Original Article

Chirurgia (2016) 111: 481-486
No. 6, November-December

http://dx.doi.org/10.21614/chirurgia.111.6.481

Sphincter-Sparing Surgery in Patients with Mid and Low Rectal Cancer - Risk Factors for Local Recurrence and Anastomotic Leakage

Denis Aslan[1,2], Florin Grama[1], Daniel Cristian[1,2], Adrian Bordea[1,2], Traean Burcoș[1,2]

[1]Department of General Surgery, Colțea Clinical Hospital, Bucharest
[2]University of Medicine and Pharmacy "Carol Davila", Bucharest

Rezumat

Chirurgia de prezervare a sfincterului anal în cancerul rectal mediu și inferior - factori de risc pentru recidiva locală și fistula anastomotică

Introducere: Cancerul rectal reprezintă o problemă majoră de sănătate. Tratamentul actual al cancerului rectal distal implică o abordare multimodală cu scopul de a realiza un control oncologic optim și o calitate crescută a vieții.
Scop: Scopul acestui articol este acela de a identifica factorii de risc pentru apariția recidivei locale și fistulei anastomotice după intervenția chirurgicală de prezervare a sfincterului anal în cancerul rectal mediu și inferior.
Material și metodă: Am analizat prospectiv un grup de 38 de pacienți cu cancer rectal mediu și inferior situat care au beneficiat de chirurgie de prezervarea a sfincterului anal. Intervenția chirurgicală a constat în rezecție anterioară joasă în 32 (84,2%) de cazuri și rezecție anterioară ultrajoasă în 6 (15,8%) cazuri. Stadializarea cTNM a inclus 3 (7,9%) pacienți în stadiul T1, 11 (28,9%) pacienți în stadiul T2, 24 (63,2%) de pacienți în stadiul T3. Radioterapia preoperatorie a fost efectuată în 33 (86,4%) de cazuri, iar chimioterapia a fost asociată în 20 (52,6%) de cazuri.
Rezultate: Stadiile tumorale I și II au fost predominate (63,2%), fiind urmate de tumorile în stadiul III (23,7%) și stadiul IV (13,2%). Rata complicațiilor a fost de 52,6% (20 de cazuri) și a fost asociată cu stadiul T3. Fistulele anastomotice au apărut în 4 cazuri (10,5%) și recidiva tumorală s-a dezvoltat în 3 cazuri (7,9%). Rata de recurență locală și rata fistulelor anastomotice a fost asociată cu numărul de ganglioni limfatici pozitivi (mai mult de 4 noduri, 5,3%, $p = 0,023$). Nu am găsit nicio asociere între chimioradioterapie și riscul de recidivă locală ($p > 0,05$). Alte complicații postoperatorii au inclus ocluzia intestinală prin aderențe sau volvulus intestinal (5 cazuri, 13,2%), colita postradică (3 cazuri, 7,7%), stenoza anastomotică coloanală (1 caz, 2,6%), fistula rectovaginală (1 caz, 2,6%), sângerare ileostomă (1 caz, 2,6%), infecția de plagă (2 cazuri, 5,3%).
Concluzii: Factorii de risc asociați cu recurența locală și fistula anastomotică sunt reprezentați de stadiul agresiv tumoral, invazia nodulilor limfatici, terapia neoadjuvantă și anemia postoperatorie. Evoluția postoperatorie după intervenția chirurgicală de prezervare a sfincterului anal a fost favorabilă și absența colostomiei definitive a avut un impact important asupra calității vieții pacienților cu cancer rectal distal.

Cuvinte cheie: cancer rectal, prezervarea sfincterului anal, radiochimioterapia neoadjuvantă, excizia totală a mezorectului

Abstract

Background: Rectal cancer is a major health problem. The current treatment of distal rectal cancer involves a multimodality approach aimed at achieving an optimal oncologic control and an increased quality of life.
Purpose: The purpose of this article is to identify the risk

