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Review article

# Functional results after treatment for rectal cancer

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ABSTRACT

*Introduction:* With improving survival of rectal cancer, functional outcome has become increasingly important. Following sphincter-preserving resection many patients suffer from severe bowel dysfunction with an impact on quality of life (QoL) – referred to as low anterior resection syndrome (LARS).
*Study objective:* To provide an overview of the current knowledge of LARS regarding symptomatology, occurrence, risk factors, pathophysiology, evaluation instruments and treatment options.
*Results:* LARS is characterized by urgency, frequent bowel movements, emptying difficulties and incontinence, and occurs in up to 50-75% of patients on a long-term basis. Known risk factors are low anastomosis, use of radiotherapy, direct nerve injury and straight anastomosis. The pathophysiology seems to be multifactorial, with elements of anatomical, sensory and motility dysfunction. Use of validated instruments for evaluation of LARS is essential. Currently, there is a lack of evidence for treatment of LARS. Yet, transanal irrigation and sacral nerve stimulation are promising.
*Conclusion:* LARS is a common problem following sphincter-preserving resection. All patients should be informed about the risk of LARS before surgery, and routinely be screened for LARS postoperatively. Patients with severe LARS should be offered treatment in order to improve QoL. Future focus should be on the possibilities of non-resectional treatment in order to prevent LARS.



## Resultados funcionais após tratamento de câncer retal

*Palavras-chave:*
Câncer retal
LARS
Disfunção intestinal
Resultado funcional
Qualidade de vida

RESUMO

*Introdução:* Com o aumento da sobrevida após câncer retal, o resultado funcional se tornou cada vez mais importante. Após ressecção com preservação do esfíncter, muitos pacientes sofrem de disfunção intestinal com um impacto sobre a qualidade de vida (QdV) – denominada síndrome da ressecção anterior baixa (LARS).
*Objetivo do estudo:* Fornecer uma visão geral do conhecimento atual da LARS com relação à sintomatologia, à ocorrência, aos fatores de risco, à fisiopatologia, aos instrumentos de avaliação e às opções de tratamento.

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*Resultados:* A LARS é caracterizada por movimentos intestinais repentinos e frequentes, dificuldades de esvaziamento e incontinência e ocorre em até 50-75% dos pacientes em longo prazo. Os fatores de risco conhecidos são anastomose baixa, radioterapia, lesão direta do nervo e anastomose direta. A fisiopatologia parece multifatorial, com elementos de disfunção anatômica, sensorial e da motilidade. O uso de instrumentos validados para avaliação da LARS é essencial. Atualmente, não há comprovações de tratamento da LARS. Ainda hoje, a irrigação transanal e a estimulação do nervo sacral são comprometidas.
*Conclusão:* A LARS é um problema comum após ressecção com preservação do esfíncter. Todos os pacientes devem ser informados sobre o risco de LARS antes da cirurgia, e o rastreamento da LARS deve ser rotineiro após a cirurgia. Pacientes com LARS severa devem receber tratamento para melhorar a QdV. O foco futuro deve ser nas possibilidades de tratamento sem ressecção a fim de evitar a LARS.



## Introduction

Rectal cancer is a common disease worldwide with an increasing incidence. During the last few decades, development of new treatment strategies has resulted in markedly increased survival.

At present, surgical resection with radical removal of the tumor with curative intent is the primary treatment for most patients. Depending on the height of the tumor, the resection can be done as a sphincter-preserving resection (low anterior resection, LAR) or an abdomino-perineal resection (APR).[1] Sphincter-preserving resection of rectal cancer, with the creation of a colorectal or coloanal anastomosis, follows the principle of total mesorectal excision (TME) as first described by Heald in 1982.[2] Tumors located in the uppermost part of the rectum can be excised by a partial mesorectal excision (PME) with similar oncological results.[3] APR is used in cases where the tumor is threatening the sphincter or when expectations of creating an anastomosis with acceptable functional results are low. Within the last decades, the use of APR has decreased substantially, and several trials have investigated the possibility of creating ultra-low anastomoses with partial or full resection of the internal sphincter (ISR) to avoid a permanent abdominal colostomy.[4,5]

Unfortunately, many patients develop severe pelvic dysfunction following a sphincter-preserving resection of the rectum. These include bowel, urinary and sexual dysfunctions.[6-8] Studies have shown that up to 25-50% of all patients experience major dysfunction on a daily basis with a significant impact on quality of life (QoL).[9-12] The extent of these problems varies greatly with some patients obtaining near-normal function after a postoperative recovery of a few months, and others being severely disabled physically and socially for the rest of their lives.[10,11]

The increase in survival has led to an increased attention to the importance of functional outcome and QoL. Knowledge of not only oncological, but also long-term functional outcome is essential for all colorectal surgeons in order to manage these patients, both in terms of choosing the optimal treatment option and in terms of managing the functional deficits after recovery.

