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Preoperative Versus Postoperative Chemoradiation in Stage III Cancer Rectum: A Single Institution Experience

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Abstract

The optimal management of locally advanced rectal cancer requires a multidisciplinary strategy involving surgical resection with total mesorectal excision and combined use of radiotherapy and chemotherapy. The sequence of treatment can either be preoperative chemoradiation followed by surgery or upfront surgery followed by postoperative chemoradiation. This study compared survival outcomes of these two aforementioned approaches in 76 stage III rectal cancer patients, identified in the hospital database and treated between 2008 and 2014. The median locoregional recurrence free survival in the preoperative group was 34 months whereas it was 33 months in the postoperative group (p=0.583). The median distant metastases free survival was 17 months in the preoperative group versus 38 months in the postoperative group (p=0.039). The mean survival in the whole cohort was 46.97 months with 27 deaths reported at the time of last follow up. The mean survival in the preoperative group was 35.927 months versus 51.519 months in the postoperative radiotherapy group (p=0.129). In our set of patients, the sequence of chemoradiation whether preoperative or postoperative does not lead to differential survival.

Key words

Cancer, Rectum, Preoperative, Postoperative Chemoradiation

Introduction

The management of rectal cancer has evolved tremendously over the past few decades, thanks to the well thought of randomized controlled trials. They have placed the pieces of jigsaw puzzle in place and now we know that preferred approach of treatment in locally advanced operable rectal cancer (clinically staged T3,T4, N1,N2) is preoperative chemoradiation (CRT) followed by surgical resection with total mesorectal excision (TME) and adjuvant chemotherapy (partly depending on postoperative histopathology report) (1). Performing neoadjuvant chemoradiation in patients with T3 or T4 or node positive rectal cancer has become a clinical routine in most institutions (2).

Those patients who undergo upfront surgery for clinically and radiologically staged T1/T2/N0 and per-operatively turn out to be pathological pT3/T4/N1/N2 can be treated with postoperative chemoradiation and adjuvant chemotherapy (3). The decision to advise postoperative radiation therapy is guided by the pathological extent of the disease.

The NCI Consensus Conference concluded in 1990 that chemoradiation was the standard postoperative adjuvant treatment for patients with pT3 and/or N1/N2 disease (4-6). This recommendation was based on phase III trials that compared postoperative chemoradiotherapy arms with control arms of surgery alone or surgery and postoperative radiation without chemotherapy (Mayo Clinic/NCCTG79-47-51) and demonstrated improvement in Disease Free Survival and Overall Survival. The standard design in US trials was to deliver 6 cycles of bolus fluorouracil based chemotherapy, two of which were given with concurrent radiation during cycle 3rd and 4th

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(7). Neoadjuvant and adjuvant chemotherapy and radiotherapy serve as important adjuvants to improve the outcome after surgery, the dose and timing of these adjuncts are variable based on the disease stage and patient related factors. The debate of superiority of one regime over the other is still going on. The updated analysis of the German trial showed that both the approaches are equivalent in terms of survival outcomes (8). Rate of distant metastases in cancer rectum overall usually ranges 11-13%. The expected 5-year survival in stage I is 75-85%, in stage II 67-73% and stage III 51-60%.

In this retrospective analysis of stage III rectal cancer patients, we have collected individual patient data and assessed the outcome and correlated with patient related,tumour related and treatment related variables. This study provides an insight into the long term prognostic implications of the two chemoradiation strategies, exploring if the sequence of chemoradiation leads to differential survival in stage III rectal cancer.

Material and Methods

This retrospective analysis was conducted on clinicopathological records of 76 patients of stage III,histopathologically proven adenocarcinoma rectum retrieved from the database of patients registered from January 1, 2008- December 31, 2014. 48 patients received preoperative chemoradiation and 28 patients underwent upfront surgery followed by adjuvant chemoradiation. Preoperative radiation therapy dose was delivered on a telecobalt machine to a dose of 45Gy/25# by three fields or two AP/PA fields. Concurrent capecitabine was administered orally (625mg/m2 twice a day, 5 days a week).

