A Meta-analysis of the Prevalence of Low Anterior Resection Syndrome and Systemic Review of Risk Factors

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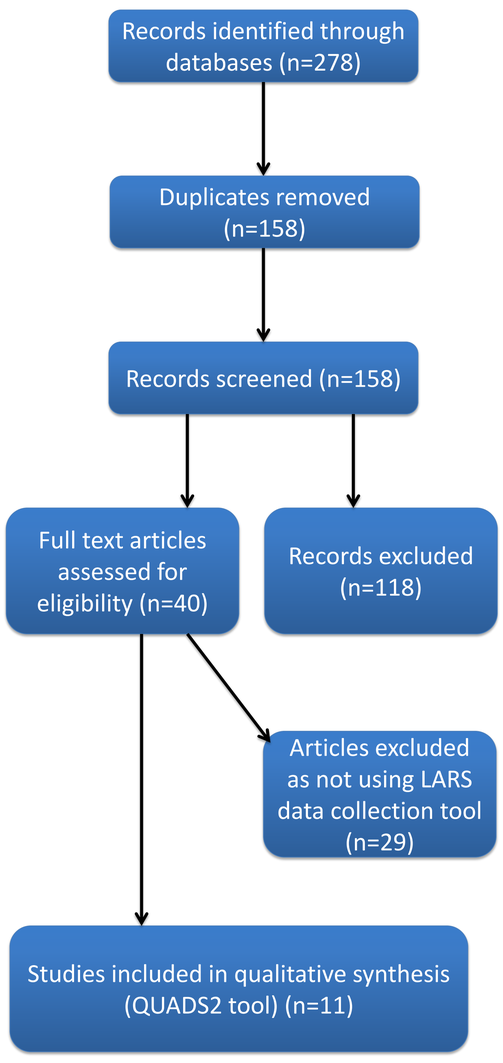
Background

- Low anterior resection + TME is the preferred procedure for mid and low rectal cancers.[1]
- Low Anterior Resection Syndrome (LARS): Incontinence (faeces +/- flatus), urgency, diarrhoea, frequency and clustering of bowel motions.[2,3]
- Bowel adaptation occurs by 18 months.[4]
- Estimated prevalence of LARS 19-52%.[6]
- Variability due to non-specific data collection tools that do not take QOL into consideration.
- 'LARS score' - validated scoring system specific for LAR taking into account impact on overall quality of life.[3]
- Aim of this review was to analyze published data on the prevalence of LARS, from studies utilizing the LARS score. Risk factors also assessed.

Methods

- Pubmed, Ovid Medline, Cochrane
- MeSH: "Low anterior resection syndrome", "Anterior Resection syndrome", "Prevalence", "Incidence", "bowel function", "Quality of life" and "Low anterior resection syndrome score"
- Screened by title and abstract
- Inclusion criteria: English language studies using LARS score assessing prevalence and causative factors.
- Articles scored using QUADAS2 tool – 11 good quality studies found
- Prevalence of major, minor and no LARS, patient variables and treatment variables recorded
- All studies, with the exception of 2,[1,14] had a mean or median follow >or= 18 months.



