Original Article

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Sphincter preserving surgery after preoperative radiochemotherapy for low rectal cancer

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ABSTRACT

Background: Total mesorectal excision (TME) is now the standard approach for rectal cancer. The introduction of TME in rectal cancer surgery may lead to a reduction in local recurrence rates to below 10%. However, prevention of local recurrence remains one of the key problems in resectable rectal cancer. **Aim:** The aim of this study was to evaluate the feasibility and the effectiveness of preoperative radio-chemotherapy followed by total mesorectal excision (TME) and sphincter-preserving procedures for T3 low rectal cancer. December 2016 to st **Methods:** This study conducted on selected patients from 1November 2018 in Gastroenterology-hepatology teaching hospital in Baghdad. th 30 Patients with rectal cancer and T3 tumors located within 1-6 cm of the dentate line received preoperative radio-chemotherapy. Concurrent 5-fluorouracil-based radio chemotherapy was used. Radical resection with TME and sphincter-preserving procedures were performed during the six to eight weeks following radiotherapy. **Results:** A total of 40 patients were included. The mean ± standard deviation age was 61.4 years ± 12.35 years, and range from 35-78 years, 23 (57.5%) of the Patients were male, and 17 (42.5%) of them were females. Overall down-staging of T classification was 75%. Complete regression of the rectal tumor was observed in 5 patients (12.5%). Twelve patients (30%) had a reduction of >50% and 23 patients (57.5%) had a reduction of >30%.No tumor progression was found. Pathological complete response was 15%. The anastomotic fistula rate was 5%. The complication rate was 15%; in form of urinary incontinence (33.3%), fecal incontinence (50%), and changed sexual function among male patients (75%). A median follow-up showed the local recurrence rate to be 5% and the distant metastasis rate to be 7.5%. **Conclusion:** Preoperative radio-chemotherapy was found to improve tumor down-staging, reduces local recurrence, increase the sphincter preservation rate, and is therefore of benefit to patients withT3 low rectal cancer.
Key words: Total mesorectal excision, radio-chemotherapy, rectal cancer.

Introduction:

The mainstay of treatment for locally advanced rectal cancer (T3-4 and/or N+) has been surgery. With the introduction of the total mesorectal excision method, a substantial decrease in the risk of locoregional failure has been achieved [1]. However, even with the total mesorectal excision (TME) method, surgery alone was found to have an inferior outcome compared to surgery combined with chemo radiotherapy (CRT) for locally advanced rectal cancer. The results of prospective randomized trials demonstrated that local control and survival were improved with adjuvant CRT [2]. TME is now the standard approach for rectal cancer (3). The introduction of TME in rectal cancer surgery may lead to a reduction in local recurrence rates to below 10% (4). However, prevention of local recurrence remains one of the key problems in resectable rectal cancer (5). Findings of randomized trials showed that neoadjuvant therapy improves local control (6).

Preoperative radio-chemotherapy combined with TME has led to significant improvements in local control in patients with locally advanced rectal cancer and a reduction in the local recurrence rate (7). Preoperative radio-chemotherapy combined with TME not only improves local control and oncological cure, but provides support and a greater probability of sphincter preservation in patients with low-middle rectal cancer (8). However, the role of preoperative radio chemotherapy in enhancing sphincter-preserving surgery for rectal cancer is controversial (9). Previously, abdominoperineal resection was the main option for treatment of the patients, particularly for low rectal cancers with T3 tumors. The sphincter preservation rate was low in order to obtain a complete resection to prevent local recurrence. Postoperative radio-chemotherapy followed.

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The conventional treatments were established for local control and disease-free interval following surgical resection [10, 11], but improving sphincter preservation constituted a challenge. Colostomy caused serious inconvenience to the patients and limited their quality of life. Reducing local recurrence and improving sphincter preservation continue to be the challenges in the treatment of rectal cancer [12].

Ideal surgery for rectal cancer should not only obtain adequate radial and circumferential margins, but also preserve normal sphincter function.

