



Low Anterior Resection Syndrome: Description, Measurement, Risk Factors

Celia Keane¹ and Ian Bissett^{1,2*}

¹Department of Surgery, University of Auckland, New Zealand

²Department of Surgery, Auckland City Hospital, New Zealand

Abstract

Low anterior resection syndrome (LARS) is increasingly recognized as a concern after low anterior resection for the treatment of rectal cancer. The lack of a precise definition outlining the symptoms and the time course that constitute LARS hinders ongoing research into the incidence, risk factors, pathophysiology, and treatment of this syndrome. This review will outline the current characterization of LARS, the approach to measuring LARS, and the risk factors for development of LARS. It will highlight the significant heterogeneity in the literature to date and the limitations in our understanding of LARS.

Keywords: Low anterior resection syndrome (LARS); Abdominoperineal resection (APR); Anterior resection syndrome (ARS)

Introduction

Miles described the abdominoperineal resection (APR) in 1908 [1] and it remained the gold standard for the treatment of rectal cancer until the introduction of the anterior resection procedure in 1948 [2]. The requirement for a 5cm distal resection margin initially limited anterior resection surgery to tumours in the upper and mid rectum [3]. In the 1980s the “5 cm rule” was challenged when multiple studies found that a 5 cm distal resection margin had little effect on the oncological outcome and the circumferential resection margin (CRM) was identified as the key to reducing local recurrence [4-7]. During the same period, Heald and colleagues emphasized strict adherence to anatomical planes of dissection and introduced total mesorectal excision (TME) [8]. Using this principle they achieved a local recurrence rate of 8% [9] in an era when the local recurrence rate was 20% to 40% [3,10]. These advances meant that distal colorectal and even coloanal anastomoses were theoretically possible [7]. The advent of circular stapling devices made the creation of these anastomoses easier, quicker, and safer [3,11].

Until the 1980s improvements in the treatment of distal rectal cancer were focused on improving mortality, survival, and local recurrence. The advances in the 1980s allowed another goal to emerge - preserving continence. During the 1980s and 1990s, attempts to improve functional outcome after sphincter preserving surgery resulted in the introduction of different reconstruction techniques including the colonic J pouch and the transverse colectomy [12-14]. Stoma avoidance was challenged as the most important determinant of quality of life after distal rectal cancer resection as the explosion of literature examining functional outcomes highlighted how common defaecatory dysfunction was after low anterior resection [15-18].

Clinical Characteristics of LARS

An anterior resection involves removal of the rectum and restoration of bowel continuity by creating an anastomosis between the colon and the rectal remnant or the anal canal [19]. Unsurprisingly, the removal of the rectum with its associated storage capacity and specialized sensory and motor function results in a change in bowel function [20]. Anterior resection syndrome (ARS) or low anterior resection syndrome (LARS) describes the dysfunction experienced after a sphincter-preserving rectal cancer resection. LARS is common and has been reported in 10% to 90% of patient's post-rectal resection [20-22]. Substantial heterogeneity in the functional outcomes reported after low anterior resection makes it impossible to pool the data and to draw externally valid conclusions regarding LARS [23]. This prompted Bryant and her colleagues to propose a pragmatic definition of (L) ARS: “disordered bowel function after rectal resection, leading to a detriment in quality of life” [20]. This definition captures the major features of LARS but it lacks specificity.

OPEN ACCESS

*Correspondence:

Ian P. Bissett, Department of Surgery,
University of Auckland, Private Bag
92019 Auckland Mail Centre 1142, New
Zealand,

E-mail: i.bissett@auckland.ac.nz

Received Date: 07 Sep 2016

Accepted Date: 21 Nov 2016

Published Date: 05 Dec 2016

Citation:

Keane C, Bissett I. Low Anterior
Resection Syndrome: Description,
Measurement, Risk Factors. *Clin Surg.*
2016; 1: 1194.

Copyright © 2016 Ian Bissett. This is
an open access article distributed under
the Creative Commons Attribution
License, which permits unrestricted
use, distribution, and reproduction in
any medium, provided the original work
is properly cited.

A consensus definition that specifies the symptoms and time frame required to constitute LARS, is needed to enable standardized research to advance the understanding of the incidence, risk factors, pathophysiology, and treatment of this syndrome.

LARS is used to describe a variety of symptoms. The bowel dysfunction may be categorized into storage dysfunction, which includes bowel frequency, faecal urgency and incontinence, and evacuatory dysfunction, which includes stool fragmentation or clustering [20,22,24,25]. Gas-stool discrimination, tenesmus, anal pain, passage of blood or mucus per anus have also been reported within the construct of LARS [24]. Some researchers also include urinary and sexual dysfunction within LARS, but these features will not be addressed in this review [24]. Frequency is usually reported as the number of bowel motions over a 24-hour period but may be differentiated into diurnal and nocturnal bowel frequency [26]. Reports of faecal incontinence may include the presence or severity of flatus, liquid, or solid stool incontinence, mucus discharge, and diurnal or nocturnal incontinence [26]. Patients may also be questioned about pad usage [26]. Faecal urgency is usually measured by asking patients if they have an urgent need to pass a bowel motion with the implication that incontinence would result if they were unable to reach the toilet. Deferral time, the length of time that the passage of stool can be deferred following the onset of the urge to evacuate, may also be used to assess urgency [26]. Bowel fragmentation or 'clustering' refers to the need to pass multiple bowel motions within a defined period of time, most often 1 hour [22,26]. Evacuatory dysfunction may include constipation, a sense of incomplete evacuation or of residual stool, inability to evacuate the bowel within a certain amount of time, use of evacuatory aids, or straining [26]. The ability to differentiate between gas and stool or to 'safely release flatus' is often measured as a marker of impaired anorectal sensation [26].

Lack of consensus on the symptoms that constitute LARS has led to heterogeneous reporting of symptoms deemed to be significant by individual research groups. Scheer and colleagues reviewed the literature and found 48 papers that reported functional outcome after anterior resection [27]. They calculated the frequency that each symptom was reported and showed that there was significant variation in outcome measures reported between studies [27]. However all studies included in their meta-analysis evaluated urgency and incontinence (of some kind) [27]. Over half of the studies measured pad usage (86%), incontinence of liquids (58%), solids (53%), or gas (53%), clustering (53%), and inability to differentiate gas from stool (53%) [27]. Incomplete evacuation and increased frequency (four or more bowel motions per day) were assessed in 35% of studies and nocturnal bowel motions were assessed in 12% of studies [27].

