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Systemic chemotherapy and short-course radiation in metastatic rectal cancers: A feasible paradigm in unresectable and potentially resectable cancers

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Abstract

Background: The optimal use and sequencing of short-course radiotherapy (SCRT) in metastatic rectal cancers (mRCs) are not well established. **Materials and Methods:** We retrospectively reviewed the records of mRC patients receiving SCRT followed by palliative chemotherapy between January 1, 2013, and December 31, 2016, in Tata Memorial Hospital. Patients were classified as having "potentially resectable" disease (local and metastatic) or "unresectable" disease at baseline based on prespecified criteria. **Results:** A total of 105 consecutive patients were available for analysis. The median age of patients was 48 years (range: 16–62 years), and 57.1% were male patients. Signet ring histology was seen in 13.3% of patients. The most common site of metastases was liver limited (29.5%), nonloco-regional nodes (12.4%), and lung limited metastases (9.5%). Chemotherapeutic regimens administered were capecitabine-oxaliplatin (70.5%), modified 5 fluorouracil (5 FU)-leucovorin-irinotecan-oxaliplatin (10.5%), and modified 5 FU-leucovorin-irinotecan (8.6%). Targeted therapy accompanying chemotherapy was administered in 27.6% of patients. About 42.1% of patients with potentially resectable disease and 11.1% with the unresectable disease at baseline underwent curative-intent resection of the primary and address of metastatic sites. With a median follow-up 18.2 months, median overall survival (OS) was 15.7 months (95% confidence interval: 10.42–20.99). Patients classified as potentially resectable had a median OS of 32.62 months while patients initially classified as unresectable had a median OS of 13.04 months ($P = 0.016$). The presence of signet ring morphology predicted for inferior mOS ($P = 0.021$). **Conclusions:** SCRT followed by systemic therapy in mRC is a feasible, efficacious paradigm for maximizing palliation, and achieving objective responses. The classification of patients based on resectability was predictive of actual resection rates as well as outcomes. Signet ring mRC show inferior outcomes in this cohort of patients.

Key words: Chemotherapy, metastatectomy, metastatic rectal cancers, resectability, short-course radiotherapy

Introduction

Outcomes in metastatic colorectal cancers (mCRCs) have improved with the greater use of chemotherapy, monoclonal antibodies and recently, immunotherapy.[1-4] Increasing resection rates for resectable liver metastases (LM) (up to 93%) and conversion rates for unresectable LM (up to 49%) to resectability by chemotherapy with or without monoclonal antibodies means that there is a need for addressing the rectal primary adequately as well.[5-8] There also remains the unanswered question of potential benefit with surgical resection of the primary in patients with the unresectable metastatic disease with multiple retrospective studies suggesting a survival benefit for the strategy.[9,10] There are also no firm guidelines regarding criteria for resectability of metastatic sites in CRC, though few exist for liver metastatectomy.

The effect of radiotherapy (RT) in the local symptom and disease control of locally advanced rectal cancers (LARCs) has ensured that it is a part of the standard of care in the treatment of such cancers. While conventionally preoperative long-course chemoradiation (LCRT) was part of the treatment paradigm for LARC, there is growing evidence to suggest comparability and potential superiority of preoperative short-course RT (SCRT) and systemic chemotherapy as opposed to LCRT.[11-13] In patients with metastatic rectal cancer (mRC) at baseline, upfront SCRT provides palliation, potential stoma prevention besides avoiding undue delays in beginning systemic chemotherapy (with or without targeted therapy). It also overcomes the logistic constraints of combining RT for the primary rectal cancer and preparing the patient for potential surgery of the primary should there be adequate conversion/downstaging of primary and secondary sites post chemotherapy.[14,15]

