The Emerging Non-operative Management of Non-metastatic Rectal Cancer: A Population Analysis

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Abstract. *Aim: Recent studies have piloted a nonoperative approach in patients with a complete clinical response to neoadjuvant chemoradiation for non-metastatic rectal cancer. This study evaluated these outcomes in the Surveillance, Epidemiology, and End Results (SEER) database. Materials and Methods: Using SEER database 8.1.5, we identified patients diagnosed with stage II-III rectal adenocarcinoma between 2004-2011, treated with radiation alone (RT), RT then surgery (RT-S), or surgery then RT (S-RT). Utilization patterns were investigated for all three groups and evaluated using the Chi-squared test. A secondary analysis was limited to current approaches (RT or RT-S). Overall survival (OS) was compared using the log-rank test. Predictors for nonoperative management were compared by multivariable analyses. Results: From 2004 to 2011, utilization of RT increased from 4% to 8%, RT-S from 57% to 75%, and S-RT decreased from 39% to 18% (p<0.001). In the secondary analysis, predictors for nonoperative management were lower T-stage and N-stage tumors, non-White race, and male sex. With 5,909 evaluable patients at a median follow-up of 35 months, the 5-year OS in the RT group was 56% vs. 80% in the RT-S group (log-rank p<0.001). Conclusion: Nonoperative management of rectal cancer is increasing despite an apparent detriment in OS compared to a combined modality approach, that may reflect a selection bias in the SEER database.*

There will be an estimated 39,610 cases of rectal cancer diagnosed in the United States in 2015. Along with colonic cancer, it remains the third most common cancer in men and women and the second leading cause of cancer-related deaths in the United States (1, 2). Thankfully, the incidence and death rates have been declining over time, and the most recent 5-year survival outcomes for all patients with rectal cancer is approximately 65%.

Historically, rectal cancer was treated with surgical resection alone, with poor results. The Swedish Rectal Cancer Trial (3) and subsequent Dutch Trial (4) showed that neoadjuvant radiation followed by surgery, compared to surgery alone showed improved local control and overall survival. A subsequent landmark study by Sauer *et al.* compared preoperative chemoradiation to postoperative chemoradiation in T3-4 or node-positive rectal cancer followed by adjuvant chemotherapy (5). They found no difference in disease-free survival or overall survival with either therapy, but improved acute and late toxicity, higher sphincter-preservation rates and improved locoregional recurrence with preoperative chemoradiation. Since the publication of this trial, the standard-of-care for stage II-III rectal cancer includes neoadjuvant chemoradiation, followed by surgery and adjuvant chemotherapy (a category 1 recommendation in the 2016 National Comprehensive Cancer Guidelines (6). Surgical options for these patients often include an abdominoperineal resection (APR) or low anterior resection (LAR). An APR includes removal of the rectum, anus and sigmoidal colon, with the creation of a permanent colostomy, while an LAR removes the diseased rectum alone. Both operations incorporate total mesorectal excision to improve resectability and local control.

While the pathological complete response (pCR) rate was only 8% in the German, Rectal Cancer Trial (5), a review of more recent studies found a range of pCR rates up to 43% (5, 7). Given the morbidity and quality-of-life issues that surgical interventions entail, definitive high-dose chemoradiotherapy in combination with close observation consisting of serial endoscopic and imaging studies with the potential for salvage surgical resection, has become an attractive option particularly for patients with more distal lesions that would otherwise require an APR and permanent colostomy. The feasibility for this approach has been demonstrated by Appelt *et al.* in a prospective observation trial showing 78%

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Table I. *Use of treatment modality by year diagnosed.*

	RT	RT-S	S-RT	*p*-Value
2004	4	57	39	
2011	8	75	18	<0.001

RT: Radiation; RT-S: radiation then surgery; S-RT: surgery then radiation.

complete clinical response, 15.5% 1-year local recurrence rate, and 69% sphincter-preserving rate at 2 years in carefully selected and followed-up patients (8).

This retrospective epidemiological review explores this intriguing topic by evaluating the survival and patterns of care in nonoperative management of rectal cancer in the Surveillance, Epidemiology, and End Results (SEER) database.

Materials and Methods

With a signed research agreement, a retrospective analysis was performed on the National Cancer Institute's SEER database, which examines data from 18 registries compromising approximately 28% of the U.S. population. Using SEER database 8.1.5, included patients were diagnosed with rectal adenocarcinoma (ICD-0-3 codes 8140-8211, 8255-8263, 8440-8481, 8560-8576), up to 64 years old with American Joint Committee on Cancer (9) stage II or III disease (cT2-T3 or cN+, M0, excluding T0, Tis, T4, unknown T or N stage), histologic grade 1-3, diagnosed between 2004-2011 treated with radiation alone (RT), RT then surgery (RT-S), or surgery then RT (S-RT). Additional exclusion criteria were those who refused surgery or had unknown surgery status, and those of unknown race.