Bryant's definition suggests that the impact of post-operative bowel dysfunction on quality of life is inherent within concept of LARS [20]. The impact on quality of life may be assessed within the construct of LARS or may be assessed separately using validated quality of life tools, such as the European Organization for Research and Treatment of Cancer (EORTC) modules (QLQ-C30, -CR38 or -CR29) [26]. Both approaches have been used but some experts argue that it is conceptually flawed to measure bowel function using instruments designed to measure quality of life [23,26]. Behaviors such as pad use, dietary modifications, toilet dependence, and social isolation have been reported and show that the bowel dysfunction associated with LARS impacts on lifestyle and quality of life. Dissatisfaction with bowel function and affect on overall well being

have also been used to measure this feature of LARS [26]. Another, possibly more appropriate method of measuring the impact of bowel dysfunction on quality of life, is by using an instrument that incorporates symptoms shown to impact on quality of life, such as the LARS score [26].

Perhaps the greatest inconsistency in reporting of outcome is the length of the follow-up period. Bowel dysfunction immediately after rectal resection is expected, but there is no consensus regarding the time frame that constitutes pathological dysfunction after resection. Lack of a standardized post-operative time period has led to a wide range in the reported incidence of LARS. The authors are not aware of any proposed definition of LARS that incorporates a specified time period. The two scores specifically developed to measure bowel function following restorative rectal resection; the MSKCC BFI [29] and the LARS score [28], were developed and validated using patients who were at least 5 months and 2 years post-resection, respectively. However, neither the authors nor any other groups have specified the time point at which these instruments should be applied. These specific LARS questionnaires should now be used to assess incidence at various time points after restoration of bowel continuity to inform discussion as to the time point at which the dysfunction could be considered to constitute LARS. Once there is consensus over the time period that constitutes LARS, further standardization will be possible to allow for investigation into risk factors and treatments of LARS.

Measurement of LARS

Multiple instruments have been developed to measure functional outcome after LAR but none are in widespread use, presumably because they are not based on a robust definition of LARS [20]. The Colorectal Functional Outcome (COREFO) and the Hallbook questionnaires measure post-operative bowel function including incontinence, frequency, and social impact [30,31]. The COREFO questionnaire also measures the need for medication, pain or bleeding with bowel motions, and perianal skin irritation [30], while the Hallbook questionnaire assesses abdominal pain [31]. Both questionnaires have high reliability but the COREFO questionnaire has greater criterion validity [30]. Two instruments specifically developed to measure functional outcome after sphincter preserving surgery are the Bowel Function Instrument (BFI) and the Low Anterior Resection Syndrome (LARS) score. The bowel function instrument was first published in 2005 and includes 18 questions grouped into three subscales; frequency, dietary, urgency/soilage, and four individual questions [29]. An overall score can be calculated and transformed into an outcome category: excellent, good, fair, or poor function [29]. In contrast to the comprehensive BFI, the LARS score has been designed for quick, easy use in routine clinical practice including follow-up consultations [28]. The LARS score consists of five questions (Table 1) and can be used to generate an overall score that translates into no LARS (score 0-20), minor LARS (21-29), major LARS (30-42) [28]. The score for each question is weighted according to its correlation with the outcome of the following question "Overall, how much does your bowel function affect your quality of life?" [28] Patients suffering from major LARS report statistically and clinically significant differences in quality of life compared to patients with minor or no LARS [32]. Both the BFI and LARS score have good reliability and validity [28,29]. The BFI has subsequently been validated in a population of Italian patients [33]. The LARS score has been validated in Chinese, English, Swedish, Spanish, German, and Danish patient populations [34-36].

The aim of this questionnaire is to assess your bowel function. Please tick only one box for each question. It may be difficult to select only one answer, as we know that for some patients symptoms vary from day to day. We would kindly ask you to choose one answer which best describes your daily life. If you have recently had an infection affecting your bowel function, please do not take this into account and focus on answering questions to reflect your usual daily bowel function.

Do you ever have occasions when you cannot control your flatus (wind)?	
<input type="checkbox"/> No, never	0
<input type="checkbox"/> Yes, less than once per week	4
<input type="checkbox"/> Yes, at least once per week	7
Do you ever have any accidental leakage of liquid stool?	
<input type="checkbox"/> No, never	0
<input type="checkbox"/> Yes, less than once per week	3
<input type="checkbox"/> Yes, at least once per week	3
How often do you open your bowels?	
<input type="checkbox"/> More than 7 times per day (24 hours)	4
<input type="checkbox"/> 4 - 7 times per day (24 hours)	2
<input type="checkbox"/> 1 - 3 times per day (24 hours)	0
<input type="checkbox"/> Less than once per day (24 hours)	5
Do you ever have to open your bowels again within one hour of the last bowel opening?	
<input type="checkbox"/> No, never	0
<input type="checkbox"/> Yes, less than once per week	9
<input type="checkbox"/> Yes, at least once per week	11
Do you ever have such a strong urge to open your bowels that you have to rush to the toilet?	
<input type="checkbox"/> No, never	0
<input type="checkbox"/> Yes, less than once per week	11
<input type="checkbox"/> Yes, at least once per week	16

Table 1: LARS Score: questionnaire and scoring system. Adapted from Emmertsen et al. [28].

Frustratingly, studies investigating LARS employ a variety of tools to assess functional outcome. A systematic review found that 65% of the included studies did not use a validated tool to measure functional outcome after anterior resection for rectal cancer [27]. In these studies, most authors modified or developed their own questionnaires to assess outcomes [27]. Faecal incontinence scores have generally been relied upon when a validated tool is used to measure functional outcome [23,27]. This may reflect availability or author preference as clinicians have been shown to overemphasize the importance of faecal incontinence [37]. Limiting the focus to faecal incontinence overlooks symptoms such as clustering and urgency, which have been shown to correlate with quality of life [28].