The strategy of conventional surgery and post-operational radio-chemotherapy for the treatment of low rectal cancer of T3 tumors signified the loss of sphincter-preserving opportunities for the patients during curative surgical procedures. Sphincter preservation also signified facing the risk of local recurrence. However, balancing radical resection and sphincter preservation for the treatment of low rectal cancer has always been problematic [12].

The advent of preoperative radio-chemotherapy was beneficial in the treatment of local advancing rectal cancer [13, 14]. It was better tolerated by the patients and more effective for local control and down-staging compared to postoperative therapy [15-17]. Due to the response and down-staging with preoperative radio-chemotherapy, the lengthened distance between the anorectal ring and lower edge of rectal tumor facilitated radical excision and sphincter-preserving procedures [18]. This reduced the risk of local recurrence and maximized sphincter preservation. Preoperative radio chemotherapy followed by radical resection with total mesorectal excision resulted in abdominoperineal resection surgery being reduced and sphincter-saving surgery being increased significantly [12].

In the present study, preoperative radio-chemotherapy was administered followed by TME and sphincter-preserving procedures in patients with low rectal cancer with T3 tumor.

1-2 Aim of the Study:

The aim was to observe and verify the effects of preoperative radio-chemotherapy in controlling local recurrence and to improve sphincter-preserving surgery in patients with advancing low rectal cancer

2. Patients and Methods:

This study was carried out in Gastroenterology-hepatology Teaching hospital in t Baghdad during the period from 1st of December 2016 to 30th of November 2018.

All the 40 patients had rectal adenocarcinoma proven by biopsy, complete assessment was done by hematological investigations, colonoscopy, radiological imaging using magnetic resonance imaging, computed CT scan and ultrasound, all the tumors was ranging from 1 – 6 cm from dentate line. All patients was given radiotherapy targeting the rectum, mesorectum, lymph nodes in a dose of 2.0 Gy/5 times per week in a total of 50 Gy over 5 weeks , 5 florouracil chemotherapy was administered at 350 mg/m 2 /d, and leucovorin at 200 mg/m 2 /d for five days during radiotherapy in weeks one and five. Following radiotherapy, the regimen was administered as 5-FU at 350 mg/m 2 /d and leucovorin at 200 mg/m 2 /d for five consecutive days for two cycles.

Radical resection for rectal cancer was performed during the six to eight weeks following CRT. Though mid line incision, mobilization of the sigmoid colon, ligation of sigmoidal and superior rectal branches of inferior mesenteric artery, division of sigmoid colon, the rectum was mobilized in an anterior and posterior manner with sharp and blunt dissection. Lateral dissection of the rectum was performed in order not to breach the fascia propria of the rectum, remaining outside the margins of the mesorectum. The surgery achieved complete resection of the rectal cancer with adequate radial and circumferential margins.

An assessment was made as to whether a stapling anastomosis or a trans anal hand sewing or abdominal colorectal anastomosis was to be performed. Protective loop ileostomy was selectively created in some patients.

