0·4148
Emotional functioning	80·8 (19·9)	77·7 (18·7)	81·8 (18·0)	77·1 (27·0)	79·3 (19·5)	75·5 (21·8)	2·4 (−3·7 to 8·5)	0·4348
Social functioning	76·7 (22·8)	72·7 (23·5)	78·0 (21·4)	71·5 (26·9)	77·4 (22·6)	72·2 (25·5)	2·2 (−5·1 to 9·4)	0·5563
Cognitive functioning	85·5 (16·2)	85·4 (15·1)	84·3 (16·3)	82·4 (16·0)	82·5 (19·4)	79·3 (18·0)	1·2 (−3·9 to 6·3)	0·6539
Symptom scales								
Pain	11·8 (18·2)	9·6 (14·3)	9·9 (17·7)	9·3 (16·3)	8·3 (17·6)	10·8 (17·2)	−0·2 (−5·7 to 5·3)	0·9489
Fatigue	18·6 (17·7)	21·4 (16·7)	16·3 (16·5)	19·9 (16·2)	15·6 (16·0)	21·0 (20·7)	−3·5 (−9·5 to 2·5)	0·2547
Nausea and vomiting	3·1 (8·9)	3·8 (11·3)	1·6 (5·6)	3·5 (8·3)	2·7 (9·9)	5·3 (17·4)	−2·7 (−7·8 to 2·4)	0·3051
Appetite loss	7·2 (16·5)	6·6 (14·6)	5·0 (13·4)	8·3 (18·5)	3·4 (11·6)	7·4 (17·9)	−1·6 (−7·0 to 3·8)	0·5607
Constipation	8·4 (20·3)	7·1 (18·0)	12·3 (20·9)	3·9 (10·8)	11·1 (19·8)	10·5 (22·3)	2·1 (−4·6 to 8·9)	0·5340
Diarrhoea	18·7 (27·0)	9·1 (16·1)	17·5 (23·1)	13·5 (23·1)	16·8 (22·6)	11·7 (17·3)	7·8 (2·2 to 13·5)	0·0067
Dyspnoea	6·3 (14·8)	10·1 (20·2)	5·4 (13·1)	10·3 (18·1)	5·1 (13·7)	9·9 (19·0)	−3·0 (−8·7 to 2·7)	0·2995
Insomnia	18·2 (25·8)	15·2 (19·6)	21·4 (26·0)	21·2 (26·4)	15·9 (23·2)	22·8 (25·8)	−3·8 (−11·8 to 4·1)	0·3466
Financial difficulties	23·8 (25·2)	27·8 (27·8)	20·2 (21·3)	27·6 (27·0)	22·3 (24·5)	28·4 (26·2)	−3·9 (−11·6 to 3·8)	0·3223

APR=abdominoperineal resection; CI=confidence interval; GEE=generalized estimating equation; QOL=quality of life; SD=standard deviation; SPS=sphincter preservation surgery. The EORTC QLQ-C30 scores are reported on a scale ranging from 0 to 100. Higher scores indicate better function on function scales and more-severe symptoms on symptom scales.

* Multivariable regression models with linear generalized estimating equations were used to compare the mean scores of the two groups at each time point. Predictive margins were estimated from the multivariable model, which included an interaction term for treatment and time, with adjustment for baseline age, sex, body mass index, tumour size, operative time, pre-operative chemoradiotherapy, morbidity, approach method, and pathological stage [1,6,9–14,17–20,24,25].

Table 4
EORTC QLQ-CR38 scores at baseline and over 3 years according to treatment group.