The measurement of functional outcomes after LAR is difficult for many reasons. Patient-reported outcomes will be influenced by

cultural factors inherent in self-reporting, particularly when the symptoms are embarrassing or stigmatized [26,38,39]. Patients may want to avoid appearing ungrateful or may justify the poor functional outcome as the price they paid to treat the cancer and save their lives [39]. Over time, patients' perception of the symptoms may change as they adapt to a new level of functioning, particularly if they are not aware of any treatment options [39]. It is essential for clinicians to inquire about functional outcome, provide adequate explanations to patients, and to identify patients who need treatment to improve their symptoms [38]. It is also important to recognize that the patients' assessment of their functional outcome is the gold standard [23]. To compare patients' and specialists' perspectives the authors of the LARS score asked experts in the management of rectal cancer to rank symptoms, then assign weighting to the symptoms based

on how disturbing each would be to the patient [37]. This novel study illustrated that colorectal surgeons and radiation oncologists underestimate the negative consequences of clustering and urgency but overestimate the burden of incontinence and bowel frequency compared to patient reports [37].

Risk Factors or Contributing Causes

Multiple factors have been implicated as contributors to poor functional outcome after low anterior resection but lack of standardization in the timing of assessment, outcome measures assessed, and instruments used, have resulted in significant inconsistencies in the literature. Without application of a consistent definition of LARS it is very difficult to pool results and to draw generalizable or externally valid conclusions. Much of the literature reports faecal incontinence as the sole outcome of interest after rectal resection so it is not possible to extrapolate the results to LARS [23]. Despite the heterogeneity, anastomotic height and radiotherapy have repeatedly been associated with poor functional outcome after LAR [40,41].

Anastomotic height

Anastomotic height is generally accepted to be the major determinant of functional outcome after anterior resection but there are some contradictory findings in the literature. Anastomotic height, tumour height, and partial versus total mesorectal excision have all been investigated as contributors to functional outcome. Although these are interrelated as the level of the tumour will influence both the anastomotic height and whether a partial (high rectal cancer) or total mesorectal excision (mid or low rectal cancer) is performed, they do not represent the same thing which may account for some of the inconsistency in the literature. A retrospective study from our unit found that level of anastomosis was a significant predictor of ARS in the first two years (at 1 year, LAR odds ratio (OR) 2.11, ultra-LAR OR 4.34, at 2 years ultra-LAR OR 4.5) but this effect did not persist beyond 2 years [42]. A prospective study conducted at a median follow-up of 51 months found that both tumour distance from the anal ring (>1 cm, OR 5.88) and anastomotic height (>2 cm from anal verge, OR 6.59) were significant predictors of continence using the Wexner score [43]. Another prospective study found that tumour location (upper, middle, or lower rectum) was a significant predictor of change in the BFI score at 1 year follow-up (compared to pre-operative score) [44]. At a median follow-up of 18 months length of rectal remnant was shown to be a significant predictor of major LARS (adjusted OR 0.73, 95% CI 0.55 – 0.93) [41]. In this study, 46% of the 125 patients with a rectal remnant less than 4cm had major LARS versus 10% of patients with a remnant greater than 4cm [41]. A Japanese group also found a significant association between tumour distance (≤ 4 cm vs. >4 cm) from the anal verge and major LARS on univariate and multivariate (hazard ratio (HR) 2.72, 95% CI 1.04 – 7.58) analysis, at a median follow-up of 6.5 years [45]. Interestingly, the most recent publication from the Dutch TME trial, at a median follow-up of 14.6 years, did not find the distance of the tumour from the anal verge to be a significant predictor of major LARS on multivariate analysis [46].

Pre-operative radiotherapy

Preoperative radiotherapy has repeatedly been shown to negatively impact on post-rectal resection bowel function [47-49]. The Cochrane Collaboration reported a risk ratio (RR) of 2.12 (95% CI 1.49–3.03, $p < 0.01$) for incontinence in favour of patients undergoing surgery alone

compared to patients undergoing radiotherapy and surgery [47]. The relative risk of poor functional outcome when frequency, continence, and tenesmus data were pooled was not significant (RR 1.69, 95% CI 0.97–2.94) [47]. A subsequent meta-analysis reported a RR of 1.67 (95% CI 1.36–2.05, $p < 0.01$) for incontinence in favour of non-irradiated patients but no significant difference for bowel frequency (weighted mean difference (WMD) = 0.01) [48]. Despite a significant volume of literature addressing the question of radiotherapy on functional outcome after rectal surgery the Cochrane analysis was only able to pool data from two randomized controlled trials (RCTs) and the subsequent meta-analysis pooled data from three studies for each outcome. This highlights the major heterogeneity in reporting functional outcomes.

Findings from large RCTs show that radiotherapy has a negative impact on long-term functional outcome after rectal cancer resection using TME. The following discussion concentrates on assessments reported at the most recent follow-up for the Stockholm [50,51], Swedish Rectal Cancer [52], and Dutch TME [53] trials. At 15 years follow-up the Stockholm trials reported a significant difference in faecal incontinence for patients receiving radiotherapy versus those undergoing surgery alone (57% vs. 26%) [54]. The Swedish RCT found that irradiated patients reported significantly worse function 5 years after anterior resection in terms of frequency, urgency, emptying difficulties, early return to the toilet, incontinence (gas, liquid, and solid stool), pad use, and perineal excoriation [55]. At a median follow-up of 14.6 years the Dutch TME trial reported significantly higher rates of major LARS (55.9% vs. 35.5%, OR 3) and of each item in the LARS score except flatus incontinence, for patients undergoing pre-operative radiotherapy [46]. The average anastomotic height did not differ between the groups in the Swedish trials but there were more low anterior resections in the surgery only group at the most recent follow-up of the Dutch TME trial [46,54,55]. A multicentre RCT that enrolled patients with low rectal cancer undergoing coloanal anastomosis found that despite pre-operative and early post-operative differences in frequency, pad use, and urgency, at 2 years the only functional difference for irradiated patients was greater use of antidiarrhoeal agents [56]. The significant association between poor functional outcome and pre-operative radiotherapy appears to be weakened when only low rectal cancers (or coloanal anastomoses) are included. This highlights the interaction between radiotherapy and anastomotic height as contributors to functional outcome.