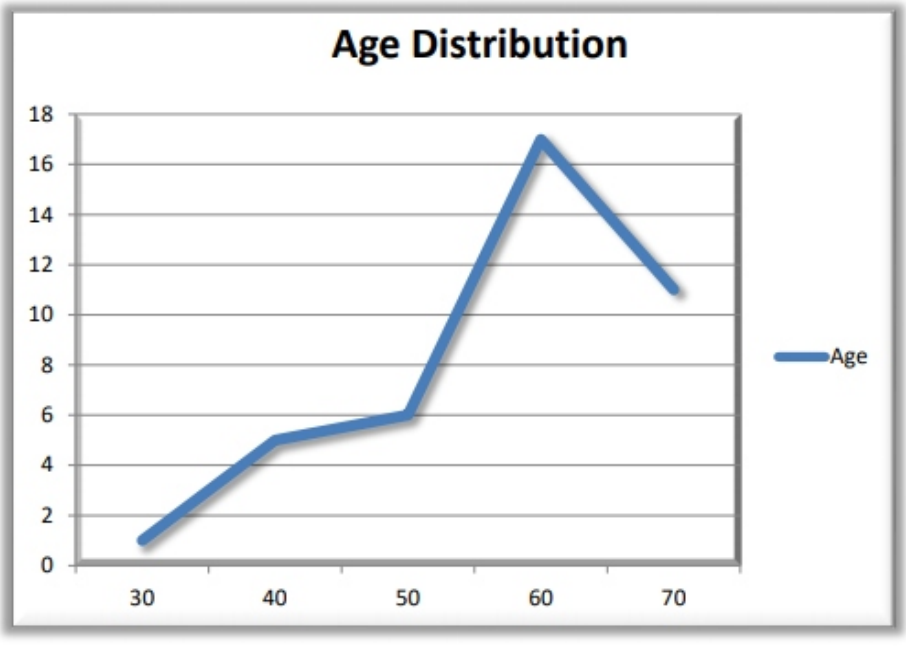
Following surgery, patients were followed up at six months. The follow-up included clinical, physical examination, blood test, serum carcinoembryonic antigen, chest radiography, abdominal ultrasound, CT, MRI, and Colonoscopy.

The study was approved by the committee of The Iraqi board, and informed consent was obtained from each patient. Data analysis was performed using SPSSVersion 22.0 for Windows. Mean and standard deviation (SD) was performed for continuous variable. 3.

Results:

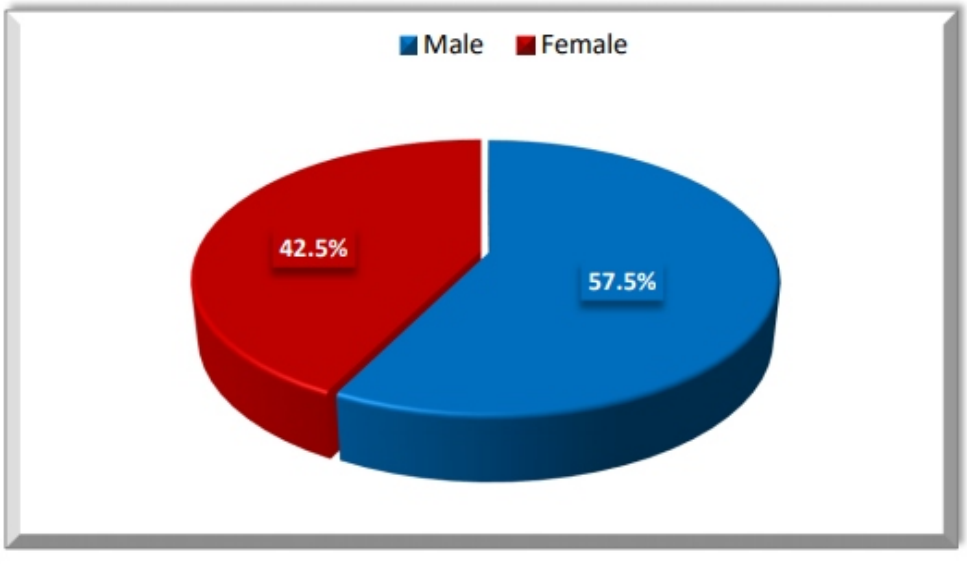
Our patients ages ranged from 35 – 78 , The mean ± standard deviation age of the patients at time of the study was 61.4 years ± 12.35 years as shown in figure (3-1), the vertical column refers to the number of patients and the horizontal column refer to the age of the patients. 17 patients was their ages around 60 years.