	1 year SPS Mean (SD)	APR Mean (SD)	2 years SPS Mean (SD)	APR Mean (SD)	3 years SPS Mean (SD)	APR Mean (SD)	Difference (SPS-APR) at 3 years Multivariable GEE* Mean (95% CI)	p value
Function scales								
Body image	74·9 (22·6)	66·3 (25·8)	74·4 (22·0)	63·9 (28·3)	77·1 (22·3)	64·2 (24·0)	9·8 (2·9 to 16·6)	0·0052
Sexual functioning	14·0 (21·2)	9·9 (16·5)	12·8 (19·6)	9·6 (15·6)	12·1 (20·5)	7·7 (17·7)	3·5 (−1·7 to 8·8)	0·1873
Future perspective	61·3 (27·7)	58·6 (29·9)	62·9 (25·7)	62·8 (26·1)	61·1 (25·4)	59·3 (28·7)	−0·7 (−8·8 to 7·5)	0·8724
Sexual enjoyment	24·2 (27·0)	13·9 (19·5)	26·6 (27·3)	17·5 (25·7)	25·6 (28·1)	24·4 (26·6)	−0·5 (−14·5 to 13·5)	0·9444
Symptom scales								
Micturition problem	11·9 (13·5)	18·4 (14·8)	12·3 (12·6)	19·2 (16·6)	14·3 (14·9)	23·3 (21·7)	−8·0 (−14·1 to −1·8)	0·0108
Chemotherapy side-effects	10·4 (15·2)	10·3 (11·4)	9·3 (12·6)	10·3 (12·2)	7·6 (10·9)	11·3 (13·2)	−2·6 (−6·7 to 1·5)	0·2116
GI symptoms	12·1 (13·4)	9·9 (9·9)	11·2 (13·1)	14·0 (14·2)	10·6 (11·8)	13·6 (13·2)	−0·9 (−4·4 to 2·6)	0·6264
Male sexual problems	38·4 (34·9)	51·3 (35·3)	42·2 (35·5)	59·7 (35·4)	46·2 (35·5)	72·9 (36·1)	−19·9 (−33·1 to −6·7)	0·0032
Female sexual problems	25·4 (30·2)	2·1 (5·9)	30·6 (37·6)	34·9 (28·3)	30·7 (31·1)	29·2 (21·4)	−3·2 (−20·2 to 13·8)	0·7107
Weight loss	8·3 (18·9)	5·6 (12·5)	4·4 (13·3)	8·3 (14·6)	3·7 (11·9)	6·2 (14·6)	−0·8(−5·3 to 3·7)	0·7277

APR=abdominoperineal resection; CI=confidence interval; GEE=generalized estimating equation; GI=gastrointestinal; QOL=quality of life; SD=standard deviation; SPS=sphincter preservation surgery. Defecation problem scale and stoma-related problem scale at 3 years after SPS or APR are not presented in this table because these scales could not be compared between SPS and APR, as shown in the appendix p 3. The EORTC QLQ-CR38 scores are reported on scales ranging from 0 to 100. Higher scores indicate better function on function scales and more-severe symptoms on symptom scales.

* Multivariable regression models with linear generalized estimating equations were used to compare the mean scores of the two groups at each time point. Predictive margins were estimated from the multivariable model, which included an interaction term for treatment and time, with adjustment for baseline age, sex, body mass index, tumour size, operative time, pre-operative chemoradiotherapy, morbidity, approach method, and pathological stage [1,6,9–14,17–20,24,25].

3.4. Pre-specified analyses

The baseline characteristics, QOL, sexual-urinary functions, and oncological outcomes of the patients with very low rectal cancer (≤3 cm from the anal verge) were similar to those of the full study cohort (Appendix p 14, 16, 19). The results of the EORTC QLQ-C30 and QLQ-CR38 analyses in the OA of per-protocol population did not differ from those in the OA-ITT population (Appendix p 21). In the subgroup analysis of APR or SPS group for global QOL scale score, there was no the risk factor for poor global QOL scale, except for pathologic stage in the SPS group (Appendix p 23).

4. Discussion

In this long-term, prospective, multicentre study, aiming to compare the QOL of patients following APR or SPS for the resection of low rectal cancer and to test the hypothesis whether APR is superior to SPS, APR failed to meet the superiority to SPS based on the QOL assessment. After 3 years follow-up, the global QOL scale scores did not differ between the two groups. However, in the OA-ITT analysis, SPS fared better on the body image, micturition symptoms, and male sexual problems scales in the EORTC QLQ-C30 and CR38 questionnaire. In addition, we observed better sexual-urinary outcomes after SPS compared with those after APR, with no increased oncological risk. Therefore, we suggest that SPS can be an acceptable alternative to APR for low rectal cancers, offering a better QOL and sexual-urinary functions after 3 years. More than three-quarters of patients with low rectal cancer in this study experienced sphincter preservation, which is higher than the rates reported in previous studies [3,27,28]. This further supports our finding that SPS does not compromise QOL or function as much as APR.