## Low anterior resection syndrome – LARS

Bowel dysfunction following LAR is often referred to as low anterior resection syndrome (LARS). Although recognized for years, a clear definition has not been established. Recently, Bryant et al. proposed a very pragmatic definition: "*disordered bowel function after rectal resection, leading to a detriment in quality of life*".[13] LARS is characterized by urgency, frequent bowel movements, emptying difficulties and incontinence for flatus and/or feces.[10,14] It is most pronounced during the first months after surgery, improves during the first year and reaches a steady state 1-2 years after surgery.

Bowel function after LAR has been investigated in several studies over the last decades, with large variations in the reported frequency of symptoms. Some studies have shown that up to 75% of patients experience severe bowel dysfunction on a long-term basis following LAR.[9,13,15] It has been established that LARS has a significant impact on overall QoL.[11]

The incontinence and urgency aspects of LARS have often been investigated, showing large variations in occurrences in different studies, ranging from 0-51% and 4-68% respectively.[16-18] Some studies have also investigated evacuation difficulties, clustering and incomplete emptying, showing prevalences ranging from 2-74%.[13]

These large variations in the occurrence of symptoms are likely a result of inconsistent terminology, with unclear definitions of symptoms and use of non-validated instruments. Nevertheless, they could also reflect, to some extent, differences between study populations.

Incontinence is one of the most commonly reported symptoms after LAR. However, it seems that this symptom might not be very important for the patients with regards to impact on QoL. A recent study investigating health-related QoL and bowel function showed that there was a statistically significant association between urgency and incomplete emptying and QoL, but not between incontinence and QoL. Similarly, in the development of a new scoring system for LARS, it was shown that urgency and clustering had a much higher impact on QoL than incontinence.[14] These results suggest that although incontinence occurs frequently after LAR, this symptom does not affect the patient's life to the same degree as urgency and fragmentation.

The reason for this might be that a patient can easily handle an occasional incontinence episode, whereas the constant fear and uncertainty of never knowing when the urge might appear, thinking that you may need a toilet within minutes, and wondering if you will need a toilet again within a short interval, can be very incapacitating.

Numerous studies have examined QoL in rectal cancer patients, but most have focused on differences between treatment options. Many studies have looked into QoL in LAR patients compared to APR patients, with conflicting results.[1] Generally, it seems that APR patients have lower QoL than LAR patients.

However, when investigating low rectal cancers within 6 cm from the anal verge, this observation changes. Even though some areas of QoL appear to be worse in APR patients (sexual function and body image), these lower scores are well balanced by better QoL scores in the areas of cognitive and social functioning, as well as better symptom scales.[19]

## Risk factors

Several factors are known to influence bowel function following LAR. Patient factors such as age, gender and preoperative function have been suggested to be influential, although with conflicting results.[10,20] However, tumor and treatment related factors seem more important for the development of LARS.

The level and stage of the tumor has been shown to be significantly associated with function. Although many studies use the level of anastomosis as a surrogate marker for tumor level, it appears to be of utmost importance for LARS.[21] In particular, the very low cancers excised by ISR seem to yield a high risk of incontinence, soiling and urgency. [22]

The true effect of tumor stage is more difficult to assess because of potential confounding factors regarding treatment regimens. Generally, the more advanced tumors receive more chemo- and radiotherapy and may need more extensive dissection, thus increasing the risk of LARS.

It has been established that the use of both pre- and postoperative radiotherapy (RT) with and without the addition of chemotherapy significantly increases the risk of LARS.[10,12,23,24] Two large randomized controlled trials (RCTs) comparing preoperative RT and postoperative RT showed significantly less acute and chronic gastrointestinal dysfunction, as well as lower local recurrence rates, in the preoperative group.[25,26] Therefore, the preoperative approach is most widely used today.