Figure (3-1): Age distribution among the patients



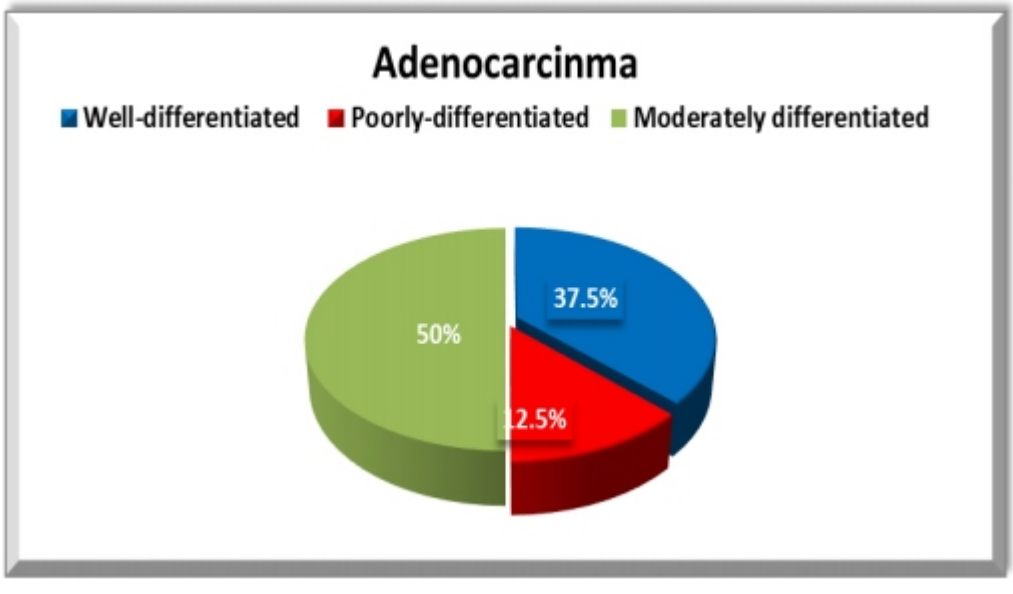
In the current study, 23 (57.5%) of the Patients were male, and 17 (42.5%) of them were females as shown in figure (3-2).

Figure (3-2): Gender distribution among the patients



Surgery was done in a period ranging from 6 – 8 weeks following the end of chemoradiotherapy, all the specimens was sent for histopathological examination, all of them was adenocarcinomas. Of them 20 (50%) were moderately-differentiated, 15 (37.5%) were well-differentiated and 5 (12.5%) were poorly differentiated. As shown in figure (3-3).

Figure (3-3): Histological findings among the patients

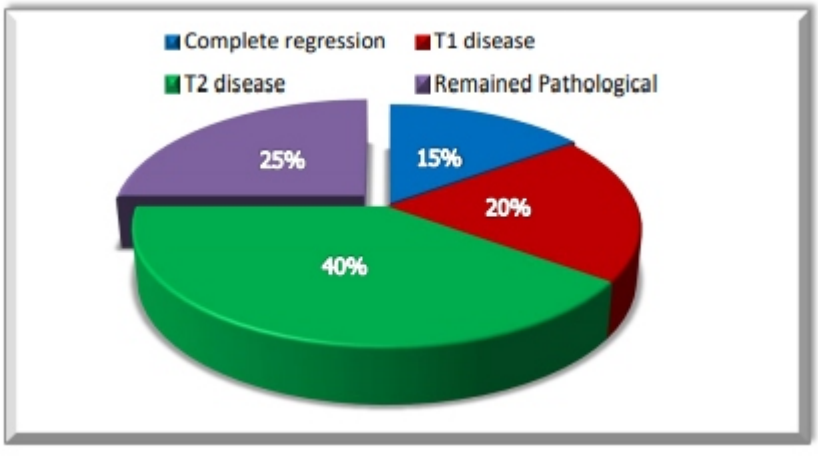


One month after the end of the chemoradiotherapy we re-evaluate our patients for response using Digital rectal examination and rigid proctoscopy and radiology. Complete regression of the rectal tumor was observed in 5 patients (12.5%). Twelve patients (30%) had a reduction of >50% and 23 patients (57.5%) had a reduction of >30%. No tumor progression was found. This is shown in figure (3-4).