All statistical analyses were performed with SPSS version 22 (IBM Corp., Armonk, NY, USA). In the primary analysis, utilization patterns were investigated in all three groups over the study period and evaluated using the chi-squared test. The secondary analysis was then limited to patients treated with RT or RT-S. Chi-square analysis was performed on categorical variables to test their interaction with treatment technique. Covariates potentially associated with treatment technique including T-stage, N-stage, grade, age, sex, race and year of diagnosis were evaluated using binary logistic regression and reported as an odds ratio (OR). All ORs are reported with a 95% confidence interval. Categorical variables were assigned a reference value denoted "REF". Variables with small patient numbers were grouped together (*i.e.*: age and race) to provide a meaningful statistical analysis. Overall survival curves for this group were calculated by the Kaplan–Meier method and compared using the log-rank test. For all analyses, a *p*-value of 0.05 or less was considered significant.

Results

A total of 6,752 patients were included in the primary analysis. From 2004 to 2011 there was an increased utilization of RT from 4% to 8%, of RT-S from 57% to 75%, and a decrease in S-RT from 39% to 18% ($p<0.001$) as seen in Figure 1 and Table I.

Table II. *Baseline study characteristics.*

	No. of patients		
Characteristic	RT-S	RT	*p*-Value
T-Stage			
T1	95	19	
T2	1013	52	
T3	4376	354	<0.001
N-Stage			
N0	2647	231	
N1	2148	166	
N2	689	28	0.001
Grade			
I	380	38	
II	4341	337	
III	763	50	0.167
Age at diagnosis, years			
20-30	78	8	
31-40	435	18	
41-50	1568	109	
51-65	3403	290	0.01
Gender			
Female	1884	110	
Male	3600	315	<0.001
Race			
White	4396	316	
Black	473	59	
Other[a]	615	50	0.001
Year diagnosed			
2004-2006	1690	100	
2007-2009	2232	183	
2010-2011	1562	142	0.005

[a]Includes "unknown" race.

In the secondary analysis (patients treated with RT or RT-S), grade, overall stage, T-stage, N-stage, race, age, gender and year of diagnosis had a statistically significant interaction with method of treatment on univariate analysis. This analysis and the baseline study characteristics can be seen in Table II. On multivariable analysis, predictors for nonoperative management were lower T-stage, lower N-stage, male sex, non-White race and later year of diagnosis, as seen in Table III. With 5,909 evaluable patients at a median follow-up of 35 months, the 5-year OS in the RT alone group was 56% *vs.* 80% in the preoperative RT group (log-rank, $p<0.001$).

Discussion

The use of nonoperative management of rectal cancer has shown increased enthusiasm since the seminal article by Habr-Gama *et al.*, that evaluated 265 patients with distal resectable rectal cancer treated with chemoradiotherapy. In this series, at 8 weeks, 26.8% (71 patients) were found to have a complete clinical response (cCR) by imaging and

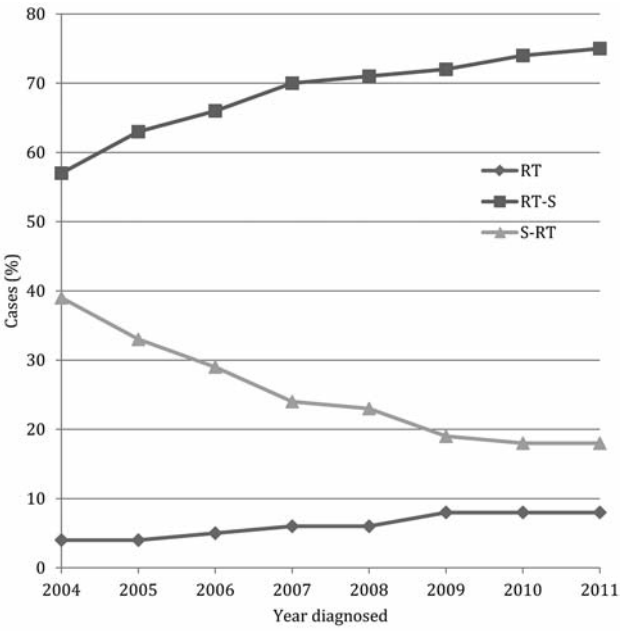

Figure 1. *Trends in the use of radiation (RT) vs. radiation then surgery (RT-S) vs. surgery then radiation (S-RT) from 2004-2011.*