Corresponding author: Denis Aslan, MD
Coltea Clinical Hospital
Bd. I. C. Bratianu, nr. 1-3, Sector 3, Bucharest
E-mail: denisasl@yahoo.com

factors for local recurrence and anastomotic leakage after sphincter-sparing surgery for low and mid rectal cancer.
Material and Methods: We prospectively analyzed a group of 38 patients with low and middle rectal cancer who underwent sphincter-sparing surgery. Low anterior resection was performed in 32 cases (84.2%) and 6 cases (15.8%) benefited of ultralow anterior resection. Clinical stadialization cTNM included 3 patients (7.9%) T1 stage, 11 patients (28.9%) T2 stage and 24 patients (63.2%) T3 stage. Preoperative radiotherapy was performed in 33 cases (86.4%), and chemotherapy was associated in 20 cases (52.6%).
Results: The stages I and II cancers were prevalent (63.2%), followed by stage III cancers (23.7%) and stage IV cancers (13.2%). The rate of complications of 52.6% (20 cases) was associated with T3 stage cancers. Anastomotic leakage has occurred in 4 cases (10.5%) and tumor recurrence has developed in 3 cases (7.9%). The rate of local recurrence and anastomotic leakage is associated with the number of positive lymph nodes (more than 4 nodes, 5.3%, $p = 0.023$). We found no association between chemoradiotherapy and the risk of local recurrence ($p > 0.05$). Other postoperative complications included intestinal obstruction by adhesions or bowel volvulus (5 cases, 13.2%), postradiation colitis (3 cases, 7.7%), coloanal anastomotic stenosis (1 case, 2.6%), rectovaginal fistula (1 case, 2.6%), ileostomy bleeding (1 case, 2.6%), wound infection (2 cases, 5.3%).
Conclusions: Risk factors associated with local recurrence and anastomotic leakage are aggressive stage tumor, lymph-nodes involvement, neoadjuvant therapy and postoperative anemia. The postoperative outcome was favorable after sphincter preservation surgery and the absence of definitive colostomy had an important impact on the quality of life of the patients with distal rectal cancer.

Key words: rectal cancer, sphincter-sparing surgery, neo-adjuvant chemoradiotherapy, total mesorectal excision

Introduction

Rectal cancer is a major public health problem, it is the third most common cancer worldwide (1). The standard therapeutic strategy consists in neoadjuvant radiochemotherapy followed by surgical resection with total mesorectal excision (TME). The incidence of rectal cancer is increasing worldwide and in terms of mortality rates, rectal cancer represents the second leading cause of death among both men (11.6%) and women (13%) (2). Therefore, the introduction of screening programs in high risk population is evidenced that will improve survival in these patients.

The primary prevention stategies cand further reduce the overall incidence of rectal cancer. The breakthrough moment in rectal cancer surgery was the introduction of the concept of total excision of mesorectum (TME) by Heald in 1982 (3). The gold-standard in rectal surgery involves sharp dissection under direct vission in well-lighted field following the Heald's „Holy Plane" and the excision of the intact unit of the rectum together with the entire mesorectum and intact perirectal fascia. The result is an oncological resected specimen R0. In this way the risk of local recurrence decreases to 10% (4). Abdominoperineal resection is still widely performed, although having important consequences on the quality of life of these patients. The permanent stoma has major psychological impact, affecting the social reintegration, the quality of life and involves permanent stoma care.

There is a continuing concern for the development of surgical techniques in order to preserve the anal sphincter and the anal continence, all the efforts will lead to a higher quality of life.

Therefore, the improvements in mechanical suture technologies brought an essential contribution in low level rectal reconstruction. The standardization of neoadjuvant chemo-radiation treatment may lead to „downstage" the tumors so the sphincter-sparing surgery can be performed even in initial locally advanced tumor stages.

Material and Method

We prospectively studied a group of 38 patients with sphincter-sparing surgery for mid and low rectal cancer at Department of General Surgery, Coltea Clinical Hospital, Bucharest, between 2012 and 2015. We included only patients with middle third and middle low rectal cancer within 9 cm from anal verge. The diagnosis was confirmed by paraffin pathology exam. Preoperative stadialization included clinical evaluation (digital rectal examination) and flexibile colonoscopy with biopsy, abdominal ultrasound, chest X-ray, high-quality imaging scans (computed tomography-CT, magnetic resonance imaging-MRI). Patients have benefited of anal sphincter preservation surgery and abdominoperineal resection.

Data were analyzed prospectively, following the criteria: age, sex, tumor location, comorbidities, neoadjuvant treatment, type of surgery, presence of ileostomy, number of lymph nodes examined and the number of invaded lymph nodes, postoperative complications. Data were processed and analyzed using statistical test Chi-Square by SPSS v20 programme for Windows. A p value less than 0.05 was considered statistically significant.