Postoperative radiation therapy was delivered with similar schedule 45Gy/25#s/5weeks with concurrent oral capecitabine. Statistical analysis was done with SPSS version 16 software. Descriptive statistics calculated included means and standard deviations for continuous data and frequencies and percentages for categorical data. Statistical significance was defined as a *p* value <0.05 with 95% confidence interval. All eligible patients were included in the survival analyses. The influence of selected factors on the patient prognosis was assessed with the Cox proportional hazards model.

Results

A total of 76 patients were evaluable. The patient and tumour characteristics are described in *Table 1.* There were 39 males and 37 females. Age of the patients ranged from 13 to 86 years, mean age being 49.21 years (SD+/-18.97). The preoperative CEA levels ranged from 3-100 ng/ml (mean 26.26+/- SD 23.83).The staging was done as per AJCC Cancer Staging Manual (7th edition). T2 stage was assigned in 11 patients, T3 in 32 patients and T4 in 33 patients. 3 patients hadonly 1 positive lymph node, 30 patients had 2-3 positive lymphnodes, 31 patients had 4-6 metastatic lymph nodes, 12 patients had 7 or more metastatic lymph nodes in the pathology specimen.Number of lymph nodes harvested is 11-27 in upfront surgery versus 10-21 after neoadjuvant chemoradiation.

48 patients received preoperative chemoradiation and 28 patients underwent upfront surgery followed by adjuvant chemoradiation. The median follow up calculated from the date of diagnosis was 20 months (range 5 to 69 months) as shown in *Table 1.*

The locoregional tumor recurrence was found in 30 (39.47%) patientsduring the follow-up. 25 patients had local failure, 3 loco regional failures and two nodal recurrences. Distant metastases were detected in 46 (60%) patients in the follow up period. Distant metastases occurred between 5 and 59 months after surgery (median time 17 months). Metastatic lesions were in liver, lungs, bones, brain and paraaortic lymphnodes.

The median distant metastases free survival was 17 months (SE 5.531;95% CI 6.16-27.84) in the preoperative group versus 38 months (SE 9.122;95%CI 20.121-55.879) in the postoperative group (p=0.039). *(Figure 1)* The median distant metastases free survival for the whole cohort was 26 months (SE 2.913; 95%CI 20.291-31.709). There were 32 distant metastases events in the preoperative group and 14 in the postoperative group. The median locoregional recurrence free survival in the neoadjuvant group was 34 months (SE 3.99,95% CI 26.161-41.839) whereas it was 33 months (SE14.143,95% CI 5.279-60.721) in the postoperative chemoradiation group (p=0.583 log rank). *(Figure 2)* The median locoregional recurrence free survival for the whole group was 33 months (SE 4.104, 95%CI 24.957-41.043).

The mean survival in the whole cohort was 46.97 months (SE 3.547; 95% CI 40.02-53.924) with 27 deaths reported at the time of last follow up. The mean survival in the preoperative group was 35.927 (SE 3.218; 95%CI 29.62-42.234) months versus 51.519 months(SE 5.750; 95% CI 40.25 -62.789) in the postoperative radiotherapy group (p=0.129). *(Figure 3)* There were 19deaths reported in the preoperative group and 8 in the postoperative group.

Table1: The Patient and Tumour Characteristics

Variable	NACTRT (n=48)	ACTRT (n=28)	Total (n=76)
Age median	46(17-86)	49(13-80)	48(13-86)
Gender M:F	25:23	14:14	39:37
CEA	3-100(19)	3-97(19)	3-100(19)
T stage			
T2	7	4	11
T3	21	11	32
T4	20	13	33
N stage			
1(N1a)	2	1	3
2-3(N1b)	19	11	30
4-6(N2a)	20	11	31
>7(N2b)	7	5	12
Stage			
IIIA	3	3	6
IIIB	30	16	46
IIIC	15	9	24
Median Follow up (range)	17(5-54)	23(7-69)	20(5-69)