To better inform patients about the likely functional outcomes after treatment for rectal cancer Battersby and colleagues made a consent aid based on their findings from a multicentre trial that reported outcomes at an average follow-up of 5 years [40]. They found that tumour height (OR 1.74 for low vs. high/mid rectal cancer) and preoperative radiotherapy (OR 1.67) were the only significant predictors of bowel-related quality of life [40]. Their results suggest that patients with high or mid rectal cancer who do not have preoperative radiotherapy have the best chance of a good functional outcome, with a 33% risk of major bowel impairment [40]. Patients with low rectal cancer who undergo pre-operative radiotherapy have the worst functional outcomes, with a risk of major bowel impairment of 60% but a risk of any bowel impairment of 93% [40]!

Reconstruction technique

Anastomotic height and use of neoadjuvant radiotherapy are largely dictated by tumour characteristics and cannot be modified without sacrificing oncological outcomes. Therefore extensive

research has been undertaken to investigate whether surgical reconstruction can improve functional outcome. Surgeons have attempted to create a neo-reservoir to alleviate the issues associated with straight (end to end) anastomoses such as high rates of faecal incontinence, faecal urgency, and increased stool frequency [57]. The neo-reservoir takes one of three forms: the side to end anastomosis [58], the colonic J pouch [12,13], or the transverse coloplasty [59]. The side to end anastomosis was described by Baker in 1950, and was purported to be technically easier and result in better post-operative function than the end to end anastomosis [58]. Subsequently, the J shaped colonic pouch was introduced to give a larger reservoir [12,13]. The transverse coloplasty involves creating a longitudinal colostomy across the site of the anastomosis that is closed transversely to create a neo-reservoir [59]. The optimal size of the reservoir has been investigated for both pouch reconstructions and side to end anastomoses. Pouches of varying sizes, ranging from 5 cm to 12 cm, have been studied and smaller pouches seem to result in less evacuatory dysfunction [60-62]. The size of the side limb (3 cm or 5 cm) in an end to side anastomosis does not impact on functional outcome [63]. Use of the sigmoid colon, rather than the descending colon, for J pouch creation has been favoured due to technical ease and lack of functional benefit with either technique, except in the presence of significant diverticular disease [64]. A stapled pouch anastomosis resulted in less urgency (5% vs. 37%) than a hand sewn anastomosis in one study [65].

Multiple RCTS and meta-analyses have examined which reconstruction gives the best functional outcome, often with conflicting results [66-73]. Few studies have compared side to end vs. end to end anastomoses but one RCT published recently reported less incontinence and reduced stool frequency with an end to end anastomosis up to 6 months post-operatively [74]. Colonic J pouch reconstruction has been reported to result in favourable outcomes compared to straight anastomoses in terms of stool frequency [67,73], urgency [67,71,73], night-time soiling [73], anti-diarrhoeal use [67,73] and prolonged evacuation [75], at various follow-up time points. One meta-analysis reported less laxative use after straight anastomosis compared to J pouch reconstruction at intermediate follow-up (6 months to 3 years) [75]. More frequently, meta-analyses have found no difference in functional outcomes between straight anastomoses and J pouch reconstructions in regards to; stool frequency, pad use, enema use, use of bowel medication, incomplete defecation, and faecal incontinence [67,71,75]. A Cochrane review concluded that until 18 months post-operatively a colonic J pouch reconstruction had superior function to a straight anastomosis, but there was insufficient data to compare the functional outcome after 18 months [67].

Few studies have compared outcomes after a side to end (or latero-terminal anastomosis) to outcomes after a pouch reconstruction and only one systematic review addresses this comparison [75]. There is some evidence for better function; stool frequency [76-78], urgency [77], continence [77,78], and ability to empty the bowel within 15 minutes [79], after pouch reconstruction. Although one study found that patients had more problems with incomplete evacuation with a pouch reconstruction when compared to patients with a side to end anastomosis [76]. However, many RCTs report no difference in functional outcome with either reconstruction method [80,81] and a Cochrane review found no difference in stool frequency, urgency, incontinence, or anti-diarrhoeal use with either method [67].

A Cochrane review [67] and a meta-analysis [69] comparing J

pouch reconstruction to transverse coloplasty found no significant differences in functional outcome. However, subsequent meta-analyses have found significantly worse fragmentation between 6 months to 3 years (OR 0.45) [75], significantly reduced stool frequency at 12 months (WMD = -0.39), and significantly reduced nocturnal leakage at 6 months after a transverse coloplasty (OR 5.88) [70].

Functional outcome is only one consideration. Safety and feasibility also influence which reconstruction type may be considered. The colonic J pouch reconstruction may not be feasible in all patients, particular obese patients with a fatty mesocolon or patients with a narrow pelvis [82]. Initially there was concern about an increased rate of anastomotic leak after a transverse coloplasty [83] but multiple pooled analyses have demonstrated no difference in the rates of anastomotic leakage with a coloplasty vs. J pouch reconstruction [67,69,70]. There are no differences in the rate of anastomotic leak between straight anastomoses and J pouch reconstructions [67].

Ileostomy

Use of a temporary diverting ileostomy has also been implicated in the development of poor functional outcome after anterior resection but there have been conflicting results. Two retrospective reviews [42,84] found diverting ileostomy to be a significant predictor of functional outcome. One study found use of an ileostomy was a significant predictor of Wexner score on univariate analysis and of Fecal Incontinence Quality of Life (FIQL) score on multivariate analysis [84]. The other retrospective study used a broad definition of anterior resection syndrome and found ileostomy to be a predictor of ARS occurrence at 2, 3, 4, and 5 years follow-up even after adjusting for anastomotic height [42]. A prospective study assessing functional outcome using the BFI also found temporary ileostomy to be a significant predictor of poor functional outcome on univariate but not multivariate analysis [85]. The only study to use the LARS score found an increased risk of developing major LARS at 12 months follow-up with use of a temporary ileostomy (OR 4.51) but this disappeared when the analysis adjusted for tumour height (OR 1.73, 95% CI 0.44–6.91) [86]. One RCT investigated the effect of diverting ileostomy on functional outcome after restoration of bowel continuity and found that the only significant difference was for stool fragmentation (need to return to the toilet within one hour) [87]. There were no significant differences in median stool frequency, incontinence, need for medication to open bowels, difficulty emptying the bowels, or urgency between patients with and without a temporary ileostomy [87].