Neoadjuvant therapy consisted of radiotherapy alone or in association with chemotherapy. The surgery was performed at the average interval of 4-6 weeks after completion of neo-adjuvant therapy. The sphincter-sparing surgery consisted in low anterior resection (LAR) with stapled end-to-end colo-rectal aanstomosis and ultralow anterior resection (ULAR) with hand-sewen coloanal anastomosis. Total mesorectal excision (TME) was performed for all patients.

The surgical management was decided by a multi-disciplinary team (MDT) with the work of colorectal surgeons, imagists, oncologists, radiation therapists, pathologists. The inclusion criteria for sphincter-sparing surgery were: the distance from the anal verge, the histopathological stage, asso-

ciated comorbidities, the surgeon's experience in colorectal cancer surgery and the accessibility to mechanical suturing devices.

Results

During a period of three years we studied 38 patients diagnosed with low and mid rectal cancer who underwent sphincter-sparing surgery. We excluded patients with transanal tumor resection.

The patients characteristics are presented in *Table 1*. The list of comorbidities included cardiovascular diseases such as hypertension (29 cases, 76.3%), ischemic heart disease (23 cases, 60.5%), heart failure (24 cases, 63.2%), diabetes mellitus type II (7 cases, 18.4%), dyslipidemia (7 cases, 18.4%). The clinical TNM stages included T1 and T2 stage cancers in 36.8% of patients (14 cases), and T3 stage tumors in 24 cases (63.2%). Of all cases in the study, 2 patients (5.3%) benefited from temporary colostoma so the neoadjuvant therapy can be followed. These two patients underwent low anterior resection. One patient developed tumor recurrence 2 years later and required abdominoperineal resection.

Neoadjuvant therapy was applied in selected cases. Most patients (33 cases, 86.8%) received external beam radiation (EBR) with conventional fraction of 45-50 Gy with administration of 1.8-2 Gy/session. Half the patients have had associated neoadjuvant chemotherapy.

Surgery was performed 4-6 weeks after completion of neoadjuvant treatment. The surgical therapeutical options included: low anterior rectal resection (LAR) with end-to-end colorectal anastomosis using circular staplers in 32 cases (84.2%) and ultralow anterior rectal resection (ULAR) followed by coloanal anastomosis in 6 cases (15.8%) (*Table 2*). Total mesorectal excision (TME) was performed in all cases. The resected rectum was a cilinder shape specimen with glossy, intact mesorectum and perirectal fascia.

The surgeons used linear staplers for resection of the rectum and colon and circular end-to-end anastomosis (EEA) staplers for colorectal anastomosis. The integrity of the anastomosis was checked by transanal air or methylene blue instillation. There were only few cases (2 patients, 5.2%) which had required staple line reinforcement using one or two sutures 2.0 or 3.0. The resected specimen was examined ex-vivo with a special attention for the integrity of the two donuts. The patient-related factors like increased visceral fat, narrow pelvis in men, pelvic postradiotherapy fibrosis, prostate adenoma, postsurgical adhesions has made the sharp dissection difficult in some cases.

Protective ileostomy was performed in 22 cases (57.9%): 16 cases (42.1%) with colorectal anastomosis and all 6 cases (15.8%) with coloanal restauration. In most cases protective ileostomy was reintegrated at about 6 weeks after the initial surgery (minimum 3 weeks, maximum 14 weeks). In all cases the integrity of the anastomosis was evaluated by digital rectal examination and flexible colonoscopy which confirmed the absence of local recurrences.

Pathology exams confirmed that well-differentiated adenocarcinoma (G1) represented the most frequent cases (68.4%).

