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Original Research Article

Oncological outcomes of obstructed locally advanced rectal cancer in the era of multi-modal therapy

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ABSTRACT

Background: The management of locally advanced rectal cancer is multi-modal. In India, a number of patients present with features of intestinal obstruction and are diverted prior to initiation of chemo-radiation therapy. The purpose of this paper is to study the demographics and oncological outcomes of obstructed locally advanced rectal cancer (OLARC) requiring pre-therapy diversion colostomy in comparison with patients who did not need pre-treatment diversion (non-obstructed group).
Methods: This is a retrospective analysis of a prospective data-base. Patients diagnosed with non-metastatic locally advanced adenocarcinoma of the rectum in a colorectal unit of a tertiary care teaching hospital between August 2012 and December 2014 were analyzed. Data was collected from hospital records and telephonic interviews.
Results: Two hundred and thirteen patients were diagnosed to have locally advanced rectal cancer. One hundred and fifty patients (70.4%) did not have features of intestinal obstruction and received NACRT upfront and 63 (29.6%) required pre-therapy diversion colostomy. Thirty-nine patients (61.9%) completed therapy (neo-adjuvant chemo-radiotherapy followed by Surgery and adjuvant chemotherapy) in the obstructed group, compared to 127(84.7%) in the non-obstructed group (0<0.05) who completed all components of cancer directed therapy. The 3-year overall survival (OS) of the obstructed and non-obstructed groups was 59% vs 90% (p<.001) and the disease-free survival (DFS) was 51% and 76% (p<0.01) respectively.
Conclusions: In the era of multi-modal therapy, patients with obstructed locally advanced rectal cancer have worse oncological outcomes with respect to overall and disease-free survival.

Keywords: Colorectal surgery, Indian rectal cancer, Obstructed rectal cancer, Rectal cancer

INTRODUCTION

The management of locally advanced adenocarcinoma of the rectum is multi-modal and has been revolutionised with the advent of neoadjuvant chemo-radiotherapy (NACRT).[1] The usual algorithm for the management of locally advanced rectal cancer within 15 centimetres of the anal verge is NACRT followed by definitive surgery and subsequent adjuvant therapy based on the pathological staging.[2] In India, a significant number of patients with adenocarcinoma rectum present with features of obstruction. These patients have colostomy to relieve obstruction prior to initiation of chemo-radiation therapy. Cancer directed therapy is delayed for these patients as the obstruction needs to be relieved first.[3] The surgical and oncological outcome of this group of patients is likely to be different. There is a paucity of literature discussing the long-term survival of patients

with obstructed non-metastatic locally advanced rectal cancer.[4,5] Most studies have combined all colo-rectal malignant obstructions in one group, drawing inferences from these studies are difficult due to heterogeneity of the study population.[4,5]

Objective of the study was to study the oncological outcomes of obstructed locally advanced rectal cancer (OLARC) requiring pre-therapy diversion colostomy and compare it with patients who do not need pre-treatment diversion (non-obstructed group).

METHODS

This is a retrospective analysis of patients diagnosed to have locally advanced rectal cancer.

Inclusion criteria

Patients diagnosed with non-metastatic locally advanced adenocarcinoma of the rectum in a colorectal unit of a tertiary care teaching hospital between August 2012 and September 2014 were included. Only patients who were managed with curative intent were included in the study.

Patients were staged using the TNM classification as defined by the AJCC 7th edition.[6] The definition of locally advanced rectal cancer included patients with stage 2 and 3 disease on the initial MRI scan at presentation.[7]

Diagnosis of intestinal obstruction and the need for pre-therapy diversion colostomy was made by the treating surgeon based on clinical signs and symptoms and appropriate radiological investigations. The decision to divert and plan for NACRT was subsequently formalized in the multidisciplinary tumour board (MDT).