Table III. *Multivariable analysis, predictors for nonoperative management.*

Characteristic	OR	95% CI Bounds		*p*-Value
		Lower	Upper	
T-Stage				
T1	REF			<0.001
T2	0.21	0.12	0.39	
T3	0.37	0.22	0.61	
N-Stage				
N0	REF			<0.001
N1	0.79	0.64	0.98	
N2	0.43	0.29	0.64	
Grade				
I	REF			0.26
II	0.77	0.54	1.10	
III	0.70	0.45	1.10	
Age at diagnosis, years				
<50	REF			0.10
50-65	1.20	0.96	1.50	
Gender				
Female	REF			<0.001
Male	1.52	1.21	1.91	
Race				
White	REF			0.004
Other[a]	1.40	1.11	1.76	
Year diagnosed				
2004-2006	REF			0.004
2007-2009	1.41	1.09	1.81	
2010-2011	1.55	1.19	2.03	

[a]Includes "unknown" and "Black" race. CI : Confidence interval; OR: odds ratio; REF: reference.

clinical examination. These patients formed the observation group, while those without cCR went on to surgery. With a median follow-up of 5 years, overall survival and disease-free survival in the observation group was 100% and 92%, respectively (10). Since the publication of this trial, the use of nonoperative management of rectal cancer has gained significant popularity and formed the basis of our study. We found that later year of diagnosis was an independent predictor for nonoperative management, reflecting the emergence of a "watch-and-wait" approach in patients who have a complete response to neoadjuvant chemoradiation.

Predicting who will achieve a cCR (and a pCR had they undergone surgery) remains quite complex. Physicians have relied on post-treatment magnetic resonance imaging to predict for clear circumferential margins on surgery, however, its ability to evaluate for residual disease and hence its reliability to predict cCR remains unclear (11). Positron-emission tomography is often utilized in the pre-treatment and post-neoadjuvant treatment assessment. A decrease in standardized uptake value at the primary site has been shown to correlate with pathological response, but like magnetic resonance imaging, its widespread use to predict cCR has yet to be established (12). Clinical examation, including digital rectal examination, has been shown to have a low positive predictive value in assessing tumor response. In one study, up to 80% of patients were underestimated in their amount of down-staging by digital rectal examination (13). Newer techniques such as gene-expression profiling have shown promise in predicting response to RT (14). It is likely not one of the above modalities, but all of them, incorporated into a comprehensive and longitudinal clinical, radiological and biochemical follow-up with the possibility of salvage surgery if needed. Thankfully, surgery as a salvage treatment in those who have achieved cCR remains an effective option, with similar local and distant control as for those that went directly to surgery after neoadjuvant therapy (15). There are other factors that may predict for a robust response to neoadjuvant therapy, such as dose, quality of radiation and use of concomitant chemotherapy (which has been shown to increase the pCR rates by 2- to 3-fold (16).

Arguably the most important factor predicting who will have a cCR to neoadjuvant therapy lies in appropriate patient selection. In this study, predictors for nonoperative management were lower T-stage and N-stage tumors, however, lower-stage tumors have not reliably correlated with initial or sustained cCR in other studies (17). Other predictors for nonoperative management included non-White race and male patients; however, this is of unclear significance. Future

investigation should continue to focus on identifying clinical tumor features that predict for cCR to chemoradiation therapy and for successful nonoperative management.

This study is not without limitations, such as selection bias within the SEER database. Although age was not an independent predictor for use/non-use of RT, many patients chosen for nonoperative management may have had comorbid illnesses that would have increased surgical risk. This likely leads to the significant survival detriment in the patients treated without surgery, which was significantly worse than modern chemoradiation studies such as that of Appelt *et al*. which saw a 2-year survival of 100% (8). An attempt was made to limit the bias of treating older patients with nonoperative approaches because of their comorbidities by applying an age cut-off of 64 years in the current study. Unfortunately, SEER does not code for the use of chemotherapy, and hence it is unknown whether the nonoperative patients were treated with radiation alone or radiation and chemotherapy. In addition, SEER does not code for local control or evaluation after initial therapy, which is critical to proper patient selection for nonoperative management. Other limitations of this study include inability to evaluate salvage treatments, morbidity, and quality of life.

Despite these limitations, this analysis offers a closer look at the patterns of care of nonoperative treatment of rectal cancer in one of the largest series to date. Currently there are at least four additional ongoing phase I or II trials evaluating nonoperative management for rectal cancer at the Memorial Sloan Kettering Cancer Center (NCT02008656, NCT02199236), Royal Marsden (NCT01047969) and Sao Paulo Brazil (NCT02052921). We await the results of these trials to help guide future management of these patients.

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