Autonomic nerve-preservation is essential for preserving the pelvic functions, including sexual and bladder function. By careful dissection, sparing of the inferior *mesenteric plexus, the superior and inferior hypogastric plexi, the hypogastric and pelvic* splanchnic nerves, as well as the urogenital bundle at the levels of the prostate and the seminal vesicles, should be feasible.[27,28]

Laparoscopic techniques have been introduced over the last decades and have shown promising results with regards to oncological, functional and QoL outcome.[29,30] However, the long-term functional results still remain to be investigated.

Traditional teaching states that splenic flexure mobilization, including high ligation of the inferior mesenteric artery, is mandatory in rectal cancer surgery in order to achieve a satisfactory surgical and oncological outcome. Currently, this approach is under debate because of the lack of evidence.[31,32]

Some surgeons may use the sigmoid colon for the anastomosis, thereby avoiding the risk of damage to the spleen associated with flexure mobilization. However, the sigmoid is often affected by diverticulosis and/or muscular hypertrophy, and may therefore be less suitable for anastomosis.[9,33] Furthermore, this method might lead to tension of the anastomosis, as well as compromising the blood supply to the sigmoid colon during ligation of the inferior mesenteric artery, especially in cases of a small or non-existing Arcade of Riolan, causing hypo-perfusion of the anastomosis. This might warrant mobilization of the splenic flexure and use of the descending colon for anastomosis.[31] The functional results after reconstruction with the sigmoid or descending colon seem similar, although further studies are needed.[33]

A temporary diverting stoma is generally recommended in all lower anastomoses to decrease postoperative morbidity including clinical anastomotic leak, pelvic sepsis, postoperative ileus and reoperation.[34] The most frequently used stoma is the loop ileostomy, which is easy to fashion and to close, but it has been indicated that the loop transverse colostomy might lower the risk of intestinal obstruction and ileus after closure.[35] Notwithstanding this, the functional consequences of a defunctioning stoma remain unclear. It has been shown that diversion can lead to stenosis of the anastomosis, atrophy or diversion colitis, with potential effects on functional outcome.[36] More studies are needed to further elucidate this area.

Some studies have shown an increased risk of LARS after an anastomotic leakage, possibly due to increased fibrosis induced by inflammation, causing a reduced neorectal capacity and compliance.[37]

## Surgical reconstruction

The type of anastomosis with or without the creation of a neoreservoir has been shown to be important for bowel function, although the effect seems to diminish over time.[38,39] A neoreservoir can be constructed by a colonic J-pouch, a side-to-end anastomosis a.m. Baker or a coloplasty (Fig. 1). Following TME surgery, the reservoir function of the rectum is destroyed and requires restoration. After PME surgery, at least part of the rectum remains and provides an acceptable neorectal reservoir, which is the reason why an end-to-end anastomosis can be chosen.[10]

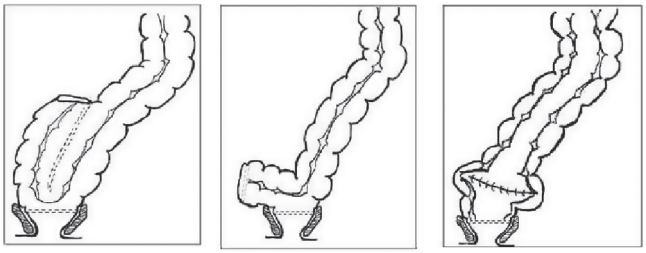

**Fig. 1 – Neo-reservoir types: Colonic J-pouch, side-to-end anastomosis and coloplasty.**

The colonic J-pouch is formed by folding a short segment of the distal colon and making a side-to-side anastomosis between the two loops using a linear stapler introduced through the apex of the pouch. The pouch is then connected to the rectal remnant by a circular stapled side-to-end anastomosis. This technique restores volume and has been shown to improve compliance and sensory function of the neorectum.[39,40] Different sizes of pouches have been explored, and it has been shown that a pouch of 5-6 cm produces the best functional results, balancing the risk of urgency and frequent stools in smaller pouches with the risk of emptying difficulties in larger pouches.[4] Nonetheless, a customization of pouch size according to patient's anal sphincteric function and tendency toward constipation or diarrhea might yield the best results. A weak sphincter and/or loose stool may suggest creating a larger pouch, while tendency of constipation could suggest a smaller pouch for optimal results.[9] However, the evidence for this approach seems limited.