Study	Significant Risk Factor	Not Significant Risk Factor	Not Discussed
Emmertsen 2012, Denmark	- Radiotherapy - Anastomotic height < 5cm from anal verge)		- Age - Gender - Anastomotic leak - Timing of reversal - Anastomotic type
Juul et al. 2015, Denmark + UK	- Neoadjuvant radiotherapy - Anastomotic height < 5cm		- Age - Gender - Anastomotic leak - Timing of reversal - Anastomosis type
Bondeven et al 2015, Denmark	- Long course Neoadjuvant chemoradiation - Anastomotic height < 4 cm	- Age - Gender - Anastomosis type (end-end vs end-side)	- Anastomotic leak (exclusion) - Timing of reversal
Hain 2016, France	- Symptomatic anastomotic leak - Anastomosis type (hand-sewn coloanal or end-side = higher risk) - Long course radiotherapy - Anastomotic height ('intersphincteric')	- Age - Gender	- Timing of reversal
Bregendahl 2013, Denmark	- Neoadjuvant radiotherapy - Anastomotic height (TME for <10cm) - Age	- Anastomotic type (colonic pouch vs straight to end or side to end) - gender -anastomotic leak	- Timing of reversal
Juul et al. 2014, multicentre international	No statistical analysis discussed - Radiotherapy: 64% Major LARS, 18.3% minor, 17% no LARS - Anastomotic height: Major LARS 9cm, Minor 9.6cm, no LARS 10.6cm - Mean age (Major LARS: 66.4, Minor LARS: 68.9, no LARS: 70.2) - Gender: Major LARS: males 56%, females: 44%		- Anastomotic leak - timing of reversal - Anastomotic type
Luca et al 2016, Italy		- Radiotherapy: long course neoadjuvant - Anastomotic height - Age - Gender *These was not displayed in the data	- Anastomotic leak - Timing of reversal - All patients: hand-sewn coloanal - standardised
Hughes 2017, UK	- Timing of reversal: ileostomy closure > 1 year increased risk of major LARS - Neoadjuvant radiation (20 fold increased risk major LARS)	- Age - Gender - Anastomotic leak - Anastomotic height	- Anastomotic type
Carillo et al. 2016, Spain	- Radiotherapy: long course - Anastomotic height*: TME > PME (TME for lower and middle rectal Ca, PME for upper rectal Ca) - Diverting stoma > no stoma - Lack of reservoir (colonic pouch/ coloplasty) = greater major LARS	- Age - Gender - Anastomotic leak (reported as 'anastomotic complications')	
Ekkarat et al. 2016, Thailand	- Adjuvant radiotherapy - Anastomotic height <5cm - Diverting stoma>no stoma	- Age - Gender - Anastomosis type	- Anastomotic leak
Sturiale 2016, Italy	- Age - Timing to reversal of ileostomy: median Major LARS: 5.4 months, minor: 3.3 months, no LARS: 2.6 months - Neoadjuvant radiotherapy - Anastomotic height <5cm	- Gender - Anastomotic leak	- Anastomotic type

Meta-analysis	Major LARS	Minor LARS	No LARS
Prevalence	41%	24%	35%

Study	Patient Number		Months from Surgery to Survey*	Major LARS	Minor LARS	No LARS
	Total	% Response				
Emmertsen	478	92.8%	Mean 55.5	40%	25%	35%
Juul et al.	579	80%	Median 58.8	47%	23%	30%
Bondeven et al	125	100% - retrospective	Median18	35%	24%	35%
Hain	135	87%	Median 43	23%	50%	31%
Bregendahl	1087	90.1%	Median 54	41%	23.5%%	35.5%
Juul et al.	1061	76%	Mean 67.2	52%	19%	29%
Luca et al	23	100%	12	23.8%	19%	57.1%
Hughes	85	80%	Median 8	56%	18%	26%
Carillo et al.	195	70%	Median 37	47%	18.9%)	34.1%
Ekkarat et al.	129	expected 100%	Median 38	17.8%	17%	65.4%
Sturiale	110	84.5%	Median 164.4	20.5%	27%	52.5%

Statistical Analysis

- Meta-analysis using a quality-effects model (factoring the QUADAS2 scores) conducted using MetaXL
- Pooled prevalence figure was calculated with 95% CI.
- Meta-analysis conducted with prevalence estimates that had been transformed using the double arcsine method. This method avoids variance moving towards zero as a result of estimate of the study tending towards 0% or 100%, resulting in over estimation of weight in meta-analysis.

Results

- Prevalence of Major LARS ranged from 17.8%-56%,
- Meta-analysis prevalence using the quality effect model was 41% (95% CI 34 -48), I^2=91%, p<0.001
- The study with the lowest rate of major LARS excluded patients who had undergone neoadjuvant therapy and had a larger percentage of patients with tumours in the upper rectum (>40%) .
- Hughes et al.[1] had highest rate of LARS (56%). Potentially because they included patients with restoration of intestinal continuity of only 12 weeks. Patients <1yr following surgery had a mean LARS of 35.5 compared to 27.9 in >4years.
- Neoadjuvant or adjuvant radiotherapy was the most consistently assessed variable affecting major LARS (statistical significance in studies).[1,3,6-9,12-13]
- Tumour height (anastomotic level): 6 of the 11 studies identified a statistically significant association.[3,7-9,12-13]
- Four studies looked at the presence of an ileostomy and duration prior to reversal, all of which found an increased risk of major LARS with ileostomy formation and/or prolonged duration.[1,6,12-13]
- Having a complication of an anastomosis was found to be associated with increased risk of developing major LARS and in one study this association was significant.[8]
- None of these studies found any significant association with gender and LARS.
- Age was statistically significantly in only one study.[13]