Table 1. *Distribution according to sex, age, tumor location, AJCC (American Joint Committee on Cancer) cancer stage*

		Frecquence	Procent
Sex	M	23	60.5%
	F	15	39.5%
Age	Average	62.8 y	
Rectum	Mid	24	63.2%
	Low	14	36.8%
Stage I AJCC	T1N0M0	3	7.9%
	T2N0M0	9	23.7%
Stage IIA AJCC	T3N0M0	12	31.6%
Stage IIIA AJCC	T1,T2N1M0	1	2.6%
Stage IIIB AJCC	T3,T4N1M0	3	7.9%
	Any T N2 M0	5	13.2%
Stage IV AJCC	Any T Any N M1	5	13.2%

Table 2. *Type of surgery and ileostomy rate distribution*

		Frecquence	Procent
Type of surgery	LAR	32	84.2%
	ULAR	6	15.8%
Ileostomy		22	57.9%

Pathologist examined an average number of lymph nodes excised of 12.7 (maximum 50 lymph nodes per specimen), and identified an average number of positive nodes of 2.9 (maximum 46 lymph nodes per specimen).

We identified 20 cases (52.6%) with postoperative complications. We have observed an association between advanced TNM stage and the complication rate (44.7% for stage T3 cancers, p=0.05).

The statistical analysis revealed an association between the complications rate and neoadjuvant radiotherapy (50% in the preoperative radiotherapy group compared with 7.9% in the group without radiotherapy). There is a similar association in case of preoperative chemotherapy (31.6% vs. 26.3%). There is a significant association between anemia and the complication rate. Preoperative hemoglobin level above 11 g/dL is a protective factor against the development of postoperative complications (42.1%, p=0.03). Postoperative hemoglobin below 11 g/dL is associated with higher rates of complications (47.4%, p=0.05). Tumor markers carbohydrate antigen CA 19-9 and carcinoembryonic antigen CEA have not been significantly associated with complication rate, but CA 19-9 level was increased mostly in T3 stage cancers (47.4%, p=0.0001). The two most important postoperative complications are anastomotic leakage (AL) and local recurrence (LR).

Anastomotic leakage (AL)

After restaurative rectal resection 4 patients (10.5%) developed grade B anastomotic leakage (AL) (according to International Study Group of Rectal Cancer) (5). In case of these 4 patients with AL we found these following data. Due to the anatomical difficulties, there were more cases in men than in women (3

males compared with 1 female). All cases of AL have occured after stage T3 tumors followed by LAR. The initial location of the tumor was at the mid rectum in 3 cases and at the low rectum in 1 case. Three patients with AL have had performed neoadjuvant radiotherapy and only one patient have had associated chemotherapy. Tumor marker carbohydrate antigen CA 19-9 has been elevated for 3 patients and CEA for 1 patient. Pathology exams revealed well-differentiated adenocarcinoma in 2 cases and moderate-differentiated adenocarcinoma in 2 cases and also a serous tumor involvement in most of the AL cases (3 cases). The perineural and lymphovascular invasion and radial margins invasion were not present in any case of AL.

The statistical data revealed that one of the significant factor associated with risk of AL was the lymph nodes invasion rate (5.3% risk of AL in cases of more than 10 positive lymph nodes were involved, p=0.01). One case had been associated with protective ileostomy. All four patients with AL have developed postoperative anemia.

For all cases of AL, the intestinal liquid flow was low, around 5 ml to 10 ml per day. The leakage had been spontaneously closed after conservative treatment, during the 3rd and the 14th day.

Local recurrence (LR)

The recurrence rate (LR) was 7.9% (3 cases) and it was associated with TNM stage T3 cancers and the number of positive lymph nodes (more than 4 nodes, 5.3%, p=0.023). The initial tumor was located at the middle rectum in 2 cases and at the inferior rectum in 1 case. Tumor markers carbohydrate antigen CA 19-9 (all 3 cases) and carcinoembryonic antigen CEA (2 cases) level have been incresed. Two patients with LR had underwernt neoadjuvant radiochemotherapy.

Local recurrence has developed on an average of 2 years (minimum 1 year, maximum 3 years) after the initial surgery. One of the three cases developed local recurrence at 1 year after restaurative rectal resection for T3N0M0 stage cancer. The patient underwent radical surgery with permanent stoma, but after another 1 year he developed another local relapse (tumoral invasion of the presacral fascia) which led to an R2 resection. The second patient developed a local recurrence at 3 year after rectal resection for T3N2M0 stage cancer. The surgical option was limited to exploratory laparotomy with permanent colostomy. In the third case the local recurrence was discovered by a follow-up colonoscopy examination. The patient had major comorbid conditions (liver and bone metastasis, cardiac failure, renal chronic failure, intracerebral tumor, ureterohydronefrosis and deep left vein thrombosis due to left piriform muscle and dorsolateral tumor involvement of the pelvis) that left no option for radical surgery. He underwernt palliative therapy. The pathology examination revealed that LR occured in 2 cases of moderate-differentiated adenocarcinoma and in 1 case of well-differentiated adenocarcinoma. There were no evidence of serous tumor involvement nor perineural and lymphovascular invasion in all LR cases, but the radial margin invasion was found in 1 case. All three patients have developed postoperative anemia. Postoperative chemotherapy was applied for all 3 patients and only 1 patient have had associated external radiotherapy.