In some patients, a large voluminous colonic J-pouch might not be suitable or feasible: in a small narrow pelvis, or in patients without sufficient length of the colon. In these patients, a simple side-to-end anastomosis could be performed, in which the side of the distal colon is anastomosed to the rectal remnant approximately 3-6 cm from the stapler line, on the antimesenterial side of the colon a.m. Baker.[9,41] Here, the blind distal end of the colon will eventually dilate, hereby increasing the neorectal volume and changing the motility pattern of the neorectum. This neo-reservoir is easier to construct than the J-pouch and leaves fewer staple lines. The functional results of the side-to-end anastomosis seem comparable to those of the J-pouch, but larger studies are required to confirm this. Several trials have tested the transverse coloplasty pouch as an alternative to the J-pouch, as it requires less space. The coloplasty is formed by a 7-10 cm long incision made along the antimesenterial side of the colon, a few cm above the distal end. The incision is closed transversally, creating a reservoir that is consequently connected to the rectal remnant by circular stapling. This results in a more voluminous neorectum with interrupted antegrade colonic peristalsis, and therefore better holding capacities.[9,42] Some have found the functional results of the coloplasty comparable to the results after J-pouch, but a large RCT of long-term functional results and QoL two years after surgery showed that it had no advantages over the end-to-end anastomosis and was significantly inferior to the J-pouch.[15]

In conclusion, in low anastomoses a colon J-pouch is superior to the straight anastomosis, whereas the coloplasty has no advantages. The side-to-end anastomosis seems comparable to the J-pouch, but further studies are needed for validation. Currently, a large international multicenter RCT is comparing the long-term functional results of the side-to-end anastomosis and the colonic J-pouch.

## Pathophysiology

Historically, the sphincter function and biomechanical properties of the neorectum has been seen as the most important factors in the development of LARS. Recently, more attention has been directed at the neurological damages after surgery and the effects on function, and a review in Lancet Oncology concluded that the syndrome seems to be multifactorial.[13]

An increasing number of studies have investigated pathophysiology and found that anatomical, sensory and muscular changes all seem likely to be involved. Neorectal capacity and compliance,[43] sphincter function,[44] pelvic floor function,[13] colonic motility[45] and postprandial response[46,47] have all been shown to be of importance.

Yet, the precise pathophysiological mechanisms behind the syndrome remain unclear.

Several studies have found that diminished rectal capacity and compliance are associated with poor functional outcome.[48] Previously, it was thought that the mere volume of the neorectal reservoir was of major importance and that this was the reason for the protective action of a reconstructed neorectum. More recently, it has been proposed that the effect is caused by a change in motility patterns in the neorectum rather than a volume increase.[49]

Some investigators have suggested that a low anorectal pressure gradient with high neorectal pressures, in combination with low sphincter pressures, is responsible for the incontinence aspect of LARS.[50]

Recently, a study showed that careful preservation of the colonic and pelvic nerves can result in less fragmentation of stools.[51] In high ligation of the inferior mesenteric artery and dissection of the lymph nodes close to the aorta, the extrinsic autonomic sympathetic nerves to the rectum and left side of the colon are resected, causing a sympathetically denervated colonic segment used for creation of the neorectum.[52] This has been suggested to be a major cause of stool fragmentation, due to the missing negative feedback of the defecation reflex, causing an urge to defecate even when only small amounts of stools are present in the neorectum.[51] Therefore, it has been suggested that resection with preservation of the left colonic artery might preserve autonomic function without compromising oncological outcome.[53] Recently, it was shown that patients with major LARS have an increased postprandial response, with significantly increased pressures in the neorectum after a minor meal compared to patients with no LARS, indicating a hyperactive postprandial response. This is possibly due to the lack of a sympathetic breaking action on colonic motility following the ingestion of a meal.[47]

The exact mechanisms for the detrimental effects of RT on bowel function remain unclear. Postoperative RT has been shown to cause lower sphincter pressures and induce fibrosis and rigidity in the neorectum, thereby affecting function significantly.[54]

However, with the use of preoperative RT, the neorectum is constructed from non-irradiated colon, and therefore is not directly affected by the RT. Nevertheless, preoperative RT still increases the risk of LARS significantly, possibly through fibrosis of the surrounding tissues, including nerves. It may also cause direct or indirect damage to the sphincters, even when the sphincters are excluded from the irradiation field.[55] Recently, it was shown that preoperative RT induces neorectal hyposensitivity to mechanical and thermal stimuli, possibly due to impaired afferent nerve function.[56]

In summary, physiological changes in motility and sensibility seem to be the most important factors contributing to

the development of LARS, although biomechanical and anatomical changes might also affect function. Further studies are needed to elucidate this subject.

