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PREOPERATIVE RADIOTHERAPY VERSUS POSTOPERATIVE RADIOTHERAPY IN RECTAL CANCER: REAL-WORLD OUTCOMES FROM A TERTIARY CANCER CENTRE

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ABSTRACT

Background:
Rectal adenocarcinoma presents unique treatment related challenges because of its anatomical location and higher chances of local recurrences. Preoperative chemoradiation is standard for mid and lower rectal diseases whereas it is not equally established in upper rectal cancers. This study aims to evaluate the 3-year overall survival and disease-free survival in curatively treated rectal cancer patients, focusing on tumour location and use of preoperative radiotherapy for upper rectal cancers.

Methods:
Total 123 patients who underwent curative treatment for rectal cancer between January 2019 and December 2021 were included in this study. Tumour location was classified based on distance from anal verge into upper (10-15 cm), mid (5-10 cm) and lower (up to 5 cm). Data were collected retrospectively from case sheets and electronic medical records, analysed using SPSS version 29.

Results:
Majority had stage II-III disease. 91% were non metastatic on presentation. Preoperative radiation was given to 95.9%, (61% SCRT NACT and 39% long course chemoradiation). 3-year overall

survival was 75.6% with median not reached, and disease-free survival was 74.6% with median of 67 months. No statistically significant difference in survival was observed based on tumour location, although mid rectal tumours had a lower 3-year OS compared to upper and low rectal group. Preoperative radiotherapy was not associated with significant change in OS or DFS compared with postoperative radiotherapy. Post operative morbidity was comparable between preoperative and post operative radiation groups.

Conclusion:
Tumour location and radiation timing did not impact the survival significantly in this retrospective study. Preoperative radiotherapy achieved excellent local control without any significant increase in morbidity. Certain low risk upper rectal cancers may be omitted preoperative radiation without compromising on the 3-year survival outcomes. Prospective studies are required for validation.

Key words: Carcinoma rectum, radiotherapy, upper rectum.

INTRODUCTION:

Carcinoma rectum comprises approximately one third of the colorectal cancers and is a major malignancy worldwide [1]. Total mesorectal excision (TME), neoadjuvant therapy has significantly improved the patent outcomes [2]. German Rectal Cancer Trial and Swedish Rectal Cancer Trial have demonstrated the role of preoperative chemoradiotherapy or short course radiotherapy in improving local control and tumour downstaging [3,4] TME has reduced local recurrence to less than 10%, and when preoperative radiotherapy is applied, this drops even further [5]. Short course radiation has added logistic benefits over long course protocol [6]. Recently total neoadjuvant therapy (TNT) has come up as a promising strategy with trials like RAPIDO and PRODIGE 23 showing improved disease-free survival and systemic control, particularly in high-risk cases [7,8]. Lower rectal cancers usually go for neoadjuvant therapy due to the proximity to sphincters and higher rates of local recurrences, whereas upper rectal cancers may go for upfront resection as they behave more like sigmoid cancers [9,10]. 2023 ASTRO rectal cancer guideline favours omitting preoperative treatment in select upper rectal disease in favourable stage11]. Recent organ preservation approaches like wait and watch after complete clinical response and employing immunotherapy for MSI high tumours signify the evolving scenario in the management of this disease [12,13]
This study evaluates 3-year overall survival and disease-free survival of curatively treated rectal cancer patients and aims to evaluate the effect of tumour location on the survival; and whether upper rectal cancer survival differ based on whether they received preoperative radiotherapy or not.

MATERIALS AND METHODS:

The Aim of this retrospective study was to find out any difference in survival among upper rectal disease between those who received radiation and those who did not receive radiation, and to find out three-year disease-free survival in rectal adenocarcinoma patients undergoing curative surgery. Patients with a second primary, who received prior pelvic RT, incomplete data in case sheets were excluded.
Overall Survival will be assessed from date of diagnosis to death or last follow-up. Disease-Free Survival will be assessed from date of diagnosis to recurrence or last follow-up. The Upper rectum is found out by colonoscopy measurement (10 cm till 15 cm from anal verge).
Descriptive statistics used where ever appropriate. Survival calculated using Kaplan– Meier analysis. Log-rank test used for survival comparison among patients and Cox proportional hazards model to identify predictors of survival. Study was cleared by Institution Ethical Committee and consent was waivered off due to the retrospective nature.

RESULTS:
Baseline characteristics are given in Table 1.