Materials and Methods

Patient selection

The study is a retrospective analysis of mRC patients with metastases who were offered SCRT followed by chemotherapy, (with or without monoclonal antibodies based on feasibility) during January 1, 2013, to December 31, 2016, at the Department of Gastrointestinal Oncology, Tata Memorial Hospital (TMH) in Mumbai. The study was approved by the Institutional Review Board and Ethics Committee (IEC/0516/1664/001) and was conducted as per the Declaration of Helsinki guidelines. Patient data were extracted from a prospectively maintained rectal cancer database at TMH. Patients included in the study satisfied all the following criteria:

1. Histologically confirmed adenocarcinoma of the rectum, either T3/T4 and or node (N) positive as per clinical diagnosis and contrast-enhanced magnetic resonance imaging (CE-MRI) of the rectum
2. Evidence of metastases based on contrast-enhanced computed tomography (CT) scans or 18-fluorodeoxyglucose contrast-enhanced positron emission tomography scan.

Institution criteria for the potential liver-directed therapy of metastatic liver disease

1. Technically R0 resection possible of all visible lesions
2. Greater than 30% future liver remnant (FLR) post planned resection at baseline or >40% FLR postchemotherapy

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3. Size of hepatic lesions <5 cm and/or <4 LM
4. Lesions in proximity to all hepatic veins or both branches of the portal vein, which may undergo potential downstaging and further resection.

Patients not satisfying the above criteria were classified as unresectable metastatic disease, though a surgical evaluation was considered at a later point for all patients if they had a good response at metastatic sites and controlled primary.

Resectability criteria of the primary rectal cancer

1. Circumferential margin (CRM) negativity
2. The absence of extension through the greater sciatic notch, encasement of external iliac vessels, paraaortic lymphadenopathy, or sacral invasion above S2–S3 junction
3. R0 resection possible.

Patients with extensive side-wall involvement were considered for local resection based on a case-to-case scenario.

Short-course radiotherapy protocol

Patients received SCRT to a dose of 5 Gy per fraction for a total of five fractions given on 5 consecutive days.

Systemic chemotherapy protocol

Patients were planned for starting chemotherapy 5–10 days postcompletion of SCRT. Targeted therapy was added to chemotherapy backbone based on results of mutation testing. Regimens considered as first-line therapy in our institution include capecitabine-oxaliplatin (CAPOX), single-agent capecitabine, 5 fluorouracil (5 FU)-leucovorin-oxaliplatin (FOLFOX-7), modified 5 FU-leucovorin- irinotecan (mFOLFIRI without bolus 5 FU), and modified 5 FU-leucovorin-irinotecan-oxaliplatin (mFOLFIRINOX without bolus 5 FU). Dosages and schedules were as per standard schedules. Toxicity assessment during chemotherapy was done at every patient visit and recorded as per NCI-CTCAE (National Cancer Institute- Common Terminology Criteria for Adverse Events).

Tumor response assessment

CT scans were reported as per RECIST 1.1 criteria.[16] In situations where response could not be quantified by RECIST, then the response was quantified based on collusion between treating physician and the gastrointestinal radiologist as follows: complete response (CR) – disappearance of all baseline lesions; partial response (PR) – significant regression of lesions at baseline; stable disease (SD) – no significant regression of baseline lesions and no new lesions; progressive disease (PD) – appearance of new lesions or significant increase in baseline lesions. Responses in the rectal primary were evaluated by CE-MRI and responses were recorded as CR, PR, SD, or PD based on changes in signal tumor intensity, regression in tumor and nodal size, regression in CRM status and the presence of fibrosis on T2-weighted sequences.[17,18]

Prognostic factors

Predefined prognostic factors evaluated for correlation with overall survival (OS) were younger age at diagnosis (≤50 years vs. >50 years), degree of differentiation, signet ring histology CEA levels, Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0/1 vs. ≥2), and the presence of obstruction at baseline and resectability status potentially resectable versus unresectable metastatic disease at baseline.