Anastomotic leakage

Multiple studies have assessed the impact of anastomotic leakage or pelvic infection on functional outcome but most studies have assessed faecal incontinence solely and only two studies used the LARS score [46,86]. The majority of studies have found no significant difference in outcome [42-44,86,88-91] but two case-control studies [92,93] report a significant difference in functional outcomes after anastomotic leakage. One study reported significant differences in stool frequency (4 vs. 2 motions per 24 hours) and urgency at 30-month follow-up, between patients who had symptomatic anastomotic leakage (requiring drainage, abscess evident on imaging or discharged via a fistula or per anus) and those that did not [93]. Another case-control study found that patients with a radiologically detected, clinically occult, anastomotic leak had significantly lower scores on the BFI (worse function) at least one year post-operatively

[92]. Major LARS was also found to be independently predicted by pelvic infection (not otherwise specified) on univariate analysis (HR 4.02, 95% CI 1.13–14.18) in one study but this was not significant on multivariate analysis [45].

Other factors

Other factors have been investigated as contributors to poor functional outcome after low anterior resection, including patient age, gender, and use of adjuvant chemotherapy. Gender has not been shown to predict poor functional outcome [41-46,84]. Multiple studies have investigated age as a contributing factor but only one study reported that age significantly predicted major LARS at a median follow-up of 14.6 years (OR 2.4 for age >75 years vs. age ≤ 75 years, 99% CI 1.1–5.5) [46]. A retrospective study found post-operative chemotherapy significantly predicted the occurrence of symptoms that the authors associated with ARS at 1 year follow-up but not at subsequent follow-up [42]. They concluded that chemotherapy resulted in temporary adverse effects on function rather than persisting ARS [42]. A study of 297 patients found significant differences in frequency and urgency at 12 and 24 months follow-up favoring patients who had radiotherapy alone compared to patients who had radiotherapy and post-operative chemotherapy [56]. A study comparing preoperative radiotherapy and subsequent surgery to a protocol of initial surgery with post-operative chemotherapy if the circumferential resection margin (CRM) was less than 1mm found that patients having radiotherapy had significantly worse faecal incontinence (53.2% vs. 37%) [94].

Conclusion

LARS is common and it is important that patients are adequately informed about the possibility of suffering from bowel dysfunction after low anterior resection, particularly if they also require pre-operative radiotherapy. There is extensive literature regarding functional outcome after low anterior resection but inconsistencies in methodology have resulted in an inability to draw robust conclusions about LARS. This review focused on the literature investigating risk factors that contribute to the development of LARS to highlight the significant heterogeneity in reporting of functional outcomes. In particular there are issues with the measurement of LARS and with the focus on faecal incontinence as the sole outcome of interest. With a consensus definition of the symptoms and time frame that constitutes LARS and with consistent application of specifically designed instruments to measure LARS, standardized research can be conducted to further the understanding of this syndrome. Future work is needed to address the definition of LARS and to champion the use of validated tools such as the LARS score to enable meaningfully investigation into the incidence, risk factors, pathophysiology, and treatment of LARS.

References

- Miles WE. A method of performing abdominoperineal excision for carcinoma of the rectum and of the terminal portion of the pelvic colon. *The Lancet*. 1908; 172: 1812-1813.
- Dixon CF. Anterior Resection for Malignant Lesions of the Upper Part of the Rectum and Lower Part of the Sigmoid. *Ann Surg*. 1948; 128: 425-442.
- Bordeianou L, Maguire LH, Alavi K, Sudan R, Wise PE, Kaiser AM. Sphincter-sparing surgery in patients with low-lying rectal cancer: techniques, oncologic outcomes, and functional results. *J Gastrointest Surg*. 2014; 18: 1358-1372.
- Williams NS, Dixon MF, Johnston D. Reappraisal of the 5 centimetre rule of distal excision for carcinoma of the rectum: a study of distal intramural spread and of patients' survival. *Br J Surg*. 1983; 70: 150-154.
- Pollett WG, Nicholls, RJ. The relationship between the extent of distal clearance and survival and local recurrence rates after curative anterior resection for carcinoma of the rectum. *Ann Surg*. 1983; 198: 159-163.
- Quirke P, Durdey, P, Dixon, MF, Williams, NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. *Lancet*. 1986; 2: 996-999.
- Williams NS. The rationale for preservation of the anal sphincter in patients with low rectal cancer. *Br J Surg*. 1984; 71: 575-581.
- Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet*. 1986; 1: 1479-1482.
- Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978-1997. *Arch Surg*. 1998; 133: 894-899.
- Llaguna OH, Martz JE. Function outcomes after sphincter-preserving surgery for rectal cancer. *Semin Colon Rectal Surg*. 2010; 21: 102-109.
- Ravitch MM. Varieties of stapled anastomoses in rectal resection. *Surg Clin North Am*. 1984; 64: 543-554.
- Lazorthes F, Fages P, Chiotasso P, Lemozy J, Bloom E. Resection of the rectum with construction of a colonic reservoir and colo-anal anastomosis for carcinoma of the rectum. *Br J Surg*. 1986; 73: 136-138.
- Parc R, Tiret E, Frileux P, Moszkowski E, Loygue J. Resection and colo-anal anastomosis with colonic reservoir for rectal carcinoma. *Br J Surg*. 1986; 73: 139-141.
- Z'graggen K, Maurer CA, Mettler D, Stoupis C, Wildi S, Büchler MW. A novel colon pouch and its comparison with a straight coloanal and colon J-pouch--anal anastomosis: preliminary results in pigs. *Surgery*. 1999; 125: 105-112.
- Pachler J, Wille-Jørgensen, P. Quality of life after rectal resection for cancer, with or without permanent colostomy. *Cochrane Database Syst Rev*. 2012; 12.
- Camilleri-Brennan J, Steele RJC. Objective assessment of morbidity and quality of life after surgery for low rectal cancer. *Colorectal Disease*. 2002; 4: 61-66.
- Grumann MM, Noack EM, Hoffmann IA, Schlag PM. Comparison of quality of life in patients undergoing abdominoperineal extirpation or anterior resection for rectal cancer. *Ann Surg*. 2001; 233: 149-156.
- Digennaro R, Tondo M, Cuccia F, Giannini I, Pezzolla F, Rinaldi M, et al. Coloanal anastomosis or abdominoperineal resection for very low rectal cancer: what will benefit the surgeon's pride or the patient's quality of life? *Int J Colorectal Dis*. 2013; 28: 949-957.
- Keighley MRB, Williams NS, Church JM, Pahlman L, Scholefield JH, Scott NA. Management of Carcinoma of the Rectum. In: Keighley MR, Williams NS, editor. *Surgery of the anus rectum & colon*. 3rd ed. Hungary: Elsevier. 2008; 2: 115-262.
- Bryant CL, Lunniss PJ, Knowles CH, Thaha MA, Chan CL. Anterior resection syndrome. *Lancet Oncol*. 2012; 13: e403-408.
- Bleier JI, Maykel JA. Outcomes following proctectomy. *Surg Clin North Am*. 2013; 93: 89-106.
- Pucciani F. A review on functional results of sphincter-saving surgery for rectal cancer: the anterior resection syndrome. *Updates Surg*. 2013; 65: 257-263.
- Chen TY, Emmertsen KJ, Laurberg S. What are the best questionnaires to capture anorectal function after surgery in rectal cancer? *Curr Colorectal Cancer Rep*. 2015; 11: 37-43.
- Ziv Y, Zbar A, Bar-Shavit Y, Igov I. Low anterior resection syndrome