As per protocol, patients were scheduled to receive neoadjuvant conventional long course chemo-radiation therapy (LCCRT) or intra-venous infusion of 5-fluorouracil (5 FU) along with radiation therapy based on multidisciplinary tumour board decision

After completion of NACRT and a delay of 6 to 10 weeks, they were re-assessed clinically and with MRI pelvis.[8] After re-discussion in the MDT, patients underwent surgical resection if the rectal growth was deemed operable. The patients who underwent definitive surgery after NACRT were offered adjuvant therapy based on the histopathology report as dictated by an MDT discussion. Follow up consisted of bi-annual clinical examination, carcino-embryonal antigen (CEA) and annual CT scan of the abdomen and pelvis for the first three years and subsequently annual CEA, CT scans for two more years. Colonoscopy was done three years post therapy and subsequently every five years. Follow up was also symptom directed. Radiological or clinical recurrence in the pelvis was considered as Local recurrence and all other areas were considered as systemic recurrence.[1] The demographic details were accessed from a prospective data base. Survival data was obtained from the electronic database and telephonic conversations with patients or their relatives.

Statistical analysis

Data was analyzed using SPSS for windows, version 16.0 (Chicago, SPSS Inc.) and STATA/IC 13.1 for windows (StataCorp, TX, USA). Frequency tables were used for the description of demographic variables. Statistical significance for the comparison demographic variables was done by using the Chi-square test or Fisher's exact test. Survival analysis was done using Kaplan Meier curves and compared using Log Rank (Mantel-Cox) test. Univariate and Multivariate Cox proportional hazard regression analysis was used to find the significant prognostic factors of overall and disease-free survival.

RESULTS

Two hundred and thirteen patients were diagnosed to have locally advanced rectal cancer and treated with curative intent in our institution during the study period. The mean age of patients was 48 years. One hundred and fifty patients (70.4%) did not have features of intestinal obstruction and receive NACRT upfront and 63 (29.6%) had intestinal obstruction requiring pre-therapy diversion colostomy. Thirty-nine patients (61.9%) completed multi-modal therapy in the obstructed group, whereas 127(84.7%) completed therapy in the non-obstructed group (p value <0.05) (Figure 1).

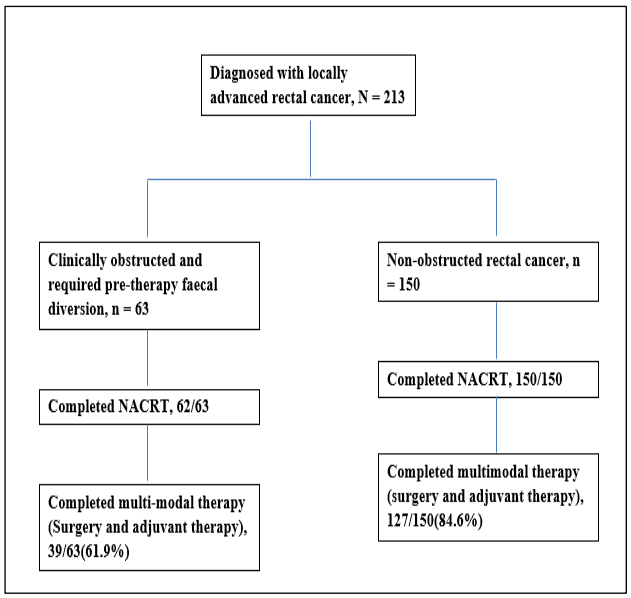

Figure 1: Flow diagram of study participants

Table 1: Peri-operative baseline clinical and histopathological demographics.

Variables	Obstructed and required diversion (N=63) n (%)	Non-obstructed (N=150) n (%)	p value
Sex			
Male	43 (68.3)	92 (61.3)	.339
Female	20 (31.7)	58 (38.7)	
Age in years			
<50	36 (57.1)	66 (44.0)	.080
>50	27 (42.9)	84 (56.0)	
MRI pre-treatment TNM Staging			
2	10 (15.8%)	22 (14.6%)	.294
3	53 (84.1%)	127 (84.6%)	
Missing	0	1	
MRI pre-treatment CRM			
Maintained	6 (9.5%)	37 (24.6%)	.009
Lost	56 (88%)	106 (70.6%)	
Missing	1 (1.6%)	7 (4.7%)	
Differentiation (Grade)			
Well	1 (1.6%)	9 (6%)	
Moderate	41 (65.1%)	92 (61.3%)	.050
Poor	14 (22.2%)	15 (10%)	
Missing	7 (11.1%)	34 (22.6%)	
Signet ring			
Yes	6 (9.5%)	11 (7.3%)	.395
No	57 (90.5)	139 (92.7%)	
Mucinous			
Yes	9 (14.2%)	13 (8.6%)	.377
No	54 (85.8%)	137 (91.4%)	
LVI			
Yes	5 (7.9%)	12 (8%)	.569
No	58 (92.1%)	144 (142%)	
PNI			
Yes	10 (15.8%)	18 (12%)	.123
No	53 (84.2%)	132 (88%)	

The clinical, demographic and survival comparison between the two groups of patients (obstructed and non-obstructed rectal cancer) is depicted in Table 1 and 2.

