

## Neo-adjuvant chemoradiotherapy; an opportunity in sphincter preserving procedure for rectal cancer

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### ABSTRACT

**Aim:** The present study was designed to assess the impact of neo-adjuvant chemoradiotherapy on the possibility of utilizing sphincter preserving techniques in rectal cancer surgery.

**Background:** For both patients and surgeons anal sphincter preserving surgery serves as the ideal procedure to treat rectal cancer.

**Patients and methods:** Patients with rectal cancer who were admitted to Shohadaye Tajrish hospital between 2001 and 2011 and underwent sphincter preserving or non-preserving surgery were identified. They were divided into those who had received neo-adjuvant chemo-radiotherapy prior to surgery and those who didn't, and the type of surgical procedure they underwent was compared between the two arms. Data regarding tumor pathology, tumor size and distance from anal verge before and after neo-adjuvant therapy, together with the duration of chemo-radiotherapy were also assessed.

**Results:** 103 patients with documented rectal cancer were included in our analysis. Among 47 patients who had not received neo-adjuvant therapy, 26 (55%) underwent APR while 15(32%) and 6(13%) patients were treated with LAR and VLAR respectively. Of the 56 patients who had gone through chemo-radiotherapy prior to surgery, 30 (53%) underwent APR while 14 (25%) and 10 (18%) patients were treated with LAR and VLAR respectively. 2 patients had unresectable tumor. Tumor staging before and after neo-adjuvant therapy showed a statistically significant difference ( $p=0.0001$ ).

**Conclusion:** Neo-adjuvant chemo-radiotherapy can decrease tumor size, increase the distance between the tumor and anal verge, and downgrade the staging. However, it does not necessarily increase the possibility of performing sphincter preserving surgery on patients suffering from low-lying tumors.

**Keywords:** Neo-adjuvant chemoradiotherapy, Abdomino-perineal resection, Anal sphincter preserving surgery, Rectal cancer.

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### Introduction

Surgery for rectal cancer continues to develop towards the ultimate goals of improved local control and overall survival, maintaining quality of life, and preserving sphincter, genitourinary and sexual function (1). Since the introduction of

Abdomino-Perineal Resection (APR) in 1908, this method has been used as the standard treatment for low-lying rectal cancer, but as surgical procedures that do not spare anal sphincter result in the impairment of anorectal function, other techniques including low anterior resection (LAR) and very low anterior resection (VLAR) that preserve the sphincter function have emerged.

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The evidence on comparison of quality of life between these procedures are unequivocal (2-3). While some studies show patients with low rectal cancer who are treated by modern sphincter saving resection have a quality of life superior to those treated by APR (4-5), others claim that the overall quality of life does not differ between the two techniques (6-8).

Since sphincter preserving techniques maintain anorectal function in >90% of cases (9), both patients and surgeons consider anal sphincter preserving surgery as the ideal procedure to treat rectal cancer (10), and despite the fact that it has not yet been demonstrated whether sphincter preservation compromises local disease control and disease free survival (11-12), abdominoperineal resections for rectal carcinoma are being performed with decreasing frequency in favor of sphincter sparing resections.

Considering the growing tendency towards sphincter preservation, employment of strategies that can shift surgical management to sphincter preserving (SP) procedures can serve as a great asset to current practice. Neo-adjuvant chemoradiotherapy is one of the strategies that are presumed to improve pathologic and surgical outcomes of rectal cancer treatment.

Due to limited number of studies on this subject, it's still unclear whether neo-adjuvant chemoradiotherapy can affect the possibility of performing sphincter preserving surgery on low lying rectal tumors. To achieve definite results more studies are needed to evaluate this matter. Therefore, we conducted this study to assess the impact of Preoperative chemo-radiotherapy (PCRT) on surgical management of rectal cancer.

## Patients and Methods

The present study is a retrospective non-randomized analysis of patients with adenocarcinoma of rectum that was managed

surgically between 2001 and 2011 at Shohadaye Tajrish Hospital.