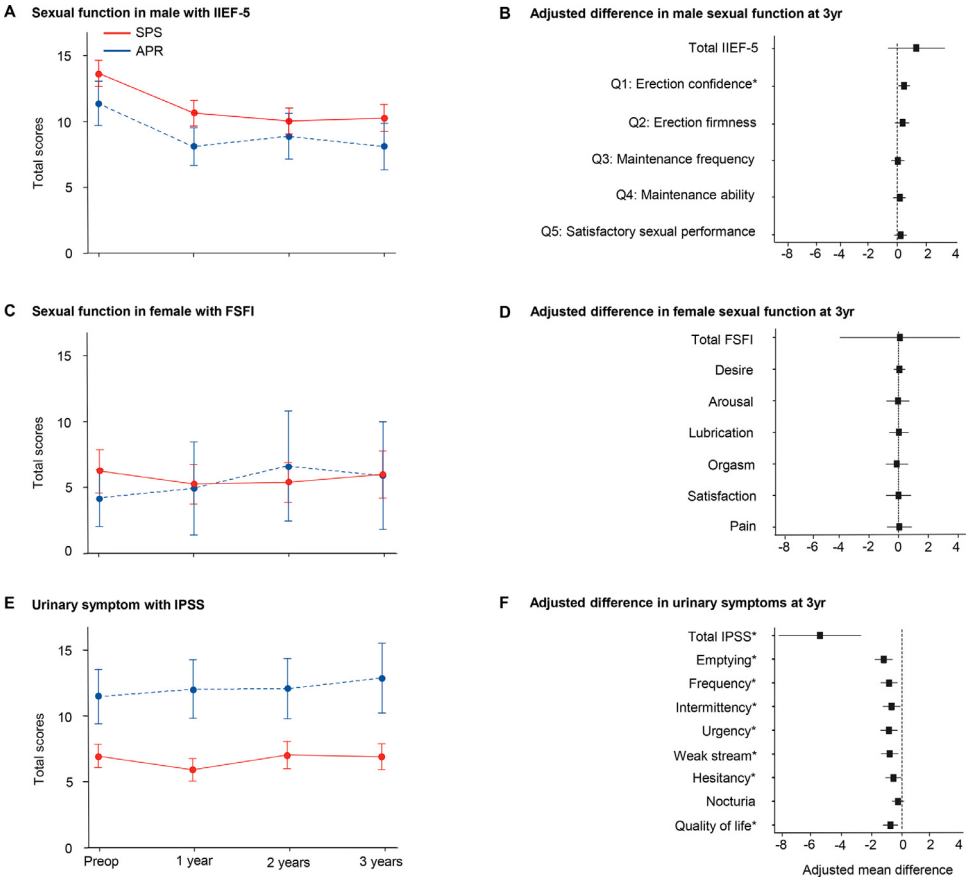

Fig. 2. Sexual and urinary functions from baseline to 3 years after surgery.
(A) Sexual function in men scored with IIEF-5; range of unadjusted mean scores: 5–25, with higher scores indicating better function; vertical lines show 95% CIs. (C) Sexual function in women scored with FSFI; range of unadjusted mean scores: 2–36, with higher scores indicating better function; vertical lines show 95% CIs. (E) Urinary symptom scored with IPSS; range of unadjusted mean scores: 0–35, with higher scores indicating worse symptom; vertical lines show 95% CIs. (B, D, F) $^{*}p < 0{\cdot}05$ in multivariable regression with linear GEEs at each time point, with adjustment for baseline values, age, sex, body mass index, pathological stage, tumour size, preoperative chemotherapy, operative time, morbidity, and approach. Positive values in B and D represent better function in the sphincter preservation surgery group, and negative values in F represent worse symptoms for the abdominoperineal resection group. IIEF-5=Five-item version of the International Index of Erectile Function; FSFI=Female Sexual Function Index; IPSS=International Prostate Symptom Score.

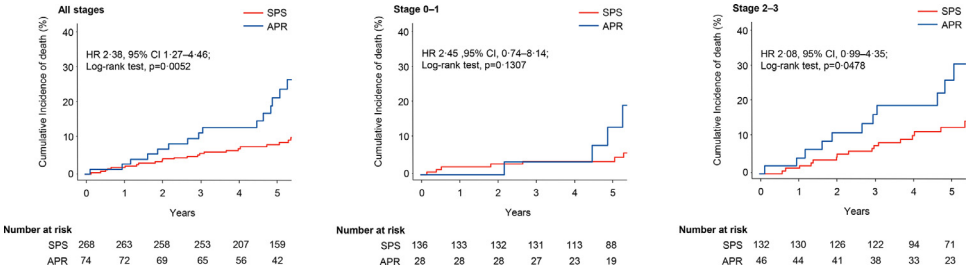

Fig. 3. Kaplan-Meier analyses of mortality.
APR=abdominoperineal resection (reference); SPS=sphincter preservation surgery.

