The pattern of recurrence and survival after treatment failure in patients with rectal cancer treated with combined modality therapy

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Purpose and Objective:

Rectal cancer is one of the most common types of cancer. Although surgery is the cornerstone curative treatment, combined modalities with radiotherapy and or chemotherapy have been proved to be an important component of treatments for locally advanced rectal cancer including Stage II and Stage III in terms of decreased local recurrence and increased overall survival in addition to surgical resection. Although total mesorectal excision (TME) has resulted in a significant reduction of local recurrence, neoadjuvant or adjuvant radiotherapy with or without chemotherapy is still an important modality for local control in the era of TME. The definitive treatment with the combined modalities including surgery, radiotherapy, and chemotherapy have significantly improved the treatment outcomes of patients with rectal cancer but cancer recurrence of both local regional and distant is still significant (1-9). It is important to analyze the patterns of such treatment failures and to explore possible ways to reduce the rate of recurrence, to treat the recurrence, and thus to improve the survival after recurrence.

Materials and Methods:

A cohort of consecutive patients seen during the period of 2005 to 2017 is retrospectively studied. All patients were treated surgically with either low anterior resection (LAR) or abdominoperineal resection (APR) as previously reported (10-11). Very few patients had local excision. Some patients received neoadjuvant treatment with chemo-radiotherapy or radiotherapy alone followed by definitive surgery, other patients had surgical resection before adjuvant treatment and most of these patients were treated in the early years. The long-course chemo-radiotherapy was typically in two phases with 45 Gy in 25 fractions to the pelvis followed by 5.4 Gy in 3 fractions boosting. Three dimensional conform radiotherapy (3D-CRT) technique was used. The concomitant chemotherapy was either infusional 5-FU or oral Capecitabine. Some patients were treated with short-course neoadjuvant radiotherapy alone with 25 Gy in 5 fractions (12). After treatments, patients were followed up regularly with blood work, CT scan, and endoscopy.

Results:

A total of 364 patients are identified (Table 1), male 235, age 28-90 years old, median 62; female 129, age 35-89 years old, median 63. Majority of the patients received tri-modality of treatments either neoadjuvant chemo-radiotherapy followed by definitive surgery (n=152) or surgery followed by adjuvant chemo-radiotherapy (n=117). A smaller portion of patients were treated with neoadjuvant radiotherapy alone followed by surgery (n=26) or surgery followed by adjuvant radiotherapy alone (n=5). There were 17 patients who received adjuvant chemotherapy only after surgery, and 44 patients had surgical resection only. A few patients (n=3) had total neoadjuvant treatment followed by surgery.

There are 83 patients (22.8%) who had recurrence (Table2). Among those, 26 patients (31.33%) had pelvic local recurrences and 8 out of these 26 patients (30.77%) also developed distant metastases in the same time. Out of these 26 patients, 16 patients (61.54%) had recurrence in the pre-sacral space alone or with other sites of recurrence while 13 patients (50.00%) developed recurrence at the anastomosis and perineal recurrence were found in 2 patients (7.69%). The remaining 57 patients (68.67%) developed distant metastases without local failure. Pulmonary metastases were the highest with 32 out of 83 patients (38.55%) while hepatic metastases were the second most common ones with 29 out of 83 patients (34.94%). The median time for pulmonary recurrence is 15 months (3-72 months) while the median time for liver metastases is 11 months (1-34 months). The median time for local recurrence is somewhat longer with a median of 17 months (3-51 months). After aggressive treatments

which included surgical resection alone or combined with radiotherapy and or chemotherapy, long term survivors were identified with 3 patients who had isolated local recurrence and who have survived 8 to 11 years without evidence of further recurrence. There were 5 patients with hepatic and or pulmonary metastases who are still alive without evidence of further recurrence 7 to 14 years after treatments for recurrence.

Discussion and Conclusion:

For patients with rectal cancer, treatment failure includes local recurrence and distant metastases. Most of the local recurrences are not salvageable with a complete surgical resection and the most common site of local recurrence is pre-sacral space and the second common local recurrence is at the anastomosis in our cohort of patients although the involvement of adjacent organs and bony structures of the pelvis in some patients were observed.

Local recurrence often results in a short life expectancy which is complicated by debilitating pelvic pain, malodorous discharge, and uncontrollable tenesmus, affecting quality of life significantly (13).

It has been noted in the literature that neoadjuvant radiotherapy has changed the clinical nature and prognosis of local recurrence for rectal cancer with the reduction of local recurrence at all subsites and most recurrence after pelvic radiotherapy are at non-anastomotic sites. Besides, many patients with local recurrence after radiotherapy present with simultaneous distant metastases as well (12, 14).