- (LARS): cause and effect and reconstructive considerations. *Tech Coloproctol.* 2013; 17: 151-162.
25. Ng KS, Nassar N, Bhan C, Gladman M. Phenotypic variation of bowel dysfunction following anterior resection: More than a syndrome. *Colorectal Dis.* 2014; 16: 36-37.
 26. Kwaan MR. Bowel Function after Rectal Cancer Surgery: A Review of the Evidence. *Semin Colon Rectal Surg.* 2011; 22: 235-242.
 27. Scheer AS, Boushey RP, Liang S, Doucette S, O'Connor AM, Moher D. The long-term gastrointestinal functional outcomes following curative anterior resection in adults with rectal cancer: a systematic review and meta-analysis. *Dis Colon Rectum.* 2011; 54: 1589-1597.
 28. Emmertsen KJ, Laurberg S. Low anterior resection syndrome scores: development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. *Ann Surg.* 2012; 255: 922-928.
 29. Temple LK, Bacik J, Savatta SG, Gottesman L, Paty PB, Weiser MR, et al. The development of a validated instrument to evaluate bowel function after sphincter-preserving surgery for rectal cancer. *Dis Colon Rectum.* 2005; 48: 1353-1365.
 30. Bakx R, Sprangers MAG, Oort FJ, van Tets WF, Bemelman WA, Slors JFM, et al. Development and validation of a colorectal functional outcome questionnaire. *Int J Colorectal Dis.* 2005; 20: 126-136.
 31. Hallböök O, Sjødahl R. Surgical approaches to obtaining optimal bowel function. *Semin Surg Oncol.* 2000; 18: 249-258.
 32. Juul T, Ahlberg M, Biondo S, Espin E, Jimenez LM, Matzel KE, et al. Low anterior resection syndrome and quality of life: an international multicenter study. *Dis Colon Rectum.* 2014; 57: 585-591.
 33. Zotti P, Del Bianco P, Serpentine S, Trevisan P, Barba MC, Valentini V, et al. Validity and reliability of the MSKCC Bowel Function instrument in a sample of Italian rectal cancer patients. *Eur J Surg Oncol.* 2011; 37: 589-596.
 34. Juul T, Battersby NJ, Christensen P, Janjua AZ. Validation of the English translation of the low anterior resection syndrome score. *Colorectal Dis.* 2015; 17: 908-916.
 35. Juul T, Ahlberg M, Biondo S, Emmertsen KJ, Espin E, Jimenez LM, et al. International validation of the low anterior resection syndrome score. *Ann Surg.* 2014; 259: 728-734.
 36. Hou XT, Pang D, Lu Q, Yang P, Jin SL, Zhou YJ, et al. Validation of the Chinese version of the low anterior resection syndrome score for measuring bowel dysfunction after sphincter-preserving surgery among rectal cancer patients. *Eur J Oncol Nurs.* 2015; 19: 495-501.
 37. Chen TY, Emmertsen KJ, Laurberg S. Bowel dysfunction after rectal cancer treatment: a study comparing the specialist's versus patient's perspective. *BMJ Open.* 2014; 4: e003374.
 38. Taylor C, Bradshaw E. Tied to the toilet: lived experiences of altered bowel function (anterior resection syndrome) after temporary stoma reversal. *J Wound, Ostomy Continence Nurs.* 2013; 40: 415-421.
 39. DeSnoo L, Faithfull S. A qualitative study of anterior resection syndrome: the experiences of cancer survivors who have undergone resection surgery. *Eur J Cancer Care.* 2006; 15: 244-251.
 40. Battersby N, Bouliotis G, Emmertsen K, Laurberg S, Moran B. An externally validated nomogram to predict the risk of bowel dysfunction following an anterior resection. *Gut.* 2015; 64: A48.
 41. Bondeven P, Emmertsen KJ, Laurberg S, Pedersen BG. Neoadjuvant therapy abolishes the functional benefits of a larger rectal remnant, as measured by magnetic resonance imaging after restorative rectal cancer surgery. *Eur J Surg Oncol.* 2015; 41: 1493-1439.
 42. Wells CI, Vather R, Chu MJ, Robertson JP, Bissett IP. Anterior resection syndrome--a risk factor analysis. *J Gastrointest Surg.* 2015; 19: 350-359.
 43. Denost Q, Laurent C, Capdepon M, Zerbib F, Rullier E. Risk factors for fecal incontinence after intersphincteric resection for rectal cancer. *Dis Colon Rectum.* 2011; 54: 963-968.
 44. Ihn MH, Kang SB, Kim DW, Oh HK, Lee SY, Hong SM. Risk factors for bowel dysfunction after sphincter-preserving rectal cancer surgery: a prospective study using the Memorial Sloan Kettering Cancer Center bowel function instrument. *Dis Colon Rectum.* 2014; 57: 958-966.
 45. Beppu N, Kimura H, Matsubara N, Tomita N, Yanagi H, Yamanaka N. Long-Term Functional Outcomes of Total Mesorectal Excision Following Chemoradiotherapy for Lower Rectal Cancer: Stapled Anastomosis versus Intersphincteric Resection. *Dig Surg.* 2016; 33: 33-42.
 46. Chen TY, Wiltink LM, Nout RA, Meershoek-Klein Kranenburg E, Laurberg S, Marijnen CA, et al. Bowel function 14 years after preoperative short-course radiotherapy and total mesorectal excision for rectal cancer: report of a multicenter randomized trial. *Clin Colorectal Cancer.* 2015; 14: 106-114.
 47. Wong RKS, Tandan V, De Silva S, Figueredo A. Pre-operative radiotherapy and curative surgery for the management of localized rectal carcinoma. *Cochrane Database Syst Rev.* 2007; 18.
 48. Loos M, Quentmeier P, Schuster T, Nitsche U, Gertler R, Keerl A, et al. Effect of preoperative radio (chemo) therapy on long-term functional outcome in rectal cancer patients: a systematic review and meta-analysis. *Ann Surg Oncol.* 2013; 20: 1816-1828.
 49. Gavaruzzi T, Lotto L, Giandomenico F, Perin A, Pucciarelli S. Patient-reported outcomes after neoadjuvant therapy for rectal cancer: A systematic review. *Expert Rev Anticancer Ther.* 2014; 14: 901-918.
 50. Cedermark B, Johansson H, Rutqvist LE, Wilking N. The Stockholm I trial of preoperative short term radiotherapy in operable rectal carcinoma. A prospective randomized trial. *Stockholm Colorectal Cancer Study Group. Cancer.* 1995; 75: 2269-2275.
 51. Martling A, Holm T, Johansson H, Rutqvist LE, Cedermark B; Stockholm Colorectal Cancer Study Group. The Stockholm II trial on preoperative radiotherapy in rectal carcinoma: long-term follow-up of a population-based study. *Cancer.* 2001; 92: 896-902.
 52. Pahlman L, Glimelius B. Improved survival with preoperative radiotherapy in resectable rectal cancer. *Swedish Rectal Cancer Trial. N Engl J Med.* 1997; 336: 980-987.
 53. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med.* 2001; 345: 638-646.
 54. Pollack J, Holm T, Cedermark B, Altman D, Holmström B, Glimelius B, et al. Late adverse effects of short-course preoperative radiotherapy in rectal cancer. *Br J Surg.* 2006; 93: 1519-1525.
 55. Dahlberg M, Glimelius B, Graf W, Pahlman L. Preoperative irradiation affects functional results after surgery for rectal cancer: results from a randomized study. *Dis Colon Rectum.* 1998; 41: 543-549.
 56. Parc Y, Zutshi M, Zalinski S, Ruppert R, Furst A, Fazio VW. Preoperative radiotherapy is associated with worse functional results after coloanal anastomosis for rectal cancer. *Dis Colon Rectum.* 2009; 52: 2004-2014.
 57. de la Fuente SG, Mantyh CR. Outcomes Review of Reconstructive Techniques Following Proctectomy. *Semin Colon Rectal Surg.* 2008; 19: 41-47.
 58. Baker JW. Low end to side rectosigmoidal anastomosis; description of technic. *Arch Surg.* 1950; 61: 143-157.
 59. Fazio VW, Mantyh CR, Hull TL. Colonic "colooplasty": novel technique to enhance low colorectal or coloanal anastomosis. *Dis Colon Rectum.* 2000; 43: 1448-1450.