Freedom from stoma in patients with low rectal cancer is a major objective of colorectal surgeons. However, APR may still be necessary for selected patients with very low rectal cancer invading the anal sphincter or preoperative loss of anal sphincter function [1]. This factor may account for some baseline differences in this non-randomised study. Although preoperative chemoradiotherapy has shifted the treatment paradigm towards organ preservation, its impact on QOL is somewhat controversial when compared with no radiotherapy. Minimally invasive surgery may have clinical benefits on QOL compared with open surgery, but no randomized controlled trials have demonstrated whether laparoscopic or robot-assisted, provide superior effects on QOL. To overcome this potential bias, the analyses of QOL and sexual-urinary functions were adjusted for pre-specified covariates, including age, sex, body mass index, tumour size, operative time, preoperative chemoradiotherapy, morbidity, approach method, and pathological stage [1,6,9–14,17–20,24,25]. In addition, because missing data due to attrition or non-response is a common problem in longitudinal studies, we performed two additional analyses: a full OA-ITT analysis with multiple imputed outcomes [26] and a sensitivity analysis after excluding deceased patients. In these pre-specified analyses, including the OA of per-protocol analysis and propensity score matching, the advantages of SPS on QOL and sexual-urinary functions did not differ from those in the OA-ITT analysis.

In this study, global QOL scores, which were used for sample size calculation based on the recommendations of a previous study [22], did not show a significant difference between the SPS and APR groups, although APR is expected to have a better effect on QOL than SPS at 3 years after surgery, based on the outcomes of a previous study in which APR provided better QOL in long-term survivors [13]. However, body image, micturition, and male sexual problems determined with the QLQ-CR38, which is specific for colorectal cancer, were better in the SPS group than in the APR group, as noted in a previous study [10]. Although diarrhoea symptoms were worse in the SPS group, this is unsurprising when we consider that LARS occurs after SPS [8]. The QOL benefit of SPS was also maintained in patients with very low rectal cancer, which differs from the results of a retrospective study of long-term survivors [13]. We consider that this discrepancy may be attributable to attrition bias because the previous study included patients with ≥2 years of follow-up and only selected disease-free patients without recurrence or metastasis [13]. Nevertheless, the majority of patients who undergo SPS suffer from LARS [8] and faecal incontinence, although LARS is expected to decrease once new treatments, including bowel rehabilitation programmes, are developed [29]. Therefore, we will analyse the long-term functional outcomes of this SPS group in a future study to identify a highly selective group of patients with worse function or QOL, for whom APR would be justified.

This was the first long-term, prospective study to compare the effects of APR and SPS on sexual-urinary functions in patients with low rectal cancer, with similar questionnaire response rates to a previous prospective study of rectal cancer [24,25]. We found that the confidence to get and maintain an erection in males was better in the SPS group, although the sexual function was difficult to evaluate because sexual activity was low. Urinary symptoms, except nocturia, were better on all scales after SPS, and these results are similar to those of a previous prospective study [25]. The better sexual-urinary functions after SPS may be explicable by the anatomical differences in the two techniques: APR removes the levator ani muscles, which are fixed anteriorly to the prostate, and could damage the anterior cavernous nerves or the urethral sphincter because there is no clear dissection plane around the recto-urethralis muscle. In contrast, SPS does not remove the levator ani muscles, allowing more autonomic nerve preservation. This phenomenon may also be associated with psychological factors, including body image [24]. Therefore, patients should receive information about postoperative sexual-urinary symptoms, and their function should be evaluated before surgery [11].

In this study of patients with low rectal cancer, the overall survival rate was better in the SPS group than in the APR group and was similar to the survival rate in a previous study of rectal cancer [27]. In a propensity-matched analysis of patients included in the National Cancer Database, APR was associated with worse overall survival outcomes than coloanal anastomosis [30]. The worse oncological outcomes in the APR group may have been attributable to the presence of more advanced tumours, which are more likely to perforate intraoperatively [28], or more positive circumferential margins [28,30]. However, in our study, the surgical method was not a prognostic factor after adjustments were made for confounders, although the overall survival of patients with pathological stage 2–3 was better in the SPS group. Therefore, the oncological harm of APR, if any, may become clearer with longer follow-up.