Figure (3-4): Clinical response among the patients

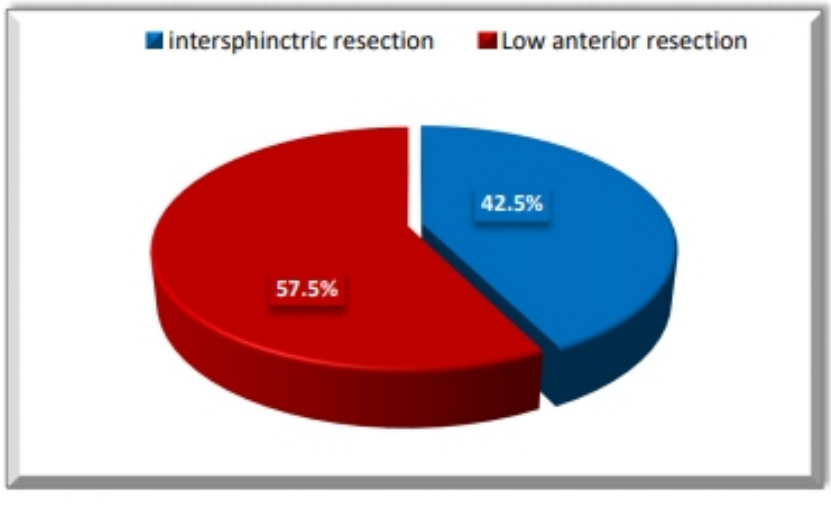
Surgery was done and the specimens sent for histopathological examination overall pathological response was found in 30 patients (75%). Pathological complete response was found in 6 patients (15%). T1 disease was observed in 8 patients (20%) and T2 in 16 patients (40%). Ten patients (25%) remained T3 pathologically. This is shown in figure (3-5).

Figure (3-5): Pathological response among the patients



Surgery was done for all patient with complete resection of the tumor including the rectum and mesorectum, and reconstruction was done either by Low anterior resection which was carried out for 23 patients, or intersphinctric resection which was carried out for 17 patients. As shown in figure (3-6). Two patients (5%) developed fecal fistula which was treated conservatively.

Figure (3-6): Type of surgical resection performed.



The complication rate was 15%; 4 (66.6%) were male and 2 (33.3) were female. Two patients (33.3%) report urinary incontinence and 3 (50%) patients report fecal incontinence. From all male 4, only1 (25%) of them report unchanged sexual function, while 3 (75%) report changed sexual function.

Table (3-1): Postoperative complications

Postoperative complications	Number	%
urinary incontinence	2	33.3%
fecal incontinence	3	50%
sexual function among male	3	75%

A 6 month follow-up for the patients, two of the patients presented with signs and symptoms of intestinal obstruction, investigations showed local recurrence both of them underwent re excisions with abdominoperineal resection. Distant metastasis was found in 3 patients (7.5%), sent to the oncology hospital and received chemotherapy. 4.

Discussion:

The main aim of rectal cancer surgery is to improve survival and to preserve anal function. This is achieved through introduction of preoperative chemo-radio therapy. Short term preoperative chemoradiotherapy and total mesorectal excision have each been shown to improve local control of disease in patients with resectable rectal cancer. Regarding responses to preoperative chemo radio therapy, 30 patients 75% of our patient's demonstrated pathological response and 15% achieved complete pathological response. this result was similar the studies done by Bujko et al [23], Contin et al [24],Janjan et al, [25] and Sauer et al study [6].as such, chemo radiotherapy is effective and essential in down staging of the tumor.

Regarding Local recurrence, 2 (5%) of our patients developed local recurrence both of them treated with re excision by abdomino-perineal resection, this result is similar to a study done by H. H. Wasmuth et al in 2008 in which local recurrence was 5.8% [41]. although many factors affecting local recurrence such as hospital, experience of the surgeon, T stage of the tumor, pre-operative chemoradiation play important role [26-28].