Discussion

- Radiation has also been found to have negative effects on function in LAR patients with greater numbers of incontinent episodes and decreased rectal sensation.[15] Reducing the dose leads to improvement in sphincter function.[16]
- Increased rates of Major LARS in patients with a diverting ileostomy expected to be due to underlying reason for the ileostomy.
  - Temporary ileostomy more common in lower resections – a recognized risk for LARS
  - anastomotic leaks treated with ileostomy for a prolonged period – could the increased rate of LARS be due to prolonged ileostomy
- Although colonic adaption over a period of about 12months may improve bowel function, we confirm that a significant population of patients continue to suffer into the mid and long term.
- Impaired anal sphincter function has been identified in patients following LAR and has been shown to be associated with poorer functional outcome.[2,6,18]
  - resultant impairment of the anal sphincter could be due to both direct injury to the anal sphincter as well as damage to it innervation with pelvic dissection of the rectum
  - Altered intestinal motility due to disruption of the parasympathetic innervation of the bowel has been suggested to play a role in the development of LARS
- LARS must be taken into appropriate consideration in the management of rectal cancer, although oncological considerations need to be prioritized.
- Improved selectivity for radiotherapy may result in less prevalence of post-operative morbidity
- PME rather than TME as the oncological outcomes are equivalent and functional outcomes appear to be superior.
- Pre-operative counselling and education about functional outcomes should detail LARS risk.
- Therapies such as biofeedback, sacral nerve modulation and rectal irrigation are showing promise in improving anorectal function and quality of life post LAR.