There were some limitations to this study. First, the study involved an inevitable risk balance because the patients were not randomly assigned to each intervention, and the clustering effect of some outcomes in this study was higher than the previously reported ICCs in other clinical trials [31]. However, the study showed no substantial deviations from the OA-ITT analysis after adjustments were made for pre-specified covariates of QOL and sexual-urinary functions, or after propensity score matching. Second, the lack of power to detect differences might have had an effect on the final results. The response rate at 3 years in APR group was lower than expected and the final number of participants undergoing APR was 54, which did not reach the original schedule. Third, the primary outcomes included several scales, although the sample size was estimated with the global QOL in QLQ-C30. The impact of surgical procedures on QOL is known to be one of the most difficult outcomes to estimate because it is related to a combination of multiple modalities [13,22] and many different scales based on the patient's preferences. Fourth, we did not control for preoperative chemoradiotherapy because of the practical constraints imposed by the small number of patients with low rectal cancer who can be enrolled in a prospective study. However, we included preoperative chemoradiotherapy as a covariate in the multivariable GEE analyses. Finally, the differences in the QOL scales did not meet the prespecified thresholds for clinical importance [22]. However, the adjusted mean differences in this study were about half the standard deviation suggested in a previous study [32].

5. Conclusions

In this long-term prospective study, APR failed to meet the superiority to SPS in terms of quality of life. Although the global QOL scores did not differ between groups, this study suggests that SPS can be an acceptable alternative to APR for low rectal cancer, offering a better QOL and sexual-urinary functions, with no increased oncological risk even after 3 years. Patients with low rectal cancer should receive comprehensive information about the possible impact of radical surgery on their QOL and postoperative functions, to ensure that an informed shared decision can be made.

Contributors

SBK, KJP, SYJ, JHO, SML, and SCH were responsible for the conception and design of the study. SBK, JRC, KJP, SYJ, JHO, SCH, EGY, DWK, BHL, SCP, DSL, SBR, JWP, HCP, SIK, MHK, HKO, RS, MJK, KHL, YHK, JSK, KWL, HSL, YSP, and DKS collected and assembled the data. SBK, JRC, KJP, SYJ, JHO, SA, SC, and HJK analysed and interpreted the data. SBK, JRC, KJP, SYJ, and JHO wrote the report, which was approved by all authors.

Declaration of Interests

We declare that we have no conflicts of interest. The sponsor was not involved with the collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit the paper.

Acknowledgments

We thank the patients who participated in the study, and Hye won Cha, Mi Young Jang, Myeong ja Kang, Jin Ah Kim, Min Sung Kim, and Yeoung Soon Kim, who helped in data management. We also thank SECOG for their support.

Data sharing statement

The authors confirm that the data supporting the finding of this study will be available from the corresponding author [SBK] on request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lanwpc.2020.100087.