With regards to TME procedure, the standard techniqueIs performed in radical surgery of rectal cancer,and the local recurrence is controlled [29, 30]. Preoperative radio-chemotherapy is an important factor in reducing local recurrence [31,32]. In our study Postoperative complications, especially anastomotic fistula developed in 2 patients (5%), this is approximately similar to the study done by Muratore et al in 2015 in which anastomotic fistula was (7.7%) [42]. as such primary anastomosis can be done safely without increase in mortality and morbidity. Regarding anorectal function 3 patients developed fecal incontinence which constitute about (7.5%). In their study, Ammann et al reported that neoadjuvant radio chemotherapy resulted in disordered anal sphincter function in patients with midrectal cancer [34]. this is approximately similar to a study done by Li-Guo-Liu et al in 2017 who found that low anterior resection impair anorectal function but it appears to improve with time [44] .Pedro Campelo et al in their study in 2016 found that functional out come after rectal cancer treatment are influenced by patient and tumor characteristics, surgical techniques, the use of preoperative radiotherapy and the method and level of anastomosis [43]. This mismatch may be due to shorter period of follow up so it is required to be studied more.Urinary incontinence is a known complication of rectal surgery and is a complex problem. Following surgery, the most probable causes for incontinence are the denervation of the nervous plexi and impaired motility of the pelvic muscles [35].

Impaired urological function following rectal surgery is often described as transitory.

However, long-term morbidity assessment of the Dutch TME trial demonstrated that 39 % of patients in both groups [surgery following short-term radiation and surgery alone] reported to be incontinent to urine [36].

In this study, female gender was the only variable significantly associated with urinary dysfunction. Contrary to fecal function, no statistical significant relationship was identified between preoperative neoadjuvant treatment and urinary tract dysfunction. These findings are in line with previous reports [37, 38].

Since we lack the information on the preoperative sexual status of our population, it is reasonable to assume that our treatment-related sexual dysfunction rate might be lower. Data regarding sexual function are difficult to obtain.

There are disagreements in the literature regarding the actual incidence of sexual disorders following surgery [39, 40]. Multimodal therapy of low rectal cancer negatively affects sexual function as in Contin et al study [24].

5.1 Conclusion:

- Preoperative radio-chemotherapy significantly improves tumor down-staging, decreases local recurrence for patients with T3 low rectal cancers, and increases the sphincter preservation rate.
- Preoperative radio-chemotherapy followed by TME and sphincter-preserving procedures was associated with low complication rates, minor impairment of the anal sphincter and the anal function were satisfactory in most patients.
- For T3 low rectal cancer, preoperative radio-chemotherapy is a sensible choice for reducing the local recurrence rate and increasing the sphincter preservation rate.

5.2 Recommendation:

- Future prospective studiesare required to clarify thebenefits of preoperative CRT prior to surgery.
- Postoperative follow up should be done onlong-term observations.

7. References:

1. Quirke P, Steele R, and Monson J. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomized clinical trial. Lancet 2009; 373:821-8.

2. vanGijn W, Marijnen CA, Nagtegaal ID. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial.Lancet Oncol 2011; 12:575-82.

3. Martling AL, Holm T, Rutqvist LE, Moran BJ, Heald RJ, Cedemark B. Effect of a surgical training program on outcome of rectal cancer in the county of Stockholm. Stockholm Colorectal Cancer Study Group. Basingstoke Bowel Cancer Research Project. Lancet 2000; 356: 93-6.

4. Peeters KC, Marijnen CA, Nagtegaal ID. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg 2007; 246:693-701.

5. Pacelli F, Tortorelli AP, Rosa F. Locally recurrent rectal cancer: prognostic factors and long-term outcomes of multimodal therapy. Ann SurgOncol 2010; 17:152-62.

6. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004; 351:1731-40.