## Evaluation instruments

Studies investigating the functional disturbances after rectal cancer resection have used a large variety of non-validated instruments. Function has often been described briefly as the proportion of patients experiencing incontinence or urgency, and the mean number of daily bowel movements. Several attempts have been made to conduct a meta-analysis on the functional outcome after rectal cancer resection, but these have not be successful, due to differing terminology and scales used.

Many studies have focused mostly on the incontinence aspect of LARS, probably because of the number of incontinence scores available and that fact that they are easy to use. Unfortunately, these scores only look into one facet of the LARS symptomatology and are not sufficient in describing the complex dysfunction.

In 2005, Temple et al. published a comprehensive scale developed to examine LARS.[57]

The questionnaire consists of 18 questions and can be summed up into several subscales. This questionnaire covers all aspects of LARS, but is very time consuming for both, patients and doctors. Therefore, in our opinion, it is not very suitable for use in daily clinical practice.

In 2012, we published a new instrument for the evaluation of LARS, called the LARS score. The LARS score consists of five simple questions, with score values directly correlated with the impact on QoL.[14] It was initially developed and validated in Danish, but has subsequently been translated and validated in several other languages, and is being used in a number of international trials.[58] The LARS score has been proven to have a high sensitivity and specificity for identifying patients with severe LARS. The benefit of this score is that it is easy to use in both research and clinical settings. Recently, we have shown that even rectal cancer experts do not have a thorough understanding of which LARS symptoms truly matter to the patient, nor how these symptoms affect QoL, thus underlining the necessity of using a validated instrument such as the LARS score to evaluate functional outcome according to the patient's perspective.[59]

## Treatment of LARS

Unfortunately, there is no solid evidence-based treatment available for LARS. Although most colorectal centers have an increased awareness of the condition, treatment is rarely offered to the many patients suffering from severe LARS. Recently, a systematic review confirmed that conservative management of LARS can improve anorectal function and should be recommended as the first choice of treatment.[60]

Retrograde transanal irrigation (TAI), with instillation of lukewarm water into the gut via the anal canal, has been found to be effective in up to 79% of cases in smaller series.[61,62] In addition, sacral nerve stimulation (SNS) has proven to be effective in several small studies.[63,64] However, both methods require further investigation, preferably in large RCTs, before general recommendations can be made.

## Perspectives

Bowel dysfunction following sphincter-preserving resection for rectal cancer is a major problem, with almost half of the patients experiencing severe dysfunction on a daily basis with a significant impairment of quality of life.

With increasing incidence and survival of rectal cancer, the need for knowledge of the true extent of LARS is crucial for all colorectal surgeons. All patients should be thoroughly informed of the risk of LARS before surgery, and an individual risk evaluation should be performed. This recommendation is particularly important in low rectal cancers, where the choice between LAR and APR should be made based on the risk evaluation and patient preference after being adequately informed.

Given that neoadjuvant therapy (NT) has only limited benefit on overall survival, but a detrimental effect on function, the selection of patients for NT should, in our opinion, be more conservative. Currently, many studies are investigating the potential molecular, biological, genetic and histological markers for the prediction of the effectiveness of RT.

Once we can identify the tumors that are most responsive to radiotherapy, we can diminish the proportion of patients being "over-treated" with RT, where they experience no benefit but only side effects.

However, resectional surgery is the major cause of LARS. With implementation of colorectal cancer screening programs, we hope that in the future, more rectal cancers will be curable with local excision only. Also, promising results are seen with identifying complete responders to chemoradiotherapy and watchful waiting, which could render resectional therapy unnecessary. However, the functional outcome of this patient group remains to be investigated.

More studies are needed to elucidate the full pathophysiology of LARS in order to further refine the surgical procedure and prevent severe dysfunction, possibly through a "sympaticus-preserving resection".

All patients recovering after LAR should be routinely screened for LARS using a validated instrument. Functional outcome, as well as oncological outcome, should be systematically registered for all patients, in order to monitor the quality of any treatment they receive. This will yield a baseline reference for new treatment modalities – both in terms of treatment of the cancer itself, and in terms of treatment of the functional disturbances.

All patients with severe LARS should be offered counselling and conservative treatment, or preferably be enrolled in trials investigating the effect of TAI or SNS or any other treatment targeting LARS.

## Conflicts of interest

The authors declare no conflicts of interest.

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