60. Hida J, Yasutomi M, Fujimoto K, Okuno K, Ieda S, Machidera N, et al. Functional outcome after low anterior resection with low anastomosis for rectal cancer using the colonic J-pouch: Prospective randomized study for determination of optimum pouch size. *Dis Colon Rectum*. 1996; 39: 986-991.
61. Lazorthes F, Chiotasso P, Gamagami RA, Istvan G, Chevreau P. Late clinical outcome in a randomized prospective comparison of colonic J pouch and straight coloanal anastomosis. *Br J Surg*. 1997; 84: 1449-1451.
62. Tsunoda A, Kamiyama G, Narita K, Watanabe M, Nakao K, Kusano M. Prospective randomized trial for determination of optimum size of side limb in low anterior resection with side-to-end anastomosis for rectal carcinoma. *Dis Colon Rectum*. 2009; 52: 1572-1577.
63. Tsunoda A, Shibusawa M, Kusano M. Anorectal function after anterior resection with side-to-side anastomosis for carcinoma of the rectum. *Dis Colon Rectum*. 1999; 42: 77-81.
64. Heah SM, Seow-Choen F, Eu KW, Ho YH, Tang CL. Prospective, randomized trial comparing sigmoid vs. descending colonic J-pouch after total rectal excision. *Dis Colon Rectum*. 2002; 45: 322-328.
65. Laurent A, Parc Y, McNamara D, Parc R, Turet E. Colonic J-pouch-anal anastomosis for rectal cancer: a prospective, randomized study comparing handsewn vs. stapled anastomosis. *Dis Colon Rectum*. 2005; 48: 729-734.
66. Hüttner FJ, Tenckhoff S, Jensen K, Uhlmann L, Kulu Y, Büchler MW, et al. Meta-analysis of reconstruction techniques after low anterior resection for rectal cancer. *Br J Surg*. 2015; 102: 735-745.
67. Brown CJ, Fenech DS, McLeod RS. Reconstructive techniques after rectal resection for rectal cancer. *Cochrane Database Syst Rev*. 2008; CD006040.
68. Hida J, Okuno K. Pouch operation for rectal cancer. *Surg Today*. 2010; 40: 307-314.
69. Heriot AG, Tekkis PP, Constantinides V, Paraskevas P, Nicholls RJ, Darzi A, et al. Meta-analysis of colonic reservoirs versus straight coloanal anastomosis after anterior resection. *Br J Surg*. 2006; 93: 19-32.
70. Liao C, Gao F, Cao Y, Tan A, Li X, Wu D. Meta-analysis of the colon J-pouch vs transverse colectomy pouch after anterior resection for rectal cancer. *Colorectal Dis*. 2010; 12: 624-631.
71. Siddiqui MRS, Sajid MS, Woods WGA, Cheek E, Baig MK. A meta-analysis comparing side to end with colonic J-pouch formation after anterior resection for rectal cancer. *Tech Coloproctol*. 2010; 14: 113-123.
72. Murphy J, Hammond TM, Knowles CH, Scott SM, Lunniss PJ, Williams NS. Does anastomotic technique influence anorectal function after sphincter-saving rectal cancer resection? A systematic review of evidence from randomized trials. *J Am Coll Surg*. 2007; 204: 673-680.
73. Temple LKF, McLeod RS. A meta-analysis comparing functional outcome following straight coloanal anastomosis versus a colonic J pouch. *Semin Colon Rectal Surg*. 2002; 13: 62-66.
74. Rybakov EG, Pikunov DY, Fomenko OY, Chernyshov SV, Shelygin YA. Side-to-end vs. straight stapled colorectal anastomosis after low anterior resection: results of randomized clinical trial. *In J Colorectal Dis*. 2016; 31: 1419-1426.
75. Rink AD, Sgourakis G, Sotiropoulos GC, Lang H, Vestweber KH. The colon J-pouch as a cause of evacuation disorders after rectal resection: myth or fact? *Langenbecks Arch Surg*. 2009; 394: 79-91.
76. Huber FT, Herter B, Siewert JR. Colonic pouch vs. side-to-end anastomosis in low anterior resection. *Dis Colon Rectum*. 1999; 42: 896-902.
77. Prete F, Liguori P, Nitti P, Vincenti L, Prete FP. Optimal reconstruction after resection of the rectum in cancer surgery. *Chir Ital*. 2000; 52: 323-328.
78. Doeksen A, Bakx R, Vincent A, Tets WF, Sprangers MA, Gerhards MF, et al. J-pouch vs side-to-end coloanal anastomosis after preoperative radiotherapy and total mesorectal excision for rectal cancer: a multicentre randomized trial. *Colorectal Dis*. 2012; 14: 705-713.