7. Lim YK, Law WL, Liu R, Poon JT, Fan JF, Lo OS. Impact of neoadjuvant treatment on total mesorectal excision for ultra-low rectal cancers. World J SurgOncol 2010; 8:23.

8. Kim DW, Lim SB, Kim DY. Pre-operative chemo-radio-therapy improves the sphincter preservation rate in patients with rectal cancer located within 3 cm of the anal verge. Eur J SurgOncol 2006; 32:162-167.

9. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Pudełko M, et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomized trial comparing short-term radiotherapy vs. conventionally fractionated radio-chemotherapy. RadiotherOncol 2004; 72:15-24.

10. Smalley SR, Benedetti JK, Williamson SK, Robertson JM, Estes NC, Maher T, et al. Phase III trial of fluorouracil-based chemotherapy regimens plus radiotherapy in postoperative adjuvant rectal cancer: GI INT 0144. J ClinOncol 2006; 24:3542-7.

11. Kornmann M, Staib L, Wiegel T. Adjuvant chemoradiotherapy of advanced resectable rectal cancer: results of a randomized trial comparing modulation of 5-fluorouracil with folinic acid or with interferon- α. Br J Cancer 2010; 103:1163-72.

12. BAI X, LI S, YU B, SU H, JIN W, CHEN G et al. Sphincter-preserving surgery after preoperative radiochemotherapy for T3 low rectal cancers. Oncology Letters. 2012; 3(6):1336-1340.

13. Gérard JP, Conroy T, Bonnetain F, Bouché O, Chapet O, Closon-Dejardin MT, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J ClinOncol 2006; 24:4620-5.

14. Huh JW, Kim CH, Kim HR, Kim YJ. Oncologic outcomes of pathologic stage I lower rectal cancer with or without preoperative chemoradiotherapy:

