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

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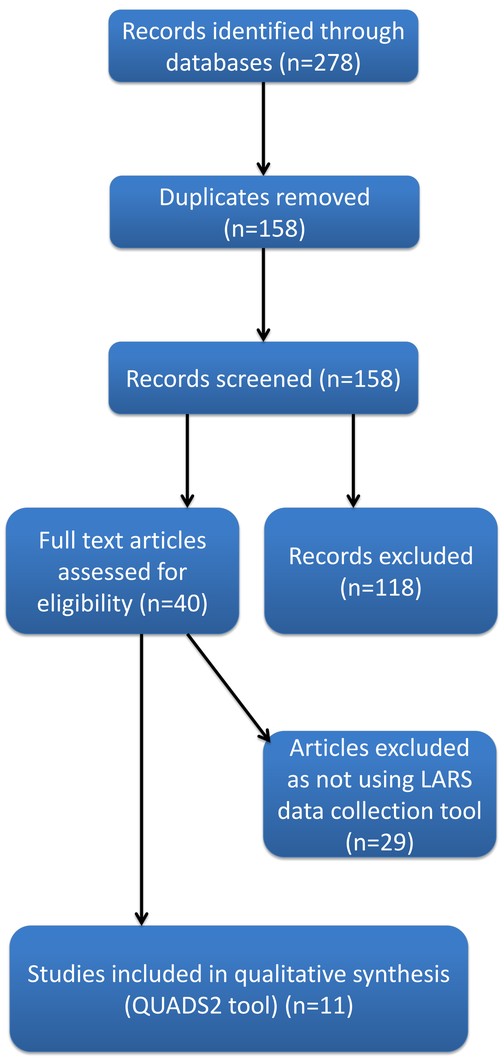
## Background

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

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