The reason for inability to complete therapy as planned prior to initiation of NACRT is depicted in Table 3.

The median follow up was 27 months. The 3-year DFS, OS and recurrence patterns in the two groups are presented in Table 4.

The Kaplan Meier survival curve revealing 3-year OS and DFS of patients with locally advanced rectal cancer is depicted in Figure 2 and 3 respectively. The 3-year OS and DFS was 81% and 69% respectively.

The Kaplan Meier survival curve revealing the 3-year OS and DFS between the two study groups have been represented in Figure 4 and 5 respectively.

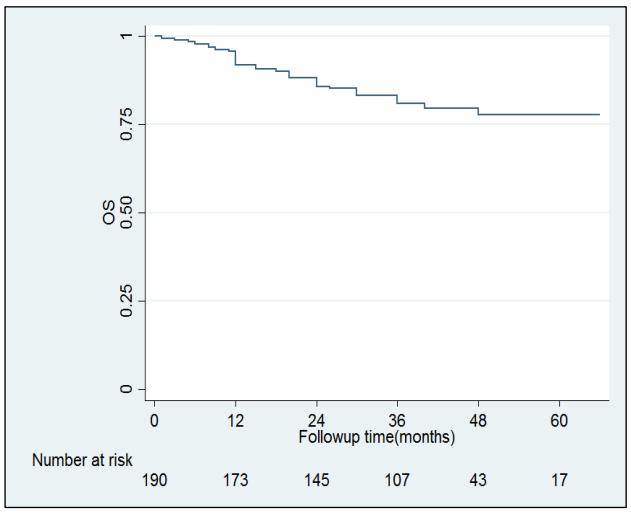

Figure 2: Kaplan Meier overall survival curve.

The 3-year overall survival (OS) of the obstructed and non-obstructed groups was 59% vs 90% (p<.001) and the disease-free survival (DFS) was 51% and 76% (p<0.01) respectively. The survival analysis of patients who have completed all aspects of multi-modal therapy for rectal cancer in both groups (obstructed and non-obstructed) was analysed and there were significant better overall survival outcomes in the non-obstructed group (Table 5).

Table 2: Details of multi-modal therapy in both study groups.

Variables	Obstructed and required diversion (N=63), n (%)	Non-obstructed (N=150), n (%)	p value
Completed NACRT			
Yes	62 (98.4%)	150 (100%)	.296
No	1 (1.6%)	0	
Completed surgery			
Yes	42 (66.7%)	133 (88.7%)	<.001
No	21 (33.3%)	17 (11.3%)	
Which surgery			
AR	6 (14.3%)	14 (10.5%)	
LAR	14 (33.3%)	52 (39%)	
APE	20 (47.6%)	66 (49.6%)	.494
Multivisceral resection	2 (4.7%)	1 (0.7%)	
Completed Adjuvant therapy			
Yes	39 (61.9%)	127 (84.6%)	
No	24 (38.1%)	23 (14.8%)	<.001
Pathological Tumour depth (T stage)	**(n = 42)**	**(n 133)**	
0	4 (9.5%)	15 (11.2%)	
1	1 (2.4%)	16 (12%)	.018
2	5 (11.9%)	36 (27%)	
3	30 (71.4%)	56 (42.1%)	
4	2 (4.8%)	10 (7.5%)	
Nodal involvement (N stage)			
0	27 (64.2%)	91 (68.4%)	
1	11 (26.2%)	29 (21.9%)	.260
2	3 (7.1%)	13 (9.8%)	
3	1 (2.3%)	0	
TNM Staging			
Complete pathological response	4 (9.5%)	15 (11.2%)	
1	4 (9.5%)	43 (32.3%)	.020
2	19 (45.2%)	34 (25.6%)	
3	15 (35.7%)	41 (30.8%)	
Pathological Circumferential resection margin (CRM)			.104
Not Involved	33 (78.6%)	117 (87.9%)	
Involved	9 (21.4%)	16 (11.5%)	

The prognostic factors affecting disease free and overall survival of carcinoma rectum has been studied in Table 6 and 7. The time to start NACRT in the OLARC group was 18.5 days (Range 6-50 days). Laparoscopic stoma formation was the preferred technique with 54/63 patients (85.7%), the remaining had laparotomy and loop colostomy formation.

Five patients needed to be re-operated for stoma related complications thereby delaying initiation of NACRT.

Table 3: Reasons for inability to complete therapy.

Variable	Obstructed and required diversion 24/63	Non-obstructed 23/150	p value
Inoperable	10	6	.001
Metastasis	4	2	.007
Not fit for further therapy	0	2	
Lost to follow up	10	13	.291

Table 4: Details of Survival and Recurrence.

Variables	Obstructed and required diversion (n 56)	Non-obstructed (n 134)	p value
Disease free 3-year survival probability (all stages)	51%	76%	<.001
Overall 3-year survival probability (all stages)	59%	90%	<.001
Stage wise 3-year overall survival			
Compete pathological response	100%	100%	
Stage 1	50%	96%	<.001
Stage 2	69%	95%	.019
Stage 3	63%	89%	.038
Stage wise 3-year DF survival			
Compete pathological response	67%	100%	.005
Stage 1	67%	94%	.028
Stage 2	71%	67%	.917
Stage 3	37%	66%	.041
Local Recurrence	7/56	8/134	
Systemic recurrence	9/56	14/134	

Table 5: OS and DFS of patients who have completed multimodal therapy.

Variables	Obstructed and competed multi-modal therapy (39/63)	Non-obstructed and completed multi-modal therapy (127/150)	p value
Disease free 3-year survival probability (all stages)	63.9%	79%	.35
Overall 3-year Survival probability (all stages)	73%	94%	.001

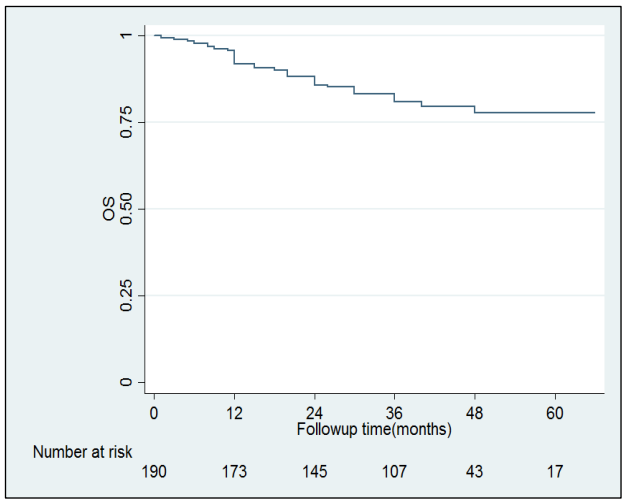

Figure 3: Kaplan Meier disease free survival curve.

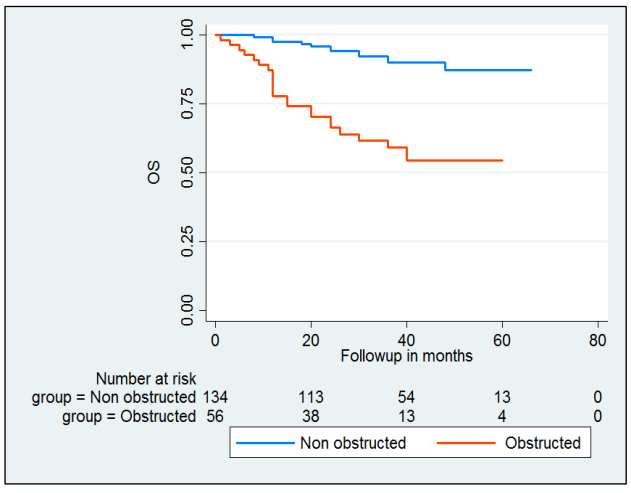

Figure 4: Kaplan Meier Overall Survival of obstructed and non-obstructed locally advanced rectal cancer.

Geographically, 99 patients (46%) hailed from north eastern India, 63 patients (20.9%) were from South India, 30 patients (14%) were from Central and north India and 21 patients (9.9%) were referred from other countries such as Bangladesh.

Table 6: Factors affecting disease free survival (DFS).

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	p value	HR (95%CI)	P value
Age				
<50 years	Ref			
≥50 years	.8 (.5,1.3)	0.313		
Group				
Obstructed	3.1 (1.8, 5.2)	<0.001	1.9 (0.9, 3.9)	0.082
Non-obstructed	Ref			
Grade				
Well	Ref			
Moderate	1.1 (.3,4.4)	0.953		
Poor	2.6 (.6,12.0)	0.228		
p TNM staging				
Complete pathological response	Ref			
1	.6 (.1,3.6)	0.572		
2	3.8 (.9,16.1)	0.077		
3	4.1 (0.9,17.7)	0.060		
Pathological CRM				
Maintained	Ref			
Lost	2.9 (1.5,5.8)	0.003	2.1 (0.9, 4.9)	0.094
Mucinous				
Yes	2.1 (1.02,4.5)	0.045	1.7 (0.7, 4.3)	0.243
No	Ref			
Signet ring				
Yes	2.0 (.8,5.2)	0.143		
No	Ref			
LVI				
Yes	1.6 (.6,4.0)	0.349		
No	Ref			
PNI				
Yes	2.1 (1.01,4.2)	0.049	1.3 (0.6, 2.9)	0.569
No	Ref			
LN harvest				
<12	1.3 (.7, 2.6)	0.439		
>=12	Ref			
Cancer surgery				
Yes	Ref			
No	4.8 (2.7,8.6)	<0.001		
Adjuvant chemotherapy				
Yes	Ref			
No	4.4 (2.5,7.6)	<0.001	2.9 (0.6, 13.1)	0.174

DISCUSSION

Large bowel obstruction secondary to rectal cancer presents unique challenges in the era of multi-modal therapy. Due to the lack of screening programs in India, rectal cancer presents at a later stage, this is reflected in the present study

During the study period 23% of all patients who had locally advanced rectal cancer had acute or chronic intestinal obstruction requiring pre-treatment diversion colostomy, when compared to 2.9% from published literature.[1] In keeping with other reports from India, the average age of patients with rectal cancer is more than a decade earlier than western countries.[9] Most pre-

treatment diversion loop colostomies were done laparoscopically. Laparoscopy was the preferred operative technique because it allows intra-peritoneal surveillance and is associated with shorter hospital stay with lesser post-operative pain.[9-11]

Table 7: Factors affecting overall survival (OS).

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	p value	HR (95%CI)	p value
Age				
<50 years	Ref			
≥50 years	0.7 (0.4, 1.3)	0.684		
Group				
Obstructed	5.4 (2.7, 11.0)	<0.001	9.8 (2.5, 37.9)	0.001
Non-obstructed	Ref			
Grade				
Well	Ref			
Moderate		0.921		
Poor		0.910		
Pathological TNM staging				
1	Ref			
2	2.4 (0.7,9.2)	0.188		
3&4	5.9 (1.8, 19.7)	0.004		
Pathological CRM				
Maintained	Ref			
Lost	3.1 (1.1, 8.9)	0.033	1.9 (0.4, 9.3)	0.447
Mucinous				
Yes	3.2 (1.2, 8.5)	0.018	6.4 (1.4, 30.1)	0.018
No	Ref			
Signet ring				
Yes	4.5 (1.6, 12.4)	0.004	0.1 (0.01, 1.5)	0.088
No	Ref			
LVI				
Yes	2.2 (0.6, 7.6)	0.213		
No	Ref			
PNI				
Yes	3.2 (1.2, 8.8)	0.021	3.6 (0.9, 15.1)	0.075
No	Ref			
LN harvest				
<12	2.2 (0.6, 7.6)	0.223		
≥12	Ref			
Cancer surgery				
Yes	Ref			
No	10.8 (5.4, 21.6)	<0.001		
Adjuvant chemotherapy				
Yes	Ref			
No	9.6 (4.8, 19.1)	<0.001	5.2 (0.8, 33.1)	0.081

Sigmoid colostomy was preferred because of the ease of management of the stoma post operatively, the transverse colostomy content is semi-solid making it difficult to manage the same. There is also a higher chance of prolapse of transverse colostomy.[12] Surgical complications associated with transverse colostomy, such as ischaemia of the stoma may hamper subsequent definitive surgery (anterior resection/abdomino-perineal excision). Stenting of obstructed rectal malignancies has not become standard of care yet (specially for lower rectal cancer), as has been elucidated by a Cochrane meta-analysis.[13] Most literature advocating stenting of colorectal malignancies have included all colonic and

rectal malignancies, this makes the study population heterogeneous.[14,15]

The average time to initiate NACRT following a diversion ostomy was around two and a half weeks. However, a little over 60% of all patients completed all components of multi-modal cancer therapy. This is much lower when compared to non-obstructed locally advanced rectal cancer where 86% of these patients complete all components of cancer directed therapy.

The reason for inability to complete therapy is multifactorial and has been equally distributed between disease progression and failure to present for treatment and follow up.

The most common reason as to why patients were unable to complete therapy is however logistical (being lost to follow up), the logistics of an additional operation (diversion colostomy) in an already prolonged therapy for rectal cancer can also be cited as a reason for inability to complete therapy.[16]

The long-term outcome of clinically obstructed rectal cancer is not well studied and therefore there is no literature to compare our results with. Hong et al have studied a cohort of endoscopically obstructed patients however most of their patients did not have obstruction severe enough to mandate pre-treatment diversion or stenting.

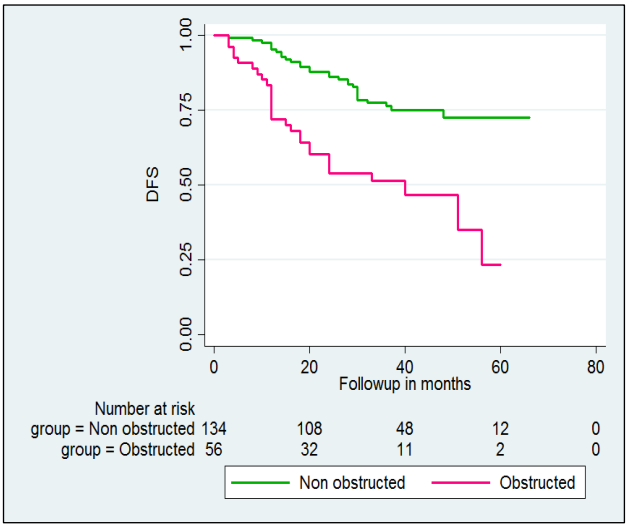

Figure 5: Kaplan Meier Disease Free Survival of obstructed and non-obstructed locally advanced rectal cancer.

In the present study, the patients without obstruction had better 3-year disease free and overall survival. This was statistically significant on univariate and multi-variate analysis. On univariate analysis stage of presentation, biology of tumour and ability to successfully complete all components of multi-modal therapy significantly predicted overall and disease-free survival. Rectal cancer presenting with intestinal obstruction requiring faecal diversion is an independent risk factor predicting poor survival, this may be attributed to inability to complete multimodal therapy. However, on comparing survival outcome of patients who have completed multi-modal therapy in both groups, there was significantly better outcome for patients who have presented without obstruction, implying that poor prognosis may be a result of un-favourable tumour biology in the obstructed group and not just their inability to complete therapy or the obstruction per se (Table 5).

While factors such as bad tumour biology are non-modifiable, various other predictors of poor outcome are modifiable. Active follow-up of patients during cancer therapy may prevent attrition during the treatment process and improve adherence to treatment and in the long run improve cancer survival.[17]

The limitations of the present study would include the retrospective study design, which is prone to bias. Being a referral centre in a developing country, patients were probably referred at a later stage which may account for the large number of patients presenting with rectal obstruction. This would make generalization of this study results difficult.

CONCLUSION

Obstructed locally advanced rectal cancer requiring pre-therapy diversion colostomy had worse long-term survival outcomes when compared to non-obstructed patients. Ability to complete all components of multi-modal cancer therapy, stage of presentation and tumour biology significantly affected long term survival of patients with locally advanced non-metastatic, operable rectal cancer..

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