are they comparable. Surgery 2011; 150:980-4.
15. Sauer R,Fietkau R,Wittekind C,Rödel , Martus P, Hohenberger W, et al. Adjuvant vs. neoadjuvant radiochemotherapy for locally advanced rectal cancer: the German trial CAO/ARO/AIO-94. Colorectal Dis 2003; 5:406-15.
16. Bosset JF, Collette L, Calais G. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006; 355:1114-23.
17. Roh MS, Colangelo LH, O'Connell MJ. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J ClinOncol 2009; 27:5124-30.
18. Weiser MR, Quah HM, Shia J. Sphincter preservation in low rectal cancer is facilitated by preoperative chemoradiation and intersphincteric dissection. Ann Surg 2009; 249:236-42.
19. Kusters M, Marijnen CA, Van de Velde CJ et al. Patterns of localrecurrenceinrectalcancer; astudyoftheDutchTMEtrial.EurJSurgOncol. 2010; 36:470–6.
20. BujkoK,Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg. 2006; 93:1215–23.
21. BossetJF, Collette L, Calais G. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med. 2006; 355:1114–23.
22. Peeters KC, Marijnen CA, Nagtegaal ID. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg. 2007; 246:693–
701.
23. Bujko K, Nowacki M, Nasierowska-Guttmejer A, Michalski W, Bębenek M, Pudełko M et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomized trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. Radiotherapy and Oncology. 2004; 72(1):15-24.
24. Contin P, Kulu Y, Bruckner T, Sturm M, Welsch T, Müller-Stich B et al. Comparative analysis of late functional outcome following preoperative radiation therapy or chemoradiotherapy and surgery or surgery alone in rectal cancer. International Journal of Colorectal Disease. 2013; 29(2):165-75.
25. Janjan N, Khoo V, Abbruzzese J, Pazdur R, Dubrow R, Cleary K et al. Tumor down staging and sphincter preservation with preoperative chemoradiation in locally advanced rectal cancer: the M. D. Anderson Cancer Center experience. International Journal of Radiation Oncology*Biology*Physics. 1999; 44(5):1027-38.
26. Kim YW, Kim NK, Min BS. Factors associated with anastomotic recurrence after total mesorectal excision in rectal cancer patients. J SurgOncol 2009; 99:58-64.
27. Das P, Skibber JM, Rodriguez-Bigas MA, Feig BW, Chang GJ, Hoff PM, et al. Clinical and pathologic predictors of locoregional recurrence, distant metastasis, and overall survival in patients treated with chemoradiation and mesorectal excision for rectal cancer. Am J ClinOncol 2006; 29:219-24.
28. Kuo LJ, Liu MC, Jian JJ. Is final TNM staging a predictor for survival in locally advanced rectal cancer after preoperative chemoradiationtherapy. Ann SurgOncol 2007; 14:2766-72.
29. Herzog T, Belyaev O, Chromik AM. TME quality in rectal cancer surgery. Eur J Med Res 2010; 15:292-6.
30. Ferenschild FT, Dawson I, de Wilt JH, de Graaf EJ, Groenendijk RP, Tetteroo GW. Total mesorectal excision for rectal cancer in an unselected population: quality assessment in a low volume center. Int J Colorectal Dis 2009; 24:923-9.
31. Theodoropoulos G, Wise WE, Padmanabhan A. T-level down staging and complete pathologic response after preoperative chemoradiation for advanced rectal cancer result in decreased recurrence and improved disease-free survival. Dis Colon Rectum 2002; 45:895-903.
32. Elwanis MA, Maximous DW, Elsayed MI, Mikhail NN. Surgical treatment for locally advanced lower third rectal cancer after neoadjuvant chemoradiation with capecitabine: prospective phase II trial. World J SurgOncol 2009; 7:52.
33. Canda AE, Terzi C, Gorken IB, Oztop I, Sokmen S, Fuzun M. Effects of preoperative chemoradiotherapy on anal sphincter functions and quality of life in rectal cancer patients. Int J Colorectal Dis 2010; 25:197-204.
34. Ammann K, Kirchmayr W, Klaus A. Impact of neoadjuvant chemoradiation on anal sphincter function in patients with carcinoma of the midrectum and low rectum. Arch Surg 2003; 138: 257-61.
35. Lange MM, Maas CP, Marijnen CA. Urinary dysfunction after rectal cancer treatment is mainly caused by surgery. Br J Surg 2008; 95:1020-8.
36. Peeters KC, van de Velde CJ, Leer JW. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients—a Dutch colorectal cancer group study. J ClinOncol 2005; 23:6199-206.

37. Birgisson H, Pahlman L, Gunnarsson U. Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial. J ClinOncol 2005; 23:8697-705.
38. Sauer R, Becker H, Hohenberger W. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004; 351:1731-40.
39. Bonnel C, Parc YR, Pocard M. Effects of preoperative radiotherapy for primary resectable rectal adenocarcinoma on male sexual and urinary function. Dis Colon Rectum 2002; 45:934-9.
40. Heriot AG, Tekkis PP, Fazio VW. Adjuvant radiotherapy is associated with increased sexual dysfunction in male patients undergoing resection for rectal cancer: a predictive model. Ann Surg 2005; 242:502-10.
.**41.** H. H. Washmuth, T. Nestvolt, O. Rokke. Low local recurrence rates after rectal cancer resection with limited use of preoperative radiotherapy. Scandinavian Jouranal of surgery. 2008; 97:231-236.
42. Muratore A, Mellano A, De Simone. Trans anal total mesorectal excision (ta TME) for cancer located in the lower rectum: short and mid-term results. Eur J Oncol 2015 April; 41(4):478-83.
43. Pedro Campelo, Elisabete Barbosa. Functional out come and quality of life following treatment for rectal cancer. J Coloproctol 2016; 36(4):251-261.
44. Liu LG, Yan XB, Shan ZZ. Yan LL, Jiang CY, Zhou J, Tian Y, Jin ZM.anorectal functional outcome following laparoscopic low anterior resection for rectal cancer