Table 1: Baseline characteristics (n=123)

Characteristics	Number
Median Age	58
Males	64 (52%)
Females	59 (48%)
Comorbidity	Diabetes 14.6% Hypertension 10.6% Both 8% COPD 4% CAD <1%
Tumour location	Upper 22 (18%) Middle 55 (45%) Lower 39 (32%) Spanning 5%
MRI cMRF clear	53.7%
Preoperative RT	95% Short course: 61.8% Long course: 38.2%
Post operative RT	5%
Acute radiation toxicity	None: 52.8% Grade II: 7.3% Grade III: 17.9% RT Interruptions: None
Type of surgery	LAR: 44.7% APR: 49.6% Other: 5.7%
Pathological margins	Clear: 115 (93.5%) CRM involved 8 (6.5%)
Complete pathological response	14.6%

32.5% patients were down staged to ypStage I following neoadjuvant therapy. Whereas 37.4% were yStage III despite neoadjuvant therapy. Among the 5 patients who underwent upfront surgery, postoperative pathology was stage II in 3 cases and Stage III in 2 cases. All of them received postoperative chemoradiation. Post operative complications are given in Table 2.

Table 2: Post operative complications

Characteristics	Number
Clavien-Dindo Grade 0, 1, 2	72 (58.5%)
Clavien-Dindo Grade 3, 4, 5	51 (41.5%)
Anastomotic leak	8 (6.5%)
Pelvic abscess	5 (4%)
Hemorrhage	3 (2.4%)

There were no intraoperative deaths. Median postoperative hospital stay was 5 days (range 3 - 15 days). Major complication rates were 49 out of 118 patients (41.5%) in preoperative RT group and 2 out of 5 patients (40%) in the postoperative RT group ($p = 0.70$). There were more wound healing issues in the preoperative RT group (15% vs 0%).

Median follow-up among survivors was 38.3 months. At time of analysis, 87 patients (70.73%) were alive and 36 (29.27%) had died. The 3-year OS 75.6% (Figure 1).

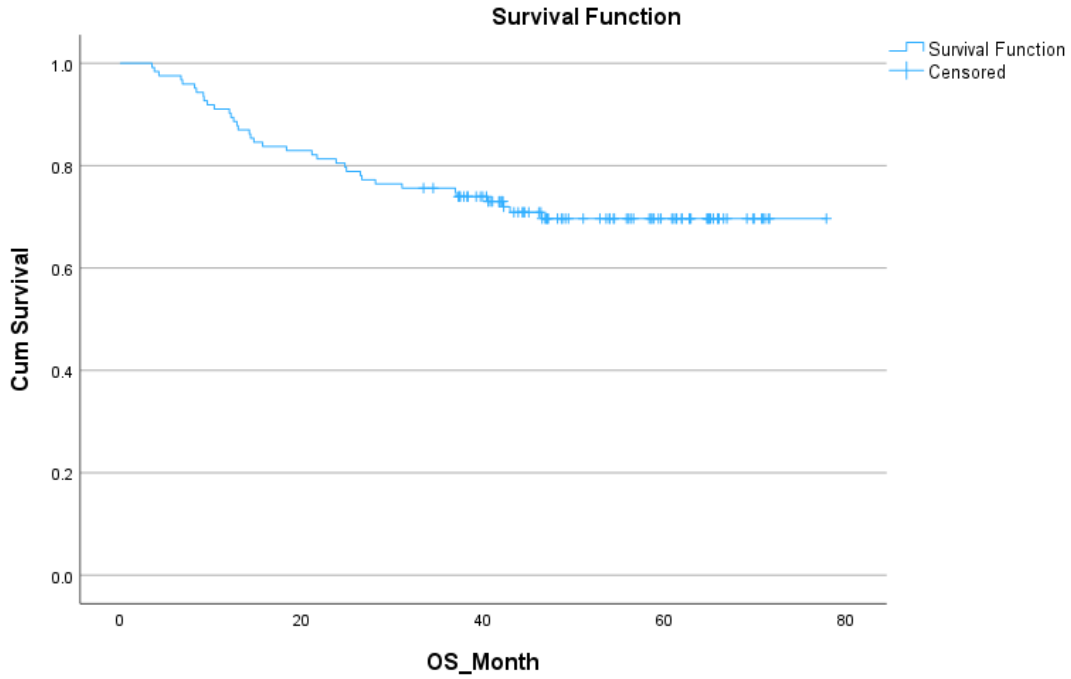

Figure 1: Overall survival analysis curve

The 3-year DFS was 74.6% (Figure 2). Patients had median DFS of 67 months.