References

[1] Benson AB, Venook AP, Al-Hawary MM, et al. Rectal Cancer, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2018;16:874–901.
[2] Schiessel R, Karner-Hanusch J, Herbst F, Teleky B, Wunderlich M. Intersphincteric resection for low rectal tumours. Br J Surg 1994;81:1376–8.
[3] Tilney HS, Heriot AG, Purkayastha S, et al. A national perspective on the decline of abdominoperineal resection for rectal cancer. Ann Surg 2008;247:77–84.
[4] Miles WE. A method of performing abdominoperineal excision for carcinoma of the rectum and of the terminal portion of the pelvic colon. Lancet 1908;2:1812–13.
[5] Garcia-Aguilar J, Renfro LA, Chow OS, 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.
[6] Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731–40.
[7] Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin 2019;69:363–85.
[8] Bryant CL, Lunniss PJ, Knowles CH, Thaha MA, Chan CL. Anterior resection syndrome. Lancet Oncol 2012;13:e403–8.
[9] Lindgren R, Hallböök O, Rutegård J, Sjödahl R, Matthiessen P. What is the risk for a permanent stoma after low anterior resection of the rectum for cancer? A six-year follow-up of a multicenter trial. Dis Colon Rectum 2011;54:41–7.
[10] Russell MM, Ganz PA, Lopa S, et al. Comparative effectiveness of sphincter-sparing surgery versus abdominoperineal resection in rectal cancer: patient-reported outcomes in National Surgical Adjuvant Breast and Bowel Project randomized trial R-04. Ann Surg 2015;261:144–8.
[11] Monastyrska E, Hagner W, Jankowski M, Głowacka I, Zegarska B, Zegarski W. Prospective assessment of the quality of life in patients treated surgically for rectal cancer with lower anterior resection and abdominoperineal resection. Eur J Surg Oncol 2016;42:1647–53.
[12] How P, Stelzner S, Branagan G, et al. Comparative quality of life in patients following abdominoperineal excision and low anterior resection for low rectal cancer. Dis Colon Rectum 2012;55:400–6.
[13] Rauch P, Miny J, Conroy T, Neyton L, Guillemin F. Quality of life among disease-free survivors of rectal cancer. J Clin Oncol 2004;22:354–60.
[14] Kasparek MS, Hassan I, Cima RR, Larson DR, Gullerud RE, Wolff BG. Quality of life after coloanal anastomosis and abdominoperineal resection for distal rectal cancers: sphincter preservation vs quality of life. Colorectal Dis 2011;13:872–7.
[15] Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC cancer staging manual. 7th editor. New York, NY: Springer; 2010.
[16] Punt CJ, Buyse M, Köhne CH, et al. Endpoints in adjuvant treatment trials: a systematic review of the literature in colon cancer and proposed definitions for future trials. J Natl Cancer Inst 2007;99:998–1003.
[17] Kang SB, Park JW, Jeong SY, et al. Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): short-term outcomes of an open-label randomized controlled trial. Lancet Oncol 2010;11:637–45.
[18] Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 2009;373:811–20.
[19] Weiser MR, Quah HM, Shia J, et al. Sphincter preservation in low rectal cancer is facilitated by preoperative chemoradiation and intersphincteric dissection. Ann Surg 2009;249:236–42.
[20] Ito M, Saito N, Sugito M, Kobayashi A, Nishizawa Y, Tsunoda Y. Analysis of clinical factors associated with anal function after intersphincteric resection for very low rectal cancer. Dis Colon Rectum 2009;52:64–70.
[21] West NP, Anderin C, Smith KJ, Holm T, Quirke P. European Extralevator Abdominoperineal Excision Study Group. Multicentre experience with extralevator abdominoperineal excision for low rectal cancer. Br J Surg 2010;97:588–99.
[22] Cocks K, King MT, Velikova G, Martyn St-James M, Fayers PM, Brown JM. Evidence-Based Guidelines for Determination of Sample Size and Interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. J Clin Oncol 2011;29:89–96.
[23] Danaei G, Rodríguez LAG, Cantero OF, Logan R, Hernán MA. Observational data for comparative effectiveness research: an emulation of randomised trials to estimate the effect of statins on primary prevention of coronary heart disease. Stat Methods Med Res 2013;22:70–96.
[24] Sörensson M, Asplund D, Matthiessen P, et al. Self-reported sexual dysfunction in patients with rectal cancer. Colorectal Dis 2020;22:500–12.
[25] Karlsson L, Bock D, Asplund D, Ohlsson B, Rosenberg J, Angenete E. Urinary dysfunction in patients with rectal cancer: a prospective cohort study. Colorectal Dis 2020;22:18–28.
[26] Biering K, Hjollund NH, Frydenberg M. Using multiple imputation to deal with missing data and attrition in longitudinal studies with repeated measures of patient-reported outcomes. Clin Epidemiol 2015;7:91–106.
[27] Bonjer HJ, Deijen CL, Abis GA, et al. A randomized trial of laparoscopic versus open surgery for rectal cancer. N Engl J Med 2015;372:1324–32.
[28] Nagtegaal ID, van de Velde CJ, Marijnen CA, et al. Low rectal cancer: a call for a change of approach in abdominoperineal resection. J Clin Oncol 2005;23:9257–64.
[29] van der Heijden JAG, van Heinsbergen M, Thomas G, Caers F, Slooter GD, Maaskant-Braat AJG. Implementation of a postoperative screening and treatment guidance for the low anterior resection syndrome: preliminary results. Dis Colon Rectum 2019;62:1033–42.
[30] Fields AC, Scully RE, Saadat LV, et al. Oncologic outcomes for low rectal adenocarcinoma following low anterior resection with coloanal anastomosis versus abdominoperineal resection: a National Cancer Database propensity matched analysis. Int J Colorectal Dis 2019;34:843–8.
[31] Cook JA, Bruckner T, MacLennan GS, Seiler CM. Clustering in surgical trials - database of intracluster correlations. Trials 2012;13:2–9.
[32] Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003;41:582–92.