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The factors affecting development of low anterior resection syndrome (LARS) in patients undergoing sphincter preserving surgery for rectal cancer

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OBJECTIVE **To investigate the incidence of major low anterior resection syndrome (LARS), using the LARS score, in patients who underwent sphincter-preserving surgery for rectal cancer, and to explore the factors affecting major LARS development.** METHOD **The medical records were retrospectively reviewed of patients, who were operated for rectal cancer at a tertiary center between January 2009 and October 2017. The inclusion criteria were: The absence of other colorectal or proctologic diseases, the application of anterior resection (high anterior resection, low anterior resection, extremely low anterior resection), follow-up of more than one year after the primary surgery, and follow-up of more than one year after protective ileostomy closure, and the absence of an unreversed stoma, ongoing treatment with chemotherapy or radiotherapy, recurrence, and metastatic disease. LARS was diagnosed using the LARS score developed by Emmertsen and Laurberg.** RESULTS **For the study period, 81 patients met the inclusion criteria, including 45 (55.5%) men and 36 (44.4%) women, with a mean age of 60.1 years. Of the 81 patients, 56 (69.1%) underwent chemotherapy and 43 (53%) underwent radiotherapy. Major LARS was detected in 29.6% of the patients. Univariate analysis revealed that radiotherapy, lower tumor location and a short interval after ileostomy closure had an effect on LARS development, and multivariate analysis indicated that incidence of LARS was higher in middle and lower rectal cancer.** CONCLUSIONS **There appears to be no harm in creating a protective ileostomy for LARS development, with regard to anastomosis safety and the planning of the adjuvant therapy. Neither radiotherapy, nor type of surgery had an effect on major LARS. As was expected, a high rate of major LARS was reported in lower rectal tumors.**

Οι παράγοντες που επηρεάζουν την εμφάνιση του συνδρόμου χαμηλής πρόσθιας εκτομής (LARS) σε ασθενείς οι οποίοι έχουν υποβληθεί σε χειρουργική επέμβαση διατήρησης του σφιγκτήρα για καρκίνο του ορθού

Περίληψη στο τέλος του άρθρου

Key words

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Advances in neoadjuvant therapy and surgical techniques have resulted in improvement in the treatment of rectal cancer, whereby sphincter-preserving resection has become the method of choice in the surgical treatment of middle and lower rectal cancer, with abdominoperineal resection decreasing in popularity.[1,2] Although sphincter-preserving resection has decreased the need for a permanent stoma, this technique has been shown to cause poor functional outcomes that impair the quality of life, such as frequent and urgent stools, liquid/solid stool incontinence, flatal incontinence, and a sense of constipation.[3–7]

The anterior resection syndrome (ARS) is defined as bowel dysfunction after rectal resection, leading to a detriment in the quality of life. It is commonly termed low anterior resection syndrome (LARS), due to the anastomosis created in the aboral part of the rectum.[7,8] The potential risk factors for LARS, including radiotherapy, chemotherapy, low anastomosis, total (as opposed to partial) mesorectal excision, temporary diverting colostomy, anastomotic complications, etc., were included in various studies.[3,5–25] Among these studies only two[12,14] revealed that radiotherapy negatively affects long-term bowel function.[6,9–11,13–16,21–25] Several studies, with one exception,[18] suggested that creating a protective ileostomy has no effect on LARS development.[6,11,12,14,16,17] Although some studies reported that the distance of the tumor from the anal verge had no effect on LARS development,[11,13,14] others proposed that the incidence of major LARS was higher for tumors localized proximal to the anal verge.[15,16,21] The literature indicates that postoperative

complications have no effect on LARS development.[10–12] LARS has been reported in from 25% to 90% of patients after rectal resection. The wide interval between these two rates can be attributed to the fact that there were no standard scoring criteria.[5,6] Until the introduction of specific criteria (LARS score) by Emmertsen and Laurberg in 2013, there was no consensus on diagnostic criteria for LARS.[9]

The present study aimed to investigate the incidence of major LARS, using the LARS score, in patients who underwent sphincter-preserving surgery for rectal cancer, and to explore the factors affecting major LARS development.

MATERIAL AND METHOD

Patients

The medical records of patients who were operated on for rectal cancer at a tertiary center between January 2009 and October 2017 were reviewed retrospectively. The inclusion criteria were: Patients who gave informed consent for participation in the study, the absence of other colorectal or proctologic diseases, the application of anterior resection (high anterior resection, low anterior resection, extremely low anterior resection), follow-up of more than one year after the primary surgery, and follow-up of more than one year after protective ileostomy closure, and the absence of an unreversed stoma, ongoing treatment with chemotherapy or radiotherapy, recurrence, and metastatic disease. A total of 81 patients met these criteria and were included in the study.

Diagnosis of low anterior resection syndrome

LARS was diagnosed using the LARS score developed by Emmertsen and Laurberg.[9] The patients were interviewed face-to-face or by telephone. During the interviews, a five-item questionnaire based on the LARS score was administered to each patient. Depending on their replies, the patients were classified into three groups: (a) no LARS (LARS score: 0–20), (b) minor LARS (LARS score: 21–29), and major LARS (LARS score: 30–42).

Surgical technique

Colorectal excision was performed via laparotomy or laparoscopy with splenic flexure mobilization, combined with high ligation of the inferior mesenteric artery. Total mesorectal excision (TME) was performed on patients with middle and lower rectal cancer, and partial mesorectal excision (PME) was performed on patients with upper rectal cancer. In each patient, either a colorectal (stapled or manual) anastomosis or a coloanal (manual) anastomosis was made.

Ethics

The study was conducted according to the principles set forth by the Helsinki Declaration of 1975. Approval from the Human Ethics Committee of the Institution was obtained, and the patients provided informed consent for participation.

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS for Windows), version 17.0. The demographic characteristics of the patients and the clinicopathological features of the tumor were analyzed using descriptive analysis, and expressed as n (%) and mean (M) with standard deviation (±SD). A logistic model was set up to describe the relationship between major LARS and variables possibly associated with major LARS development: Age, gender, tumor size, histological differentiation, level of the tumor in the rectum (distance from the anal verge), tumor extent (T stage) and lymph node involvement (N stage), cancer stage, surgical technique, postoperative complications, time from the primary surgery, time until ileostomy closure, time from ileostomy closure, and history of neoadjuvant and adjuvant therapies. Tumor size was measured based on the largest tumor diameter from the pathology report. T staging was performed by using the tumor/node/metastasis (TNM) classification described in chapter 7 of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual.[26]

The selection of variables for logistic model was started by Chi-square independence test and Mann-Whitney U test ($p<0.05$ was regarded as significant). Significant variables were included in multivariate binary logistic regression analysis. A bivariate correlation test was used to determine whether there was a relationship between independent variables to be analyzed before multivariate binary logistic regression analysis. In multivariate binary logistic regression analysis, backward stepwise method (likelihood ratio) was used. The level of significance used at the entry of the variables was 0.05, whereas the level of significance used for the removal was 0.1. The level of significance used in testing the model in general was 0.05.

RESULTS

Of the 81 patients who met the inclusion criteria, 45 (55.5%) were men and 36 (44.4%) women, with mean age of 60.1 years. Of the 81 patients, 56 (69.1%) underwent chemotherapy and 43 (53.0%) underwent radiotherapy. Laparoscopic surgery was performed on 42 (51.8%) patients, and in 8 (19.0%) of them conversion to the open technique was needed. Stapled colorectal anastomosis was performed in the majority of cases (92.5%). A protective ileostomy was created in 35 (43.2%) patients, 7 (20.0%) of which were closed within the first three months. The mean number of excised lymph nodes was 18.44. The distal and proximal surgical margins were intact in all patients, but the radial surgical margin was positive in one patient anteriorly. Complete mesorectal integrity was achieved in 70 (86.4%) patients. Complications occurred in 12 (15.6%) patients, including ureter injury (1), mesenteric artery injury

(1), both inferior epigastric injury and anastomotic leakage (1), abscess (2), stenosis (6), and anastomotic leakage with abscess formation and stenosis (1). Table 1 presents the demographic characteristics of the patients and the clinicopathological features of the tumors.

Major LARS was diagnosed in 24 (29.6%) patients. Univariate analysis revealed that patient age, gender, histological differentiation, tumor size, T stage, N stage, cancer stage, number of excised lymph nodes, number of metastatic lymph nodes, mesorectal integrity, chemotherapy, creation of a protective ileostomy, postoperative complications, time until ileostomy closure, and time from primary surgery had no effect on major LARS development (tables 2, 3). Radiotherapy, lower tumor location (location in the middle or lower parts of the rectum), short interval after ileostomy closure (as early as 12 months) were identified as risk factors for major LARS (tables 2, 3). The distance from the anal verge was analyzed as a categorical variable (tumor location; lower, middle, upper rectum) in the logistic model. The cut-off point for the distance from the anal verge was 10 cm, which was the cut-off value also for the upper rectum. Multivariate analysis indicated that tumor location was the only risk factor for major LARS development, and that a higher rate of major LARS is detected in lower rectal tumors (p: 0.037, OR [odds ratio]: 14.67 95% CI [95% confidence interval]:1.18–182.3).

DISCUSSION

LARS has been reported in between 25% and 90% of patients after rectal resection. The wide interval between these two rates can be attributed to the lack of standard scoring criteria.[6,9] Until the introduction of specific criteria (LARS score) in 2013, there was no consensus on the diagnostic criteria for LARS.[9]

Table 1. The characteristics of patients with major low anterior resection syndrome (LARS) and the clinicopathological features of the tumors (n=81).

Variables	Mean±SD	Range
Age *(years)*	60.1±13.35	25–93
Tumor size *(cm)*	4.67±2.79	0–21
Tumor distance from the anal verge *(cm)*	9.43±4.1	3–20
Time until ileostomy closure *(months)*	8.1±5.76	1–23
Time from primary surgery *(months)*	34.2±20.42	12–111
Time from ileostomy closure *(months)*	25.2±14.6	12–63
Number of excised lymph nodes	18.44±13.18	0–69
Number of metastatic lymph nodes	1.32±2.1	0–10

SD: standard deviation

Table 2. Analysis for factors associated with major low anterior resection syndrome (LARS) (Univariate analysis) (n=81).

Characteristics	Major LARS Negative n (%)	Major LARS Positive n (%)	p-value
Age (years)			
≤60	27 (77.1)	8 (22.9)	0.244
>60	30 (65.2)	16 (34.8)	
Gender			
Male	31 (68.9)	14 (31.1)	0.74
Female	26 (72.2)	10 (27.8)	
Chemotherapy			
Positive	37 (66.1)	19 (33.9)	0.205
Negative	20 (80.0)	5 (20.0)	
Radiotherapy			
Positive	26 (60.5)	17 (39.5)	*0.038*
Negative	31 (81.6)	7 (18.4)	
Tumor extent (T stage)			
≤T2	19 (76.0)	6 (24.0)	0.458
≥T3	38 (67.9)	18 (32.1)	
Lymph node involvement (N stage)			
N0	33 (75.0)	11 (25.0)	
N1	12 (63.2)	7 (36.8)	0.593
N2	12 (66.7)	6 (33.3)	
Cancer stage			
≤stage II	33 (75.0)	11 (25.0)	0.32
>stage II	24 (64.9)	13 (35.1)	
Histological differentiation (grade)			
Well differentiated	16 (76.2)	5 (23.8)	0.497
Moderate and poorly differentiated	41 (68.3)	19 (31.7)	
Tumor size			
≤4 cm	28 (62.2)	17 (37.8)	0.073
>4 cm	29 (80.6)	7 (19.4)	
Tumor location			
Lower rectum (≤5 cm)	14 (51.9)	13 (48.1)	
Midle rectum (>5, ≤10 cm)	4 (36.4)	7 (63.6)	*<0.001*
Upper rectum (>10 cm)	39 (90.7)	4 (9.3)	
Protective ileostomy			
Positive	22 (62.9)	13 (37.1)	0.196
Negative	35 (76.1)	11 (23.9)	
Surgical technique			
Laparoscopy	28 (66.7)	14 (33.3)	0.449
Open	29 (74.4)	10 (25.6)	
Mesorectal integrity			
Complete	47 (67.1)	23 (32.9)	0.109
Incomplete	10 (90.9)	1 (9.1)	
Postoperative complication			
Positive	8 (66.7)	4 (33.3)	0.761
Negative	49 (71)	20 (29.0)	

Table 3. Analysis for factors associated with major low anterior resection syndrome (LARS) (Mann-Whitney U test) (n=81).

Variables	U	Mean rank		(p)
		No LARS	Major LARS	
Time from primary surgery *(months)*	589.5	42.66	37.06	0.328
Time until ileostomy closure *(months)*	111.5	19.43	15.58	0.28
Time from ileostomy closure *(months)*	63	21.64	11.85	0.006
Number of excised lymph nodes	598.5	39.5	44.56	0.376
Number of metastatic lymph nodes	661	40.6	41.96	0.792

The current study, in which the LARS score was used, revealed that age and gender had no effect on the development of major LARS, which was consistent with most of the previous studies.[6,10–14] It has been postulated that the narrow pelvic cavity in men is a predisposing factor for hypogastric nerve injury during mesorectal excision, and that obstetric anal sphincter injury in women is a predisposing factor for bowel dysfunction.[6,11] It was also noted that the risk of LARS development is 1.9 times higher in patients aged 64 years or younger.[6] Two studies have shown women to be at increased risk of major LARS, with a further study indicating an increased risk for men.[6,11,15]

Major LARS has been reported at an incidence varying between 5.2% and 56.0% in the studies using the LARS score.[6,10–16] The wide range in rates could be attributed to differences among the inclusion criteria in the various studies. One study reported the incidence of LARS as 5.2% in patients undergoing AR and as 28.2% in patients undergoing LAR.[10] Other studies evaluated LARS in patients with a postoperative follow-up of less than one year, and found higher incidence rates of 45–56%.[4–16] In our study, patients with a postoperative follow-up of less than one year were excluded, and the incidence rate of LARS was 29.6%, which was consistent with the incidence rates reported by similar studies.[10,11] Defective defecation function caused by LARS after rectal resection has been shown to improve remarkably within a year after rectal resection. We included patients with postoperative follow-up of more than one year, or follow-up of more than one year after ileostomy closure. In this way, a well-defined patient group was formed that excluded patients with a risk of defecation problems in the early stages that resolved in the later stages. Unlike the studies that included patients with a postoperative follow-up of less than one year, in the current study it was found that the length of the postoperative follow-up period (i.e., one year and more) had no effect on major LARS.[14,16]

Numerous studies have suggested that creating a protective ileostomy has no effect on LARS development,[6,11,12,14,16,17] but one study reported that LARS was more frequently seen in patients following ileostomy.[19] In that study, evaluating 129 patients with LARS, of whom 41 (31.8%) underwent ileostomy, the presence of ileostomy was found to increase the risk of LARS in univariate analysis, but no effect was shown in 42.8% of patients who had a protective ileostomy; it was revealed that performing a temporary ileostomy had no effect on the development of major LARS. The reported mean time of ileostomy closure is three months, but the optimal timing for ileostomy closure remains controversial. Earlier randomized controlled studies suggested that early closure of temporary ileostomy is possible.[13,19,20] In a study evaluating 68 patients, LARS was 3.7 times more common in patients who underwent ileostomy closure after postoperative month 6.[13] In our study, the ileostomy was closed within the first three months in 20.0% of the patients (mean: 8.1±5.76 months; range: 1–23 months), and the timing of ileostomy closure had no effect on LARS development. We consider that since the previous study included patients that had a postoperative follow-up of less than one year, the patient series was dissimilar to that in our study. As our study included only patients with a follow-up of more than one year after protective ileostomy closure, we consider the difference in patient selection to be pronounced. To our knowledge, there has been no study in the literature investigating the effect of the time period after ileostomy closure on LARS development. In the present study, univariate analysis revealed that a short time interval after ileostomy closure increased LARS development while multivariate analysis revealed that it had no effect on LARS development.

The effect of T stage and N stage on LARS development has been investigated in a limited number of studies and has been shown to have no association with the development of major LARS.[6,10,11,13] In line with these studies, we found that T stage, N stage, and the extension of the tumor (localized [≤SII] vs spreading [>SII]) had no association with the development of major LARS. Literature review revealed no study reporting on the effect of tumor size. In the present study, we found no association between tumor size and major LARS. Since the tumor size was based on the pathological specimen, the measurements do not represent the preop-

erative tumor size, measured before neoadjuvant therapy.

All previous studies, apart from two[12,14] indicated that radiotherapy has adverse effects on the capacity of the new rectum and the development of major LARS.[6,9,10,11,13–16,21–25] In the present study, though univariate analysis indicated that radiotherapy has an effect on LARS development, multivariate analysis revealed no association.

Contradictory findings have been reported on the effect of the distance of the tumor from the anal verge on the development of major LARS. Although some studies showed no effect,[11,13,14] others reported that the incidence of major LARS was greater in tumors localized close to the anal verge,[15,16,21] although there is inconsistency about the cut-off point; cut-off points of 8 cm, 10 cm and 13.3 cm from the anal verge were determined in three studies, none of which distances was found to have an effect on the development of major LARS.[11,13,14] The common ground of these three studies is that the tumor was localized in the upper rectum in most of the patients and or the cut-off points determined in these studies were higher than those reported in other studies. These features could be the reason for the absence of a difference in the groups investigated in each of these studies. In the present study, upper rectal tumors were present in 53.0% of the patients. The cut-off distance for LARS development, based on the ROC curve, was 10 cm; the incidence of LARS was significantly lower for tumors at a distance of more than 10 cm. The analysis indicated that the risk of LARS development was lowest in upper rectal tumors.

It has been suggested that the use of robot-assisted surgery, laparotomy, and laparoscopy for rectal resection has no effect on LARS development.[11] This study indicated no difference between laparotomy and laparoscopy for rectal resection in LARS development. In the current study, laparoscopic surgery was performed on 51.8% of patients, while in the previous study laparotomy was performed on 60.7%, laparoscopy on 21.3%, and robot-assisted surgery on 18.0% of the patients.

The literature indicates that postoperative complications have no effect on LARS development.[10–12] We, also, found that although postoperative complications occurred in 14.8% of the patients, these complications had no effect on the development of major LARS.

This study was limited for several reasons. Firstly, the study had a retrospective design and a small patient series. Secondly, tumor size was measured on the pathological specimens; this measurement does not represent the preoperative tumor size before neoadjuvant therapy.

In conclusion, there appears to be no adverse effect on LARS development from creating a protective ileostomy, with regard to anastomosis safety and the planning of the adjuvant therapy, and the timing of ileostomy closure had no effect on LARS development. In addition, neither radiotherapy nor type of surgery has an effect on major LARS. A higher rate of major LARS can be expected following surgery for middle and lower rectal tumors.

ΠΕΡΙΛΗΨΗ

Οι παράγοντες που επηρεάζουν την εμφάνιση του συνδρόμου χαμηλής πρόσθιας εκτομής (LARS) σε ασθενείς οι οποίοι έχουν υποβληθεί σε χειρουργική επέμβαση διατήρησης του σφιγκτήρα για καρκίνο του ορθού

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ΣΚΟΠΟΣ Η διερεύνηση της συχνότητας εμφάνισης σοβαρού συνδρόμου χαμηλής πρόσθιας εκτομής (LARS) του ορθού σύμφωνα με τη βαθμολογία (score) LARS σε ασθενείς που υποβλήθηκαν σε χειρουργική επέμβαση προστασίας του σφιγκτήρα του ορθού και η διερεύνηση των παραγόντων που επηρεάζουν την ανάπτυξη LARS. **ΥΛΙΚΟ-ΜΕΘΟΔΟΣ** Μελετήθηκαν αναδρομικά 81 ασθενείς που χειρουργήθηκαν για καρκίνο του ορθού σε ένα τριτοβάθμιο κέντρο μεταξύ Ιανουαρίου 2009 και Οκτωβρίου 2017. Η διάγνωση του LARS έγινε με τη χρήση του score LARS, όπως αναπτύχθηκε από τους Emmertsen και Laurberg. **ΑΠΟΤΕΛΕΣΜΑΤΑ** Μείζον LARS παρατηρήθηκε στο 29,6% των ασθενών. Αν και η ανάλυση έδειξε ότι τόσο η ακτινοθεραπεία όσο και η εντόπιση του όγκου επηρέαζαν την εμφάνιση LARS, η πολυπαραγοντική ανάλυση ανέδειξε ότι η εμφάνιση του LARS ήταν συχνότερη στον καρκίνο που εντοπιζόταν στο μέσο και κατώτερο τμήμα του ορθού. **ΣΥΜΠΕΡΑΣΜΑΤΑ** Αναμένεται συχνότερη εμφάνιση μείζονος LARS στην περίπτωση όγκων στο μέσο και στο κατώτερο τμήμα του ορθού.

Λέξεις ευρετηρίου: Καρκίνος ορθού, Σύνδρομο χαμηλής πρόσθιας εκτομής (LARS), Χαμηλή εκτομή ορθού

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