A number of other complication was identified: bowel obstruction due to adhesions or bowel volvulus (5 cases, 13.2%), postradiotherapy colitis (3 cases, 7.7%), coloanal anastomotic stenosis (1 case, 2.6%), rectovaginal fistula (1 case, 2.6%), ileostomy bleeding (1 case, 2.6%), wound infection (2 cases, 5.3%). The mortality rate was 5.26 % (2 cases). One patient who benefited of restaurative rectal resection having major cardiovascular and neurological comorbidities died during the 10th postoperative day due to an intestinal dynamic obstruction. Another patient died after intestinal obstruction by adhesions at 1 year after anterior resection (patient with BMI more than 26 and major cardiovascular comorbidities).

The quality of life of these patients was assessed by a subjective analysis according to the clinical complains, digestive tolerance, bowel and urogenital function, postoperative anal continence, level of family, social and professional work reintegration. The absence of permanent colostomy had a favorable impact on the normal digestive functionality and postoperative evolution. We identified a good quality of life, with favorable postoperative evolution, encumbered by a reduced number and intensity of surgery-related complications.

The current article is limited by the small number of the patients included in study. The analysis is based on highly variable factors like surgeon-related factors (extended experience in colorectal surgery) and patient-related factors (tumor stage, pathology exams, tumor location, age, comorbidities, neoadjuvant chemoradiotherapy, type of surgery, presence of ileostomy, patient's decision). The patient was given the consent and his decision was an important factor. Although it is a subjective criteria, the patient with absolute refusal for permanent stoma, despite the MDT' recommendations, resulted in still limited oncological radicality. In exceptional cases there were performed rectal resections with colorectal anastomosis for tumor stage T3 cancers.

Discussions

Colorectal cancer incidence is still increasing, both in women and in men (1,2). Worldwide, rectal cancer is the third most frequent of all cancers and a leading cause of overall mortality (6). Relative incidence of rectal cancer increases with age. There are theories that are involving the role of lifestyle-related obesity and dietary imbalances. The risk factors may increase with age. The chances of genetic mutation or malignant transformation of colorectal adenomas and polips is directly proportional with age.

Multimodality treatment will provide an optimal oncologic outcome along with a favorable prognostic and long-term survival. Despite the remarkable technological developments in mechanical suturing devices the surgical treatment of distal rectal cancer remains a challenge.

A combination of external irradiation with neoadjuvant chemotherapy has been shown to achive significant survival benefits by „downstaging" the tumors and by improving reseca-

bility even for larger tumors. According to the studies, the local recurrence rate descreases up to 8% compared with patients with no neoadjuvant therapy (7). The usual dose of irradiation is about 45-50 Gy (8,9). The addition of 5-Fluorouracil or Capecitabine enhances the cytotoxicity, provides treatment of distant metastasis and reduces the need for postoperative chemotherapy (10,11). The studies have shown that there is an association between the complete tumor response to neoadjuvant chemoradiation for rectal cancer and the histopathological and genetic characteristics, tumor stage and lymph node involvement (12,13). According to some authors, the tumor local response may be up to 25-40% (13) or even 92.5% in highly-selected cases (14).

The introduction of the concept of total mesorectal excision (TME) by R. J. Heald in 1982, the surgical treatment of rectal cancer had a colossal breaktrough. The rectum is resected as a cilinder shape specimen along with all the perirectal fat (total mesorectum) and intact perirectal fascia. The meticulous dissection is performed staying between the visceral and parietal pelvic fascia down to the level of the levator ani muscles. Performing the sharp dissection under optimal lighted vision, following the anatomical and embryological dissection planes we will have a theoretical null risk of local recurrence (4). However, there are cases of local and distant recurrence even after oncological resections. The relapse is apparently associated with other tumor-related factors like patient-related factors or therapy-related factors.