Clinical data collection and statistics

All data were entered in IBM Statistical Package for the Social Sciences (SPSS) software version 21.0 and used for analysis. Descriptive statistics including median, frequency, and percentage for categorical variables is used to describe age, gender distribution, treatment, and response to treatment. Survival outcomes in terms of event-free survival (EFS) and OS were analyzed. Median EFS was calculated from the date of diagnosis to the date of clinical or radiological evidence of disease progression or the last follow-up date. Median OS was calculated from the date of diagnosis until the last follow-up or death. EFS and OS were calculated separately for the potentially resectable and unresectable cohorts. Survival analysis was performed using Kaplan–Meier estimates and log-rank test for bivariate comparisons. Variables achieving statistical significance ($P \leq 0.05$) on univariate analysis were evaluated for multivariate analysis by the cox-regression.

Results

Baseline characteristics

A total of 105 patients were included in the study in the specified time. Baseline demographic and clinical characteristics are detailed in Table 1.

Delivery of short-course radiotherapy and first line systemic therapy

SCRT was delivered as planned in all 105 patients, with no Grade 3 or Grade 4 toxicities. There were no unplanned delays in SCRT. The mean duration between completion of SCRT and beginning systemic therapy was 8 days (range: 2–22). The chemotherapy regimens used were as follows:

- CAPOX (70.5%)
- Modified FOLFIRINOX (10.5%)
- Modified FOLFIRI (8.6%)
- Modified FOLFOX (5.7%)
- Capecitabine monotherapy (4.8%).

Common Grade 3 and Grade 4 toxicities as well as the requirement of dose reductions are provided in Table 2.

Response rates, resection rates, and treatment of metastatic sites

Post-SCRT and chemotherapy, responses rates and disease control rates at primary and metastatic sites are shown in Table 2.

In patients with potentially resectable disease (n = 38), 16 patients (42.1%) underwent curative-intent resection of the primary. In patients with baseline unresectable disease (n = 67), 8 patients (11.1%) underwent curative-intent resection of the primary. In these patients, details of surgery of the primary site as well as treatment of metastatic sites are described in Supplementary Table 1.

Overall survival and event-free survival

With a median follow-up 18.2 months, 59 patients had died of disease for a median OS of 15.7 months (95% confidence interval [CI]: 10.42–20.99). Patients classified as potentially resectable at baseline had a median OS of 32.62 months (95% CI: 17.7–47.5) whereas patients initially classified as

Table 1: Baseline demographic and clinical characteristics

Characteristic	*n* (percentage where applicable)
Median age (years)	48 (range: 16-78)
<50	60 (57.1)
≥50	45 (42.9)
Gender	
Male	60 (57.1)
Female	45 (42.9)
ECOG PS	
0/1	37 (35.3)
≥2	68 (64.7)
2	60 (57.1)
3	8 (7.6)
Site of disease	
Upper 1/3	42 (40)
Middle 1/3	17 (16)
Lower 1/3	46 (44)
Histopathology	
PDAC	36 (34.3)
MDAC	43 (41)
WDAC	24 (22.9)
Adenocarcinoma, NOS	2 (1.9)
Mucinous histology	
Yes	8 (7.6)
No	97 (92.4)
Signet ring histology	
Yes	14 (13.3)
No	91 (86.7)
Baseline CEA status	
CEA>ULN	88 (83.8)
CEA≤ULN	17 (16.2)
Baseline obstruction requiring diversion stoma	
Yes	61 (58.1)
No	44 (41.9)
Metastatic sites of disease	
Liver limited	31 (29.5)
Lung limited	10 (9.5)
Non loco-regional nodes	13 (12.4)
Peritoneal limited	6 (5.7)
Others	3 (2.9)
>1 site of disease	42 (40)
Metastatic resectability status at baseline	
Potentially resectable	38 (36.2)
Unresectable	67 (63.8)

ECOG PS=Eastern Oncology Group performance status, PDAC=Poorly differentiated adenocarcinoma, MDAC=Moderately differentiated adenocarcinoma, WDAC=Well differentiated adenocarcinoma, NOS=Not otherwise specified, ULN=Upper limit of normal, CEA=Carcinoembryonic antigen

unresectable had a median OS of 13.04 months (95% CI: 10.2–15.8) with a statistically significant difference in survival between the cohorts (P = 0.016). Patients who underwent resection of the primary rectal cancer from the entire cohort (n = 24) had a statistically superior survival compared to patients who did not undergo surgery of the primary (n = 81) (2-year survival 58% vs. 10.7%; P < 0.001).

At the time of median follow-up, 67 patients had an event for median EFS of 10.84 months (95% CI: 9.10–12.58). Patients classified initially as potentially resectable had a

Table 2: Characteristics of first line systemic therapy postshort course radiotherapy and response rates

Characteristics	*n* (percentage where applicable)
Chemotherapeutic regimen	
CAPOX	74 (70.5)
FOLFIRINOX	11 (10.5)
FOLFIRI	9 (8.6)
FOLFOX	6 (5.7)
Capecitabine	5 (4.8)
Targeted therapy (with chemotherapy backbone)	
Bevacizumab	29 (27.6)
Cetuximab	24.(5)
Grade 3 and 4 toxicities	
Hematological	4 (4)
Vomiting	4 (4)
Diarrhoea	17 (16.2)
Hand foot syndrome (Grade 2 and Grade 3)	11 (10.5)
Fatigue (Grade 3)	2 (1.3)
Response rates in primary	
CR	3 (2.9)
PR	38 (36.2)
SD	31 (29.5)
PD	27 (25.7)
RR	41 (39.1)
DCR	72 (68.6)
Not evaluated	4 (3.8)
Lost to follow-up	2 (1.9)
Response rates in metastatic sites	
Complete response	2 (1.9)
Partial response	27 (25.7)
Stable disease	25 (23.8)
Progressive disease	43 (41.0)
Response rates	29 (27.6)
DCR	54 (51.4)
Not available	6 (5.6)
Lost to follow-up	2 (2.0)

CAPOX=Capecitabine-oxaliplatin, FOLFIRINOX=Fluorouracil-leucovorin-irinotecan-oxaliplatin, FOLFIRI=Fluorouracil-leucovorin-irinotecan, FOLFOX=Fluorouracil plus oxaliplatin, CR=Complete response, PR=Partial response, SD=Stable disease, PD=Progressive disease, RR=Response rates, DCR=Disease control rate

median EFS of 13.44 months (95% CI: 7.5–19.4) while patients classified as unresectable had a median EFS of 9.76 months (95% CI: 8.4–11.1), and this difference was statistically significant (P = 0.030). Patients who underwent resection had a median EFS of 22.9 months as compared to a median EFS of 7.8 months in patients who did not undergo resection of the primary (P < 0.001).

Prognostic factors for overall survival

Of the prognostic factors elevated, on univariate analysis, younger age (<50 years) (P = 0.021), and presence of signet ring histology (P = 0.010), predicted for a statistically significant inferior OS, while potential resectability status at baseline predicted for a superior OS (P = 0.016). On multivariate analysis, the presence of signet ring morphology (P = 0.021) and resectability status at baseline (0.027) retained their statistical significance for OS [Table 3].

Discussion

The sequence of SCRT followed by palliative chemotherapy in mRC is suggested by the ESMO treatment guidelines

and offers the paradigm of addressing the primary upfront regarding local control, and palliation, without delaying systemic chemotherapy.[19] If initial systemic treatment entails chemotherapy alone, downstaging to resectability is about 22% as opposed to about 49% with chemotherapy-targeted therapy combinations.[1,5,20-24]

The salient features of the studies we selected for evaluation and comparison with the current study.[14,15,25] The striking clinical features at baseline in patients in the current study are the younger age at diagnosis (median age –48 years), a high number of patients with ECOG PS ≥2 (64.7%), the high incidence of signet ring cancers (13.3%) and presence of obstruction requiring the creation of a stoma (58.1%). Such clinical factors suggest a different disease presentation, increased burden of disease and potentially, biology especially signet ring histology, as compared to published data from Western trials as well as the studies shown for comparison.[26-28]

SCRT in our cohort was tolerated well, with no delays in the initiation of systemic therapy. This is line with the philosophy of addressing the primary tumor early with no undue delay in the initiation of systemic therapy. A majority of patients were treated with CAPOX chemotherapy as the first line, which is in keeping with recommendations for the first line therapy for mCRC.[8,19] A small number

Table 3: Univariate and multivariate analysis of prognostic factors for overall survival

Characteristic	OS (months)	*P* (univariate analysis)	*P* (multivariate analysis)	Hazard ratio (95% CI)
Age (years)				
<50	12.06	0.021	0.134	0.66 (0.377-1.139)
≥50	21.42			
Degree of differentiation (*n*=3)				
PDAC	12.65	0.481	-	
MDAC/WDAC	16.66			
Signet ring histology				
Present	10.22	0.010	0.021	1.46 (1.060-2.015)
Absent	18.73			
Baseline elevated CEA				
Yes	13.7	0.343	-	
No	23.10			
ECOG PS				
0,1	14.16	0.888	-	
≥2	16.40			
Baseline obstruction				
Present	15.70	0.392	-	
Absent	22.77			
Resectability status at baseline				
Potentially resectable	32.62	0.016	0.027	1.95 (1.080-3.511)
Unresectable	13.04			

ECOG PS=Eastern oncology group performance status, PDAC=Poorly differentiated adenocarcinoma, MDAC=Moderately differentiated adenocarcinoma, WDAC=Well differentiated adenocarcinoma, CI=Confidence interval, OS=Overall survival, CEA=Carcinoembryonic antigen

Table 4: Studies evaluating short-course radiotherapy and systemic chemotherapy in metastatic rectal cancers

Characteristic	Van Dijk *et al*.[14]	Tyc-Szczepaniak *et al*.[15]	Yoon *et al*.[25]	Current TMH study
Study type	Phase II, single arm	Phase II, single arm	Retrospective	Retrospective
Number of patients	40	50	50	105
ECOG PS (%)				
0/1	27 (71)	50 (100)	50 (100)	37 (35.3)
≥2	11 (29)	0	0	68 (64.7)
Sequence of treatment	RT >chemotherapy	RT >chemotherapy plus bevacizumab	Chemotherapy +/- targeted therapy>RT	RT >chemotherapy +/- targeted therapy
Systemic therapy regimen	Predominantly CAPOX	CAPOX plus bevacizumab	Predominantly FOLFOX with or without cetuximab/bevacizumab	Predominantly CAPOX with or without cetuximab/ bevacizumab
Use of targeted therapy (%)	0	50 (100)	11 (22)	29 (27.6)
Radiotherapy regimen	5×5 Gy	5×5 Gy	5×5 Gy	5×5 Gy
Resectability status of metastases at baseline	100% unresectable	100% resectable or potentially resectable	70% curable 12% potentially curable 18% palliative	36.2% potentially resectable 63.8% unresectable
Creation of stoma post-SCRT (%)	8 (20)	-	-	0 (*n*=71)
Curative resection of primary (%)	0	36 (72)	41 (82)	24 (22.9)
2 (year) OS (%)	30	80	73.9	33.2

ECOG PS=Eastern oncology group performance status, RT=Radiotherapy, CAPOX=Capecitabine plus oxaliplatin, FOLFOX - 5=Fluorouracil plus oxaliplatin, OS=Overall survival, TMH=Tata memorial hospital, SCRT=Short-course radiotherapy

of patients were also treated with the mFOLFIRINOX regimen, considering the regimen's potentially greater cytoreductive capability.[7,29,30] While the hematological toxicities in our study were manageable, one-quarter of patients required dose-reductions, either upfront or during chemotherapy. Primary reasons were an attempt at the safe administration in patients with borderline (ECOG PS ≥2–64.7%) as well as nonhematological toxicities such as diarrhea (grade 3/4 – 16.2%) and HFS (Grade 2/3 – 10.5%). Besides baseline ECOG PS being a predictor for tolerance issues with chemotherapy, we have previously shown that homozygous DPD mutations may have a slightly higher prevalence in Indian patients – these reasons may account for the incidence of nonhematological toxicities seen.[31-34] Targeted therapy was used in only 27% of patients, predominantly being bevacizumab. Use of targeted therapy is limited, especially in low middle-income countries.[35-37] As compared to the current study, the study by van Dijk *et al*. used targeted therapy in 100% of their patients, while the South Korean study used targeted therapy in a comparable 22% of patients.[14]

The prespecified criteria for resectability clearly predicted for significantly increased use of liver-directed therapy (LDT) (42.1% in potentially resectable group vs. 11.1% in unresectable group) and more importantly, statistically different survival outcomes (32.62 months vs. 13.04 months; $P = 0.016$). While there are no uniform criteria for selecting patients for LDT, our institution criteria is practical and easy to use a combination of pre- and post-therapy points of reference for selection of patients.[6,7,23,24,38] We acknowledge that our institution criteria need further validation prospectively, whereas at the same time pointing out that criteria for liver resection have differed across studies and institutions.

A total of 24 patients (22.9%; $n = 105$) of patients in the entire cohort of the study underwent resection of the primary and treatment of the metastases as well. While prospective studies have shown conversion rates (to metastasectomy) of 33%–61% in patients with liver-limited disease,[7,39,40] a significant proportion of patients in this cohort had greater than one site of disease (40%), lung lesions (35.2%), and <5 liver lesions (55.9%; $n = 59$). Such a cohort is representative of an mRC cohort as against a truly oligometastatic disease cohort. The disease burden of patients in the current study (63.8% unresectable) cohort is closer to the patients in the study by Tyc-Szczepaniak *et al*. (100% unresectable) than the other studies shown for comparison. With the confines of such a flawed cross-study comparison, the resection rates of 22.9% are indicative of the feasibility of such sequencing of therapy. The studies by van Dijk *et al*. (100%) and Yoon *et al*. (70%) clearly had more patients with resectable metastatic disease, and this bears out in the final resectability rates [Table 4].

The median EFS (10.84 months) and OS (15.7 months) of the entire cohort is a reflection of patients being treated predominantly with chemotherapy and having the majorly unresectable metastatic disease.[41-43] Going beyond OS, the combination of upfront SCRT and systemic therapy allowed for good local control rates (primary disease control rates – 68.6%), effective palliation of the primary as well avoidance of palliative surgery postbeginning of treatment.

Higher incidence of signet ring cancers and their inferior outcomes (10.22 months vs. 18.73 months) suggests the need for a different approach to treating these cancers as shown in previous studies as well.[44,45]

The current study has multiple limitations, and caveats exist considering the retrospective nature of the study. The patients in this study are clearly a heterogeneous cohort with multiple sites of disease; metastasectomy of sites beyond the liver is not a uniform option in patients with mCRC. While the criteria for LDT used was uniform, this needs refinement and validation in a larger cohort of patients as only 42.1% of patients with potentially addressable secondary sites finally underwent resection of primary and secondaries. We are also unable to speculate as to the actual number of patients in whom a stoma was avoided, i.e., identification of a cohort of near obstructed patients.

Conclusions

The study suggests that's SCRT followed by systemic therapy in mRCs is a feasible, efficacious paradigm for maximizing palliation and objective responses. The classification of patients based on resectability was predictive of actual resection rates as well as outcomes. Signet ring mRC show inferior outcomes in this cohort of mRC patients.

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Conflicts of interest

There are no conflicts of interest.

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