References

1. Hughes, D., Cornish, J. and Morris, C. (2017). Functional outcome following rectal surgery—predisposing factors for low anterior resection syndrome. *International Journal of Colorectal Disease*, 32(5), pp.691-697. **2.** Bryant, C., Lunniss, P., Knowles, C., Thaha, M. and Chan, C. (2012). Anterior resection syndrome. *The Lancet Oncology*, 13(9), pp.e403-e408. **3.** Emmertsen, K. and Laurberg, S. (2012). Low Anterior Resection Syndrome Score. *Annals of Surgery*, 255(5), pp.922-928. **4.** Ho, Y. (2006). Techniques for restoring bowel continuity and function after rectal cancer surgery. *World Journal of Gastroenterology*, 12(39), p.6252. **5.** André, T., Boni, C., Navarro, M., Tabernero, J., Hickish, T.(2009). Improved Overall Survival With Oxaliplatin, Fluorouracil, and Leucovorin As Adjuvant Treatment in Stage II or III Colon Cancer in the MOSAIC Trial. *Journal of Clinical Oncology*, 27(19), pp.3109-3116. **6.** Ekkarat, P., Boonpipattanapong, T., Tantiphlachiva, K. and Sangkhathat, S. (2016). Factors determining low anterior resection syndrome after rectal cancer resection: A study in Thai patients. *Asian Journal of Surgery*, 39(4), pp.225-231. **7.** Bondeven, P., Emmertsen, K., Laurberg, S. and Pedersen, B. (2015). Neoadjuvant therapy abolishes the functional benefits of a larger rectal remnant, as measured by magnetic resonance imaging after restorative rectal cancer surgery. *European Journal of Surgical Oncology (EJSO)*, 41(11), pp.1493-1499. **8.** Hain, E., Manceau, G., Maggiori, L., Mongin, C., Prost à la Denise, J. and Panis, Y. (2017). Bowel dysfunction after anastomotic leakage in laparoscopic sphincter-saving operative intervention for rectal cancer: A case-matched study in 46 patients using the Low Anterior Resection Score. *Surgery*, 161(4), pp.1028-1039. **9.** Juul, T., Battersby, N., Christensen, P., Janjua, A., Branagan, G., Laurberg, S., Emmertsen, K. and Moran, B. (2015). Validation of the English translation of the low anterior resection syndrome score. *Colorectal Disease*, 17(10), pp.908-916. **10.** Bregendahl, S., Emmertsen, K., Lous, J. and Laurberg, S. (2013). Bowel dysfunction after low anterior resection with and without neoadjuvant therapy for rectal cancer: a population-based cross-sectional study. *Colorectal Disease*, p.n/a-n/a. **11.** Juul, T., Ahlberg, M., Biondo, S., Espin, E., Jimenez, L., Matzel, K., Palmer, G., Sauermann, A., Trenti, L., Zhang, W., Laurberg, S. and Christensen, P. (2014). Low Anterior Resection Syndrome and Quality of Life. *Diseases of the Colon & Rectum*, 57(5). pp.585-591. **12.** Carrillo, A., Enríquez-Navascués, J., Rodríguez, A., Placer, C., Múgica, J., Saralegui, Y., Timoteo, A. and Borda, N. (2016). Incidence and Characterization of the Anterior Resection Syndrome Through the Use of the LARS Scale (Low Anterior Resection Score). *Cirugía Española (English Edition)*, 94(3), pp.137-143. **13.** Sturiale, A., Martellucci, J., Zurli, L., Vaccaro, C., Brusciano, L., Limongelli, P., Docimo, L. and Valeri, A. (2016). Long-term functional follow-up after anterior rectal resection for cancer. *International Journal of Colorectal Disease*, 32(1), pp.83-88. **14.** Luca, F., Valvo, M., Guerra-Cogorno, M., Simo, D., Blesa-Sierra, E., Biffi, R. and Garberoglio, C. (2016). Functional results of robotic total intersphincteric resection with hand-sewn coloanal anastomosis. *European Journal of Surgical Oncology (EJSO)*, 42(6), pp.841-847. **15.** Ho, Y., Lee, K., Eu, K. and Seow-Choen, F. (2000). Effects of adjuvant radiotherapy on bowel function and anorectal physiology after low anterior resection for rectal cancer. *Techniques in Coloproctology*, 4(1), pp.13-16. **16.** Arias, F., Eito, C., Asín, G., Mora, I., Cambra, K., Mañeru, F., Ibáñez, B., (2017). Fecal incontinence and radiation dose on anal sphincter in patients with locally advanced rectal cancer (LARC) treated with preoperative chemoradiotherapy: a retrospective, single-institutional study. *Clinical and Translational Oncology*, 19(8), pp.969-975. **17.** Gadan, S., Floodeen, H., Lindgren, R. and Matthiessen, P. (2017). Does a Defunctioning Stoma Impair Anorectal Function After Low Anterior Resection of the Rectum for Cancer? A 12-Year Follow-up of a Randomized Multicenter Trial. *Diseases of the Colon & Rectum*, 60(8), pp.800-806. **18.** Dulskas, A., Miliauskas, P., Tikuisis, R., Escalante, R. and Samalavicius, N. (2016). The functional results of radical rectal cancer surgery: review of the literature. *Acta Chirurgica Belgica*, 116(1), pp.1-10. **19.** Emmertsen, K., Bregendahl, S., Fassov, J., Krogh, K. and Laurberg, S. (2013). A hyperactive postprandial response in the neorectum − the clue to low anterior resection syndrome after total mesorectal excision surgery?. *Colorectal Disease*, 15(10), pp.e599-e606. **20.** Nerad, E., Lambregts, D., Kersten, E., Maas, M., Bakers, F., van den Bosch, H., Grabsch, H., Beets-Tan, R. and Lahaye, M. (2017). MRI for Local Staging of Colon Cancer. *Diseases of the Colon & Rectum*, 60(4), pp.385-392. **21.** Kanso, F., Lefevre, J., Svrcek, M., Chafai, N., Parc, Y. and Tiret, E. (2016). Partial Mesorectal Excision for Rectal Adenocarcinoma: Morbidity and Oncological Outcome. *Clinical Colorectal Cancer*, 15(1), pp.82-90.e1. **22.** Ho, Y., Tan, M. and Seow-Choen, F. (1996). Prospective randomized controlled study of clinical function and anorectal physiology after low anterior resection: Comparison of straight and colonic J pouch anastomoses. *British Journal of Surgery*, 83(7), pp.978-980. **23.** Battersby, N., Juul, T., Christensen, P., Janjua, A., Branagan, G., Emmertsen, K. (2016). Predicting the Risk of Bowel-Related Quality-of-Life Impairment After Restorative Resection for Rectal Cancer. *Diseases of the Colon & Rectum*, 59(4), pp.270-280. **24.** Bartlett, L., Sloots, K., Nowak, M. and Ho, Y. (2011). Biofeedback therapy for symptoms of bowel dysfunction following surgery for colorectal cancer. *Techniques in Coloproctology*, 15(3), pp.319-320 **25.** Ramage, L., Qiu, S., Kontovounisios, C., Tekkis, P., Rasheed, S. and Tan, E. (2015). A systematic review of sacral nerve stimulation for low anterior resection syndrome. *Colorectal Disease*, 17(9), pp.762-771 **26.** Ho, Y., Chiang, J., Tan, M. and Low, J. (1996). Biofeedback therapy for excessive stool frequency and incontinence following anterior resection or total colectomy. *Diseases of the Colon & Rectum*, 39(11), pp.1289-1292. **27.** Maris, A., Devreese, A., D'Hoore, A., Penninckx, F. and Staes, F. (2013). Treatment options to improve anorectal function following rectal resection: a systematic review. *Colorectal Disease*, 15(2), pp.e67-e78.