The therapeutical options including chemoradiation followed by anterior rectal resection and TME decreases the total risk of local recurrences (15,16,17,18). Postoperative chemotherapy can be administered to patients with favorable prognosis. In case of the patients with low prognosis the option will be a combined radio-chemotherapy (19). Radiochemotherapy indication should be restricted to highly-selected patients, taking into account the associated comorbidities and the patient's tolerance to treatment.

Even in the era of embryological TME, the rectal cancer surgery is not perfect. A several complications can occur in every stage of the therapy. Anastomotic leakage (AL) after colorectal restaurative surgery is a major complication with direct impact on morbidity and mortality. Studies have shown an anastomotic leakage rate of 4-45% (20,21,22,23,24), with significant mortality of 6-22% (23,24).

Protective ileostomy does not decrease the rate of anastomotic fistula, but it lowers its clinical expression and also the need of relaparotomy rate reduces up to 4% (25). The decision to perform protective ileostomy is based on data related to the tumor location (the lower the anastomosis the higher rate of temporary ileostomy) and the extension of the tumor, also the preoperative chemoradiation and the history of comorbidities (26,27).

Conclusions

Sphincter-sparing surgery for distal rectal cancer has low rate of local recurrence and anastomotic leakage. The risk factors for both local recurrence and anastomotic leakage are aggressive tumor stages, lymph-node tumor invasion, postoperative anemia and neoadjuvant therapy. The mortality rate is also low after sphincter-sparing surgery. The introduction of national screening programs in high risk individuals will increase the prognosis of rectal cancer by improved early diagnosis and wide range sphincter-sparing surgery.

Acknowledgement

"This work received financial support through the project entitled "CERO – Career profile: Romanian Researcher", grant number POSDRU/159/1.5/S/135760, cofinanced by the European Social Fund for Sectoral Operational Programme Human Resources Development 2007-2013"

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86. doi: 10.1002/ijc.29210. Epub 2014 Oct 9.
2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374-403. doi: 10.1016/j.ejca.2012.12.027. Epub 2013 Feb 26.
3. Heald RJ. The 'Holy Plane' of rectal surgery. J R Soc Med. 1988;81(9):503-8.
4. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet. 1986;1(8496):1479-82.
5. Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: A proposal by the International Study Group of Rectal Cancer. Surgery. 2009;147(3):339-51. DOI: http://dx.doi.org/10.1016/j.surg.2009.10.012
6. World Cancer Research Fund and American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. Washington, DC: American Institute for Cancer Research; 2007.
7. Jörgren F, Johansson R, Damber L, Lindmark G. Risk factors of rectal cancer local recurrence: population-based survey and validation of the Swedish rectal cancer registry. Colorectal Dis. 2010;12(10):977-86. doi: 10.1111/j.1463-1318.2009.01930.x.
8. Bosset JF, Calais G, Daban A, Berger C, Radosevic-Jelic L, Maingon P, et al. Preoperative chemoradiotherapy versus preoperative radiotherapy in rectal cancer patients: assessment of acute toxicity and treatment compliance. Report of the 22921 randomised trial conducted by the EORTC Radiotherapy Group. Eur J Cancer. 2004;40(2):219-24.
9. Song C, Song S, Kim JS, Oh HK, Kim DW, Lee KW, et al. Impact of postoperative chemoradiotherapy versus chemotherapy alone on recurrence and survival in patients with Stage II and III Upper Rectal Cancer: A Propensity Score-Matched Analysis, PLoS One. eCollection 2015, 10(4):e0123657. doi: 10.1371/journal.pone.0123657
10. Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al. Chemotherapy with preoperative

radiotherapy in rectal cancer. N Engl J Med. 2006;355(11): 1114-23.
11. Seery TE, Ziogas A, Lin BS, Pan C-JG, Stamos MJ, Zell JA. Mortality Risk After Preoperative Versus Postoperative Chemotherapy and Radiotherapy in Lymph Node–Positive Rectal Cancer. Journal of gastrointestinal surgery: official journal of the Society for Surgery of the Alimentary Tract. 2013;17(2):374-381. doi:10.1007/s11605-012-2116-y
12. Goossens-Beumer IJ, Oosting J, Corver WE, Janssen MJ, Janssen B, van Workum W, et al. Copy number alterations and allelic ratio in relation to recurrence of rectal cancer. BMC Genomics. 2015;16:438. doi: 10.1186/s12864-015-1550-0.
13. Mignanelli ED, de Campos-Lobato LF, Stocchi L, Lavery IC, Dietz DW. Downstaging after chemoradiotherapy for locally advanced rectal cancer: is there more (tumor) than meets the eye? Dis Colon Rectum. 2010;53(3):251-6. doi: 10.1007/ DCR. 0b013e3181bcd3cc.
14. Schiffmann L, Klautke G, Wedermann N, Gock M, Prall F, Fietkau R, et al. Prognosis of rectal cancer patients improves with downstaging by intensified neoadjuvant radiochemotherapy-a matched pair analysis. BMC Cancer. 2013;13:388. doi: 10.1186/1471-2407-13-388.
15. Myint S, Lee CD, Snee AJ, Perkins K, Jelley FE, Wong H. High dose rate brachytherapy as a boost after preoperative chemoradiotherapy for more advanced rectal tumours: the Clatterbridge experience. Clin Oncol (R Coll Radiol) 2007; 19(9):711-19. doi: 10.1016/j.clon.2007.07.018
16. Faerden AE, Naimy N, Wiik P, Reiertsen O, Weyessa S, Trønnes S, et al. Total mesorectal excision for rectal cancer: difference in outcome for low and high rectal cancer. Dis Colon Rectum. 2005;48(12):2224-31.
17. Theodoropoulos G, Wise WE, Padmanabhan A, Kerner BA, Taylor CW, Aguilar PS, et al. T-level downstaging and complete pathologic response after preoperative chemoradiation for advanced rectal cancer result in decreased recurrence and improved disease-free survival. Dis Colon Rectum. 2002;45(7): 895-903.
18. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? Br J Surg. 1982; 69(10):613-6.
19. Gao P, Song YX, Sun JX, Chen XW, Xu YY, Zhao JH, et al. Which is the best postoperative chemotherapy regimen in patients with rectal cancer after neoadjuvant therapy? BMC Cancer. 2014 Nov 27;14:888. doi: 10.1186/1471-2407-14-888.
20. Cong ZJ, Hu LH, Bian ZQ, Ye GY, Yu MH, Gao YH, et al. Systematic review of anastomotic leakage rate according to an international grading system following anterior resection for rectal cancer. PLoS One. 2013;8(9):e75519. doi: 10.1371/journal.pone.0075519. eCollection 2013.
21. Rutegård M, Rutegård J. Anastomotic leakage in rectal cancer surgery: The role of blood perfusion. World J Gastrointest Surg. 2015;7(11):289-92. doi: 10.4240/wjgs.v7.i11.289.
22. Zhao WT, Hu FL, Li YY, Li HJ, Luo WM, Sun F. Use of a transanal drainage tube for prevention of anastomotic leakage and bleeding after anterior resection for rectal cancer. World J Surg. 2013;37(1):227-32. doi: 10.1007/s00268-012-1812-9.
23. Rullier E, Laurent C, Garrelon JL, Michel P, Saric J, Parneix M. Risk factors for anastomotic leakage after resection of rectal cancer. Br J Surg. 1998;85(3):355-8.
24. Borly L, Ellebșk MB, Qvist N. Leakage after Surgery for Rectum Cancer: Inconsistency in Reporting to the Danish Colorectal Cancer Group. Surg Res Pract. 2015;2015:376540. doi: 10.1155/2015/376540. Epub 2015 Nov 9.
25. Cong ZJ, Hu LH, Zhong M, Chen L. Diverting stoma with anterior resection for rectal cancer: does it reduce overall anastomotic leakage and leaks requiring laparotomy? Int J Clin Exp Med. 2015;8(8):13045-55. eCollection 2015.
26. Phatak UR, Kao LS, You YN, Rodriguez-Bigas MA, Skibber JM, Feig BW, et al. Impact of ileostomy-related complications on the multidisciplinary treatment of rectal cancer. Ann Surg Oncol. 2014;21(2):507-12. doi: 10.1245/s10434-013-3287-9. Epub 2013 Oct 2.
27. Matthiessen P, Hallböök O, Rutegård J, Simert G, Sjödahl R. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. Ann Surg. 2007;246(2):207-14.