Patients' data including their age, gender and co-morbidities were extracted, and their medical documents were examined regarding preoperative administration of chemoradiotherapy and the type of surgical procedure they had performed on them. Tumor characteristics such as distance from anal verge, TNM staging and tumor pathology including tumor type, size and degree of differentiation before and after neo-adjuvant chemoradiotherapy were also recorded.

Patients who had rectal incontinence as a result of prior hysterectomy, those who had documented distant metastasis, and those with tumor pathology other than adenocarcinoma were excluded.

For patients who had received neo-adjuvant therapy (PCRT), the chemotherapeutic regimen consisted of 5-Fluorouracil and the radiation course comprised of 45 to 50 Gy in 1.8 Gy per fraction over five weeks.

Surgical procedures that had been performed on patients were either sphincter preserving (SP) including low anterior resection (LAR) and Very Low Anterior Resection (VLAR), or were non-preserving such as abdomino-perineal resection (APR). Selection of the surgical technique was based on surgeons' intra-operative decision and was independent of possible previous neo-adjuvant chemo-radiotherapy.

Data were analyzed using SPSS v.18 for windows. A p-value of less than 0.05 was considered statistically significant.

## Results

103 patients met the inclusion criteria and were enrolled in the study. Their mean age was 45.3 ( $\pm 13.5$ ) and the male to female ratio was 65:38. The mean tumor size was 3.81 ( $\pm 1.36$ ) cm.

However, exclusively in one patient was reported to be 15 centimeters.

A total of 45 patients (43.6%) underwent sphincter preserving surgery (LAR and VLAR), while 56 (54.3%) were managed by non-preserving methods (APR).

Fifty six patients had received preoperative chemo-radiotherapy. The mean interval between the last session of neo-adjuvant therapy and surgery was 45.3 (±31.3) days.

Among the 47 patients who had not received PCRT, 26 (55%) underwent APR while 15(32%) and 6(13%) patients were treated with LAR and VLAR respectively. Of the 56 patients who had gone through chemoradiotherapy prior to surgery, 30 (53%) underwent APR while 14 (25%) and 10 (18%) patients were treated with LAR and VLAR respectively. Two patients were found to have unresectable tumor during laparotomy. (A summary of the type of surgical techniques along with additional information on simultaneous procedures such as TAH-BSO can be available in table 1.

**Table 1.** Frequency of surgical procedures operated on patients with or without PCRT

	Neo <sup>-</sup>	Neo <sup>+</sup>
APR	24 (51.1%)	27 (48.2%)
APR + TAH-BSO	2 (4.2%)	3 (5.3%)
LAR	12 (25.5%)	14 (25%)
LAR + TAH-BSO	3 (6.4%)	0
VLAR	4 (8.5%)	10 (18%)
VLAR + TAH-BSO	2 (4.3%)	0
Non-operable	0	2 (3.5%)

**Table 2.** Assessment of distal margin in patients with or without PCRT

	Tumor distance from anal verge evaluated by DRE	Distal margin in pathological assessment
Neo <sup>-</sup>	5.46 ± 3.2	3.17 ± 1.97
Neo <sup>+</sup>	5.01 ± 2.44	3.09 ± 2.08

Tumor distance from anal verge measured by digital rectal examination and sigmoidoscopy was

5.46 (± 3.2) centimeters in patients who did not receive neo-adjuvant therapy and 5.01 (± 2.44) in those who did. Reevaluation of distal margin in pathologic specimens after surgical resection yielded a mean value of 3.17 (± 1.97) centimeters for patients who hadn't received PCRT and 3.09 (± 2.08) for those who did (Table 2).

The p-value on both occasions was statistically insignificant (p=0.45 and p=0.83 respectively). Tumor differentiations reported on pathologic assessment of resected specimens are summarized in table 3.

**Table 3.** Frequency of tumor differentiation in patients with or without PCRT

	Poorly differentiated	Moderately differentiated	Well differentiated
Neo <sup>-</sup>	5 (10.6%)	19 (40.4%)	23 (49%)
Neo <sup>+</sup>	4 (7.2%)	28 (50%)	24 (42.8%)

Assessment of TNM staging before and after neo-adjuvant chemo-radiotherapy revealed a statistically significant difference (p=0.0001 for T and p=0.01 for N respectively) (Table 4).

**Table 4.** NM staging before and after receiving neo-adjuvant chemoradiotherapy

	T <sub>1</sub>	T <sub>2</sub>	T <sub>3</sub>	T <sub>4</sub>	Missing
Before Neo	0	1(1.9%)	47(83.9%)	3(5.3%)	5(8.9%)
After Neo	5(8.9%)	15(26.8%)	24(42.9%)	7(12.5%)	5(8.9%)
	N <sub>0</sub>	N <sub>1</sub>	N <sub>2</sub>	N <sub>3</sub>	Missing
Before Neo	15(26.8%)	31(55.3%)	3(5.3%)	2(35.7%)	5(8.9%)
After Neo	27(48.2%)	15(26.8%)	5(8.9%)	1(1.9%)	8(14.2%)

According to the pathologic examination of resected specimens in patients who had received neo-adjuvant chemoradiotherapy, complete pathologic response was observed in 7 (12.5%) cases. 5 (8.9%) cases showed near-complete pathologic response (>95% response) The relation between patient characteristics and tumor

specificities with the type of surgical procedure that was undertaken is summarized in table 5.

**Table 5.** Relation between patient characteristics and tumor specificities with the type of surgery

Characteristics	Sphincter preserving (SP)	Abdomino-perineal resection (APR)	p-value
Mean Age	54.73 ± 12.07	53.87 ± 14.85	0.755
Gender			
Male	27 (26.7%)	36 (35.6%)	0.081
Female	17 (16.8%)	21 (20.7%)	
Tumor distance from anal verge (clinical)	6.73 ± 2.89	4.24 ± 2.44	0.0001
Distal margin (Pathological)	2.71 ± 2.10	3.58 ± 1.89	0.016
Tumor size	4 ± 2.51	3.91 ± 1.93	0.772
Tumor differentiation			
Poor	3	5	0.315
Moderate	32	14	
Well	21	26	
Positive past medical history	9	9	0.608
Mean duration between PCRT and surgery	41 ± 15.28	48.77 ± 39.71	0.709
T staging after treatment with PCRT (T <sub>1</sub> :T <sub>2</sub> :T <sub>3</sub> :T <sub>4</sub> )	5:10:23:4	3:13:31:6	0.748
N staging after treatment with PCRT (N <sub>0</sub> :N <sub>1</sub> :N <sub>2</sub> :N <sub>3</sub> )	22:13:14:1	27:15:9:1	0.637

## Discussion

Factors that might affect the possibility of performing sphincter preserving surgery on low-lying rectal cancer include tumor size, staging, and tumor distance from anal verge.

A decrease in tumor volume may allow the surgeon to perform a sphincter sparing procedure that would not otherwise be possible (13). However, this effect is controversial and a meta-analysis of 10 randomized trials published in 2006 by Bujko et al. did not support this concept (14).

A study by Janjan et al. on 117 patients, showed down-staging as one of the factors predictive of sphincter preservation ( $p < 0.03$ ) (15). Down-staging also shows a close correlation with improved outcomes (16).

It is now well known that when the tumor is located further from the anal verge, the possibility of sphincter preserving surgery increases. A study by Baik et al. on the relation between tumor location and effectiveness of neo-adjuvant therapy, demonstrated that preoperative chemo-radiotherapy does not increase SP performance rate in rectal tumors with less than 6cm distance from anal verge (17). According to the results of another study by Janjan et al. SP was performed on 93-97% of the tumors located >6cm from the anal verge, while for tumors located <6cm from the anal verge, SP was performed in 53% of those with complete pathological response and 38% of patients with residual disease ( $p < 0.00004$ ) (15).

Neo-adjuvant chemo-radiotherapy is presumed to be one of the methods that can alter these tumor characteristics (18) and ultimately increase the chances of performing sphincter preserving surgery. However, the actual impact of preoperative chemo-radiotherapy (PCRT) on the possibility of utilizing sphincter preserving techniques in rectal cancer surgery is still controversial.

A study by Crane et al. conducted in 2003 on 238 patients showed that complete clinical response to PCRT leads to an increased rate of sphincter preservation probably by helping to overcome the mechanical limitations that make operating in lower portion of rectum difficult (19).

Another study by Sauer et al. revealed that among patients in whom APR seemed initially necessary, sphincter preservation was finally performed on 45 of 116 patients who had received PCRT compared to 15 of 78 patients who had not been treated by neo-adjuvant therapy. Authors suggested that preoperative chemo-radiotherapy is associated with an increased rate of sphincter preservation in patients with low-lying tumors (20).

The results of a phase III randomized trial (GRECCAR 1) published in 2006 which included patients with rectal adenocarcinoma

from 13 French centers, showed an 85% rate of sphincter sparing surgery due to down-staging by preoperative neoadjuvant chemo-radiotherapy (21).

In various studies, the complete pathologic response after PCRT varies from 10 to 20 percent. Our study showed complete pathologic response and minimal residual tumor in 12.5% and 8.9% of patients respectively. However, numerous studies show that despite complete pathological response of tumor to preoperative chemo-radiotherapy, the incidence of performing APR remains high. Boonnuch et al. evaluated the surgical outcome of preoperative chemo-radiotherapy in 93 patients with low-lying rectal cancer. According to their results, there was no significant difference in SP rate between those who had received PCRT and those who didn't (37% versus 36 %) (22). The following notions can in part explain this high incidence of APR despite neo-adjuvant chemo-radiotherapy:

- Tumor down staging and downsizing might not be significant enough to affect the surgical management.
- In circumferential tumors, regression after chemo-radiotherapy results in a constant distance from anal verge.
- Due to the difficulty of performing a second surgery in cases of local recurrence, and the higher probability of a tumor being inoperable in cases of pelvic recurrence, most surgeons consider APR a more reasonable choice.

Our study demonstrated a reduction in tumor size and tumor staging in those who had received PCRT; two factors that should have facilitated utilizing sphincter preserving techniques. However, as the results of our study show, the rate of sphincter preserving surgery was not affected by prior chemo-rdiotherapy (SP rate was 45% in those who had received PCRT versus 43% in those who didn't). This observation can be explained by the same reasons mentioned above.

The number of patients in our study limited our analysis. This limitation along with the retrospective nature of our study and the inevitable selection bias that follows, points to the need for large clinical trials with precise follow up.

Moreover, additional evidence regarding disease free survival, local recurrence free survival and metastasis free survival are necessary to assess the suitability of sphincter preserving surgery for treating low-lying rectal cancer.

Neo-adjuvant chemo-radiotherapy can decrease tumor size, increase the distance between the tumor and anal verge, and downgrade the staging; but it does not necessarily increase the possibility of performing sphincter preserving surgery on patients suffering from low-lying tumors.

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## References

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1. Balch GC, De Meo A, Guillem JG. Modern management of rectal cancer: a 2006 update. *World J Gastroenterol* 2006; 12: 3186.
2. Pachler J, Wille-Jorgensen P. Quality of life after rectal resection for cancer, with or without permanent colostomy. *Cochrane Database Syst Rev* 2005;18(2).
3. Sprangers MAG, Taal BG, Aaronson NK, Velde A. Quality of life in colorectal cancer. *Dis Colon Rectum* 1995; 38: 361-69.
4. Williams N, Johnston D. The quality of life after rectal excision for low rectal cancer. *Br J Surg* 1983; 70: 460-62.
5. Frigell A, Erigell A, Ottander M, Stenbeck H, Pahtman L. Quality of life of patients treated with

abdominoperineal resection or anterior resection for rectal carcinoma. *Annales chirurgiae et gynaecologiae* 1990;79:26-30.

6. Schmidt CE, Bestmann B, Longo WE. Prospective evaluation of quality of life of patients receiving either abdominoperineal resection or sphincter-preserving procedure for rectal cancer. *Ann Surg Oncol* 2005;12: 117-23.

7. Cornish JA, Tilney HS, Heriot AG, Lavery IC, Fazio V W, Tekkis P P. A meta-analysis of quality of life for abdominoperineal excision of rectum versus anterior resection for rectal cancer. *Ann Surg Oncol* 2007; 14: 2056-68.

8. Allal A, Bieri S, Pelloni S, Spataro V, Anchisi S, Ambrosetti P, et al. Sphincter-sparing surgery after preoperative radiotherapy for low rectal cancers: feasibility, oncologic results and quality of life outcomes. *Br J Cancer* 2000; 82: 1131.

9. Ng AK, Recht A, Busse PM. Sphincter preservation therapy for distal rectal carcinoma. *Cancer* 1997; 79: 671-83.

10. Zolciak A, Bujko K, Kepka L, Oledzki J, Rutkowski A, Nowacki MP. Abdominoperineal resection or anterior resection for rectal cancer: patient preferences before and after treatment. *Colorectal Dis* 2006; 8: 575-80.

11. Wolmark N, Fisher B. An analysis of survival and treatment failure following abdominoperineal and sphincter-saving resection in Dukes' B and C rectal carcinoma. A report of the NSABP clinical trials. National Surgical Adjuvant Breast and Bowel Project. *Ann Surg* 1986; 204: 480.

12. Williams N, Durdey P, Johnston D. The outcome following sphincter-saving resection and abdomino-perineal resection for low rectal cancer. *Br J Surg* 1985; 72: 595-98.

13. Do L, Syed N, Puthawala A, Azawi S, Shbeeb I, Gong IY. Low-lying rectal cancer with anal canal involvement: abdominoperineal or low anterior resection after neoadjuvant chemoradiotherapy. *Gastrointest Cancer Res* 2011; 4: 90-95.

14. Bujko K, Kepka L, Michalski W, Nowacki M P. Does rectal cancer shrinkage induced by preoperative radio (chemo) therapy increase the likelihood of

anterior resection? A systematic review of randomized trials. *Radiother Oncol* 2006; 80: 4-12.

15. Janjan NA, Khoo VS, Abbruzzese J, Pazdur R, Dubrow R, Cleary KR, et al. Tumor downstaging and sphincter preservation with preoperative chemoradiation in locally advanced rectal cancer: the MD Anderson Cancer Center experience. *Int J Radiat Oncol Biol Phys* 1999; 44: 1027-38.

16. Valentini V, Coco C, Picciocchi A, Morganti AG, Trodella L, Ciabattini A, et al. Does downstaging predict improved outcome after preoperative chemoradiation for extraperitoneal locally advanced rectal cancer? A long-term analysis of 165 patients. *Int J Radiat Oncol Biol Phys* 2002; 53: 664-74.

17. Baik SH, Kim NK, Lee KY, Sohn SK, Cho CH. Analysis of anal sphincter preservation rate according to tumor level and neoadjuvant chemoradiotherapy in rectal cancer patients. *J Gastrointest Surg* 2008; 12: 176-82.

18. Minsky BD, Cohen AM, Enker WE, Saltz L, Guillem JG, Paty PB, et al. Preoperative 5-FU, low-dose leucovorin, and radiation therapy for locally advanced and unresectable rectal cancer. *Int J Radiat Oncol Biol Phys* 1997; 37: 289-95.

19. Crane CH, Skibber JM, Feig BW, Vauthey JN, Thames HD, Curley SA, et al. Response to preoperative chemoradiation increases the use of sphincter-preserving surgery in patients with locally advanced low rectal carcinoma. *Cancer* 2003; 97: 517-24.

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

21. Rouanet P, Rivoire M, Lelong B, Rullier E, Dravet F, Mineur L, et al. Sphincter preserving surgery after preoperative treatment for ultra-low rectal carcinoma. A French multicenter prospective trial: GRECCAR 1. *J Clin Oncol* 2006;24: S3527.

22. Boonnuch W, Lohsiriwat V, Akaraviputh T, Chinswangwatanakul V, Lohsiriwat D. The surgical outcome of preoperative chemoradiation therapy for ultra low rectal cancer. *J Med Assoc Thai* 2009; 92: 1423-27.