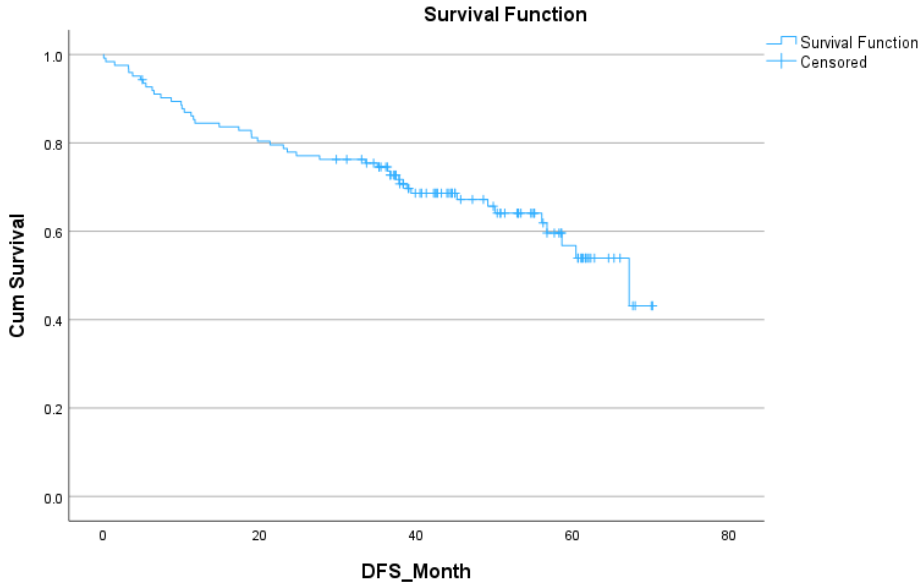

Figure 2: Disease free survival analysis curve

Majority of recurrences were distant metastasis as the first site of failure. 20 patients developed recurrence in distant sites most commonly liver or lung. Isolated locoregional recurrence (pelvic recurrence without distant metastasis) occurred in 4 patients (16.67% n=24). Only 1 patient had combined local and distant relapse. Salvage surgery or radiation was attempted in locoregional recurrence when feasible.

Survival differences by tumor location were not statistically significant (log-rank p=0.148 for OS; p=0.215 for DFS) (Figure 3 and Figure 4). 3-year OS for upper rectal tumors was 69.6%. Among the upper rectal cases who did not receive preoperative RT (5%), none had loco regional recurrence during follow-up, making their outcomes comparable to those who did receive preoperative RT. Mid rectal cases (n=55) had poorer DFS outcomes compared to the rest. The 3-year OS was 69% and DFS around 65.4%. Notably the mid rectal group had the highest node positive cases and threatened CRM. The lower rectal group (n=39) showed the highest survival in this cohort. 3-year OS 89.7%, only 4 relapses occurred in 3 years. Only 7 deaths occurred in the low rectal group in the follow-up period. There was a higher rate of complete pathological response in low rectal cancer patients in this group. In summary, tumor location was not a significant determinant of survival in our cohort.

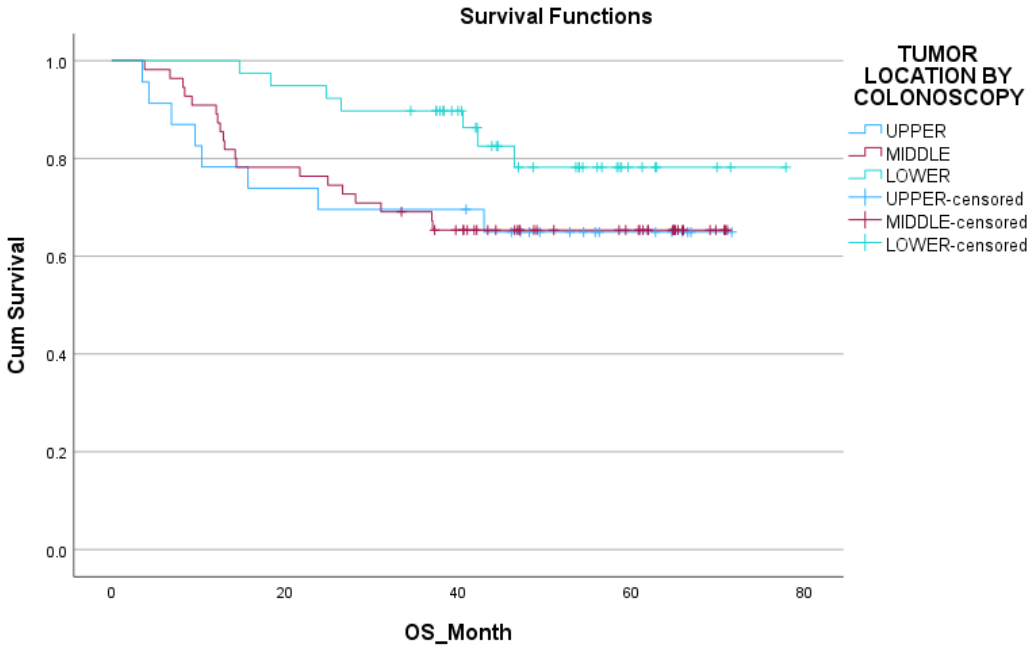

Figure 3: OS comparison among tumor location. (p value 0.148)

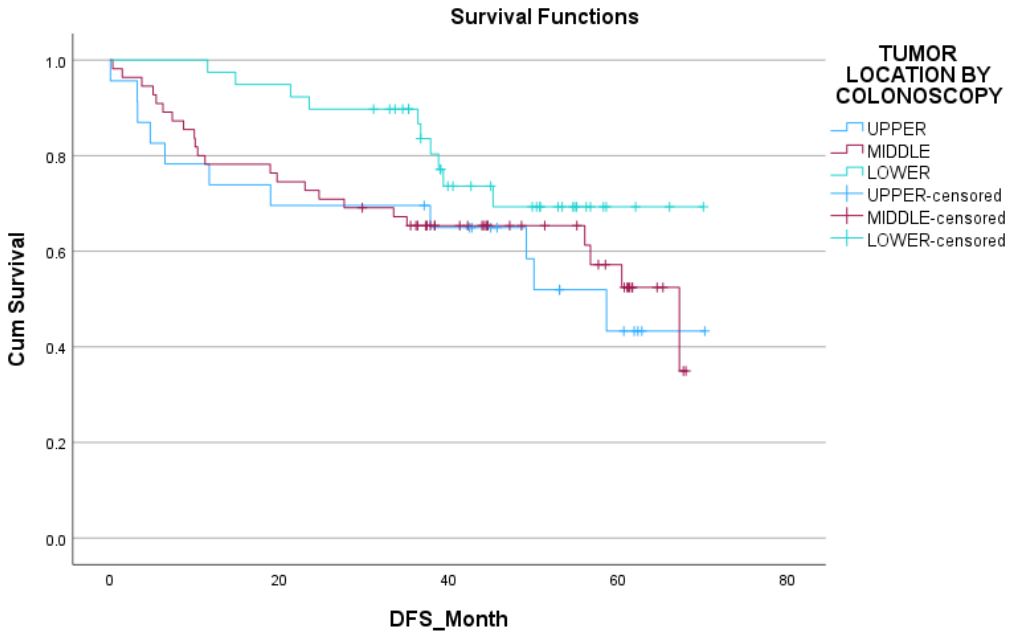

Figure 4: DFS comparison among tumor location (p value 0.215)

5 patients had undergone upfront surgery and adjuvant radiation. Adjuvant RT group disproportionally composed of more upper rectal patients (5 out of 5). 3-year OS among these groups were 76.3% in preoperative RT group versus 60% in postoperative RT group (log rank p=0.089). The 3-year DFS was 75.2% vs 60% (p=0.12). Notably the postoperative RT group showed more early events compared to the preoperative group. Isolated pelvic recurrence happened in the postop RT group.
Comparison of postoperative morbidity between these two groups was also not statistically significant. Anastomotic leaks of LAR cases were identical with or without preoperative RT (7%). Wound complications were more in APR patients after radiation (20% versus 0%).

DISCUSSION:
We observed that neither tumor location nor timing of radiotherapy had any impact on the survival endpoints which was significant. The 3-year OS was around 75.6% and DFS was around 74.6%. This was consistent with the contemporary data for stage 2 and 3 cancers, considering that around 85% of our cases were node positive or T3 or T4 disease at the baseline [14]. Baek et al reported a three-year OS of 96 percent and DFS of 74 percent in a series of robotic TME surgery for stage 1 to 3 rectal cancer [15]. Similar studies with predominantly stage 3 patients have shown 3-year OS of 75 percentage [16]. The local recurrence rate in our study was 4% similar to that of major trials in the TME era [17].
In our study the middle rectal tumors had somewhat poorer survival outcomes, but this appears to be confounded by the stage as most of these cases were having N2 disease or threatened CRM pre-operatively. Surprisingly the lower rectal group in our study had the best overall survival (around 89.7%). This group had the highest number of complete pathological responses denoting a favorable biology. Other authors have reported no significant difference of survival between mid and lower rectal cancer patients when treated with the same protocol [18]. Upper rectal cancer patients in our study had an intermediate overall survival (around 69.6%). Earlier trials have suggested that upper rectal tumors probably derive the least benefit from preoperative radiation in terms of local control [19]. In our study all of the upper rectal patients received radiation either in the preoperative or postoperative setting. Patients who did not receive preoperative radiation did well overall and did not show any worse outcomes with statistical significance. Our study suggests that tumor location should not be seen as an independent prognostic factor in terms of Survival outcomes.
The debate between preoperative and postoperative radiation in rectal cancer management was largely settled in favor of preoperative radiation due to its associated advantages. In our real-world data, among the patients who were eligible for preoperative chemo radiation, we observed excellent local control and no disadvantage compared to the few patients who received postoperative radiation. In the German trial adjuvant radiation was generally less effective and more toxic. (Only 54 percent of patients completed the planned postoperative chemoradiation versus 92 percent completion in the preoperative arm). Also, acute toxicity was significantly higher in the postoperative arm (40% versus 27% of grade 3 to 4 toxicity). In our study there was 100% completion of preoperative radiation as planned, whereas adjuvant radiation had to be modified in one patient due to postoperative complication causing significant delay in the initiation of radiation. Therefore, our institution practice remains in favor of preoperative chemoradiation whenever feasible for stage 2 and 3 rectal cancers. Lack of significant difference in the overall survival in pre versus postoperative radiation groups in our patients were as expected as with randomized trials which did not show any OS benefit and only improvement in local control [20].
No significant increase in anastomotic leak or operative mortality with preoperative radiation. Our leak rate of around 6.5% with chemoradiation is comparable to the leak rates reported with the TME series without radiation (5-10%). De-intensifying the preoperative treatment for upper rectal cancer patients might be done without harming outcomes [21]. Upper rectal cancer patients are sometimes treated similar to other rectal cancers with preoperative chemo radiation. With TME surgery local recurrence rates are low even without preoperative radiation. Our data shows 0% local recurrence in upper rectal tumors where neoadjuvant chemoradiation was omitted (with adjuvant chemo radiation

given as indicated). A 2024 Chinese study has found no OS, local control or distant metastatic benefit from radiation in 363 upper rectal Cancer patients (5-year OS of around 82% in RT and no RT arm p=0.44). However, the UK MRC CR 07 trial did show a small reduction in the 3-year local recurrence of upper rectal tumors with the short course radiation (1.2% vs 6.2%), although there was no OS difference. Thus, the decision to omit preoperative radiation should be individualized. Factors to be considered are tumor location in the upper rectum, clinical T3a or T3b disease, with clear mesorectal facia, cN0 or limited cN1 status on high quality MRI scans and an absence of any extramural vascular invasion or tumor deposits [22]. In such cases one could follow the PROSPECT trial and give neoadjuvant systemic therapy alone and proceed with surgery and reserve radiation only if there is tumor progression or margin related concerns. Although the PROSPECT trial does not specify the upper rectum and has predominantly enrolled mid and upper tumors, they have found non-inferior 3-year DFS of 78% in the chemo alone arm. Thus, unnecessary radiation and its side effects may be avoided in select patients who may not need it. Our institution practice is to avoid preoperative radiation in favorable upper rectal tumors, especially if the disease is above the peritoneal reflection on MRI. However, we do not employ neoadjuvant chemotherapy and proceed with upfront surgery, with appropriate adjuvant therapy based on intraoperative findings and postoperative pathology [23]. The retrospective nature, preoperative versus postoperative radiation was not given in a randomized manner, small sample size for subgroup analysis, single institution nature are all limitations. However, the homogeneity of treatment protocol, surgical techniques and multidisciplinary care at our center is strength and it ensures uniformity in treatment quality.

CONCLUSION:

We found excellent 3 year overall and disease-free survival. Local recurrence rate (4%). 3-year OS was 75.6% percent and DFS was 74.6% percent. Survival was not significantly altered by tumor location. Middle rectal tumors showed a trend towards worse outcomes, probably due to the advanced presentation in this group. Patients who received preoperative radiation had similar survival to those who received postoperative radiation. There were no significant differences in postoperative morbidity rates. Preoperative radiation may be avoided in upper rectal cancer patients when carefully selected, and appropriate adjuvant therapy is given if there is high risk of local failure. Future research and prospective studies will help in better patient selection and confirming the long-term safety of these strategies, leading to improved survival and quality of life while minimizing treatment related morbidity.

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