79. Machado M, Nygren J, Goldman S, Ljungqvist O. Similar outcome after colonic pouch and side-to-end anastomosis in low anterior resection for rectal cancer: a prospective randomized trial. *Ann Surg*. 2003; 238: 214-220.
80. Machado M, Nygren J, Goldman S, Ljungqvist O. Functional and physiologic assessment of the colonic reservoir or side-to-end anastomosis after low anterior resection for rectal cancer: a two-year follow-up. *Dis Colon Rectum*. 2005; 48: 29-36.
81. Jiang JK, Yang SH, Lin JK. Transabdominal anastomosis after low anterior resection: A prospective, randomized, controlled trial comparing long-term results between side-to-end anastomosis and colonic J-pouch. *Dis Colon Rectum*. 2005; 48: 2100-2108.
82. Fürst A, Suttner S, Agha A, Beham A, Jauch KW. Colonic J-pouch vs. colectomy following resection of distal rectal cancer: early results of a prospective, randomized, pilot study. *Dis Colon Rectum*. 2003; 46: 1161-1166.
83. Ho YH, Brown S, Heah SM, Tsang C, Seow-Choen F, Eu KW, et al. Comparison of J-pouch and colectomy pouch for low rectal cancers: a randomized, controlled trial investigating functional results and comparative anastomotic leak rates. *Ann Surg*. 2002; 236: 49-55.
84. Walma MS, Kornmann VNN, Boerma D, De Roos MAJ, Van Westreenen HL. Predictors of fecal incontinence and related quality of life after a total mesorectal excision with primary anastomosis for patients with rectal cancer. *Ann Coloproctol*. 2015; 31: 23-28.
85. Ihn M, Kang S, Park J, Son I, Oh H, Kim D. Preoperative anal dysfunction is a predictor of permanent stoma in rectal cancer patients: Results of the first prospective cohort analysis of clinically relevant risk factors. *Dis Colon Rectum*. 2015; 58: e359-e360.
86. Emmertsen KJ, Laurberg S. Rectal Cancer Function Study Group. Impact of bowel dysfunction on quality of life after sphincter-preserving resection for rectal cancer. *Br J Surg*. 2013; 100: 1377-1387.
87. Lindgren R, Hallböök O, Rutegård J, Sjö Dahl R, Matthiessen P. Does a defunctioning stoma affect anorectal function after low rectal resection? Results of a randomized multicenter trial. *Dis Colon Rectum*. 2011; 54: 747-752.
88. Riss S, Stremitzer S, Riss K, Mittlböck M, Bergmann M, Stift A. Pelvic organ function and quality of life after anastomotic leakage following rectal cancer surgery. *Wien Klin Wochenschr*. 2011; 123: 53-57.
89. Mongin C, Maggiori L, Agostini J, Ferron M, Panis Y. Does anastomotic leakage impair functional results and quality of life after laparoscopic sphincter-saving total mesorectal excision for rectal cancer? A case-matched study. *In J Colorectal Dis*. 2014; 29: 459-467.
90. Bittorf B, Stadelmaier U, Merkel S, Hohenberger W, Matzel KE. Does anastomotic leakage affect functional outcome after rectal resection for cancer? *Langenbecks Arch Surg*. 2003; 387: 406-410.
91. Chen TYT, Wiltink LM, Nout RA, Meershoek-Klein Kranenbarg E, Laurberg S, Marijnen CAM, et al. Bowel function 14 years after sphincter-preserving total mesorectal excision for rectal cancer: Report of a multicentre randomised trial. *Eu J Cancer*. 2013; 49: S489.
92. Killeen S, Souroullas P, Ho Tin H, Hunter IA, O'Grady H, Gunn J, et al. Outcomes of asymptomatic anastomotic leaks found on routine postoperative water-soluble enema following anterior resection for cancer. *World J Surg*. 2013; 37: 2700-2704.
93. Hallböök O, Sjö Dahl R. Anastomotic leakage and functional outcome after anterior resection of the rectum. *Br J Surg*. 1996; 83: 60-62.
94. Stephens RJ, Thompson LC, Quirke P, Steele R, Grieve R, Couture J, et al. Impact of short-course preoperative radiotherapy for rectal cancer on patients' quality of life: Data from the Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 randomized clinical trial. *J Clin Oncol*. 2010; 28: 4233-4239.