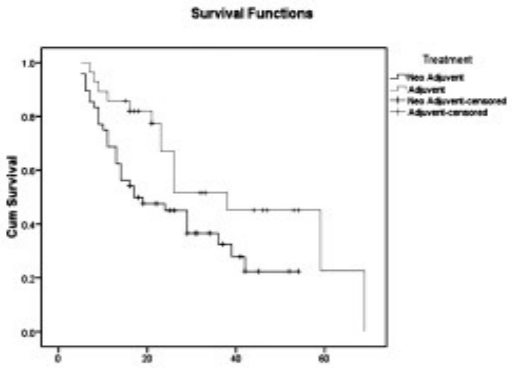

Figure 1 : Kaplan-Meier Curve Distant Metastases Free Survival

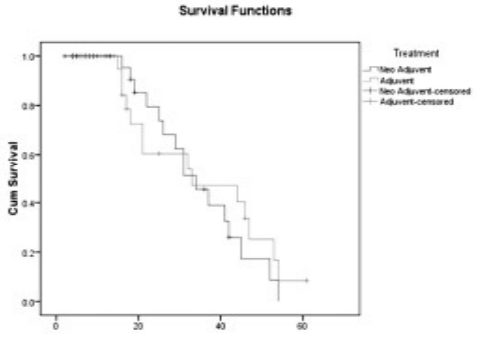

Figure 2: Kaplan-Meier Curve Locoregional Recurrence Free Survival

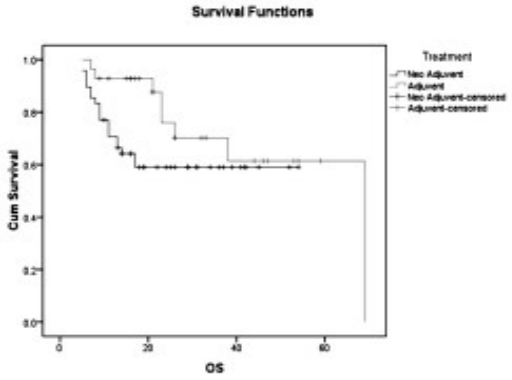

Figure 3: Kaplan-Meier Curve Overall Survival

Discussion

Trimodality therapy remains the hallmark of rectal cancer treatment with optimal surgical resection and neoadjuvant or adjuvant radiation therapy (RT) and chemotherapy playing an important role in maximizing cure and minimizing risk of subsequent local or pelvic recurrence and maintaining quality of life. Therefore, the treatment paradigm for locally advanced rectal cancer has been shifting continuously over the past three decades to incorporate these three treatment modalities in varying sequences.

We evaluated survival outcomes of stage III rectal

cancer patients who underwent preoperative or postoperative chemoradiation. There were no statistically significant differences in the time course patterns of overall survival and locoregional relapse free survival. Our results are similar to those reported by the German CAO/ARO/AIO-94 trial, long term population data of Surveillance, Epidemiology and End Results database and National Cancer Database analysis (8-11). The study by Lim et al. compared long term population based survival outcomes of preoperative and postoperative radiotherapy approaches in rectal cancer. Patients with stage II and III rectal cancer between 1998 and 2013 were identified using the Surveillance, Epidemiology, and End Results (SEER) database. The 10-year OS and DSS rates were higher in patients with preoperative RT than the postoperative group (51.6% vs. 49.8%, p<.001 and 65.45 vs. 64.8%, p=0.037, respectively). (9) In multivariate analyses, selection of combined RT sequence did not affect the survival (HR 1.04 and 95% CI 0.98-1.1 for OS; HR 0.97 and 95% CI 0.90-1.05 for DSS) (11).

Among the three historical phase III trials comparing pre and postoperative RT, the German trial CAO/ARO/AIO-94 was the largest one suggesting clinical benefits of the preoperative approach in local tumor control, downstaging effect, conversion rate of sphincter preservation and severe acute and late toxicity. Long term analysis of the same data found no survival advantage (59.9% vs. 59.6%,p=0.85