Based on our observation, the pre-sacral space is the area that tends to be under-dosed because its adjacency to the bone. Also, this location makes a complete surgical resection for recurrence extremely challenge. Therefore, a careful dosimetry review is warranted to avoid under-dosing. Furthermore, it is reasonable to advocate higher radiotherapy dose other than the standard 45 to 50.4 Gy to the pre-sacral space since it is the most common site of local recurrence and the recurrence at this site is mostly unsalvageable if organ dose constraints can be met.

The most common distant metastatic site in this cohort is the lungs and the livers are the second most common site. The explanation for higher pulmonary metastases is probably due to the fact that almost half of the patients in this study cohort had low rectal cancer. Also, this finding is also in line with the literature reports (15). Our study demonstrates that some of the patients with either local recurrence or distant metastases at the lung or liver are potentially curable. Our approach has been to identify those patients through a multidisciplinary team which includes radiation oncologists, medical oncologists, surgical oncologists, radiologists, and pathologists. Radiotherapy is often required to manage the local recurrence in addition to chemotherapy and surgical resection. It is important to recognize that it is possible to salvage the isolated local recurrence and insignificant pulmonary or hepatic metastases with the possibility for cure though most of the treatment failures were not salvageable. To decrease the local in-field recurrence, it is conceivable to increase the radiotherapy dose to the common sites of recurrence while avoiding under-dose in the future.

1. **References:**
   Sauer R, Becker H, Hohenberger W, Rodel C. etal. Preoperative versus postoperative chemoradiotherapy for rectal cancer. The New England Journal of Medicine. 2004:351 (17): 1731-40.
2. Van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM. et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of multicentre, randomised controlled TME trial. The Lancet Oncology. 2011; 12(6):575-82.
3. Hofheinz RD, Wenz F, Post S, Matzdorff A. et al. Chemotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. The Lancet Oncology. 2012; 13(6):579-88.
4. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J. et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 2009; 373(9666):811-20.
5. Bosset JF, Collette L, Calais G, Mineur L. et al. Chemotherapy with preoperative radiotherapy in rectal cancer. The New England Journal of Medicine. 2006; 355(11):1114-23.
6. Bujko K, Nowacki MP, Nasierowska-Guttmejer

A, Michalski W. et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs conventional fractionationed radiochemotherapy. Radiotherapy and Oncology 2004; 72(1):15-24.

7. Lo SS, Moffatt-Bruce SD, Dawson LA, Schwarz RE. et al. The role of local therapy in the management of lung and liver oligometastases. Nature Reviews Clinical Oncology. 2011; 8(7):405-16.
8. Jegatheeswaran S, Mason JM, Hancock HC, Siriwardena AK. et al. The liver-first approach to the management of colorectal cancer with synchronous hepatic metastases: a systematic review. JAMA Surgery. 2013; 1489(4):385-91.
9. Liu J, Liu H, Mou B, Nugent Z. et al. The determinants of small bowel volume in pelvis of patients receiving radiotherapy for rectal cancer: A multivariate analysis. International Journal Radiation Oncology Biology Physics. 2010; 78(3): S325-326.
10. Liu J. The Factors affecting small bowel volume in the pelvis of patients receiving radiotherapy for rectal cancer. The Journal of Clinical Case Reports and Case Studies. 2017:1-5.
11. Folkesson J, Birgisson H, Pahlman L, Cedermark B. et al. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. Journal of Clinical Oncology. 2005;23 (24):5644-5650
12. Camilleri-Brennan J, Steele RJ, The impact of recurrent rectal cancer on quality of life. European Journal of Surgical Oncology 2001;27(4):349-353.
13. Peeters KC, Marijnen CA, Nagtegaal ID, Kranenbarg EK. Et al. 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. Annals of Surgery. 2007;246 (5):693-701.
14. Ikoma N, You YN, Bednarski BK, Rodriguez-Bigas MA. et al. Impact of recurrence and salvage surgery on survival after multidisciplinary treatment of rectal cancer. Journal of Clinical Oncology. 2017; 35(23):2631-2638.

Table 1 Patient characteristics

Age Group	Men	women
≤30:	1	0
≤40:	6	5
≤50:	31	9
≤60:	66	36
≤70:	76	39
≤80:	44	28
≤90:	11	12
Range	28-90	35-89
Median	62	63
Total	235	129

Table2. The correlation of tumor location and the pattern of recurrence‡

Tumor location*	The site of recurrence			
	Liver	Lung	Other distant sites	pelvis
Upper rectum	4	9	6	9
Middle rectum	14	7	3	7
Lower rectum	11	16	12	10
Total	29	32	21	26

‡ a patient might have several sites of recurrence at the same time

*Upper rectum: ≥ 12 cm above anal verge, n=94; recurrence=22=23.40%

Middle rectum: ≥8 cm <12 cm from anal verge, n=104; recurrence=26=25.00%

Lower rectum: <8cm from anal verge, n= 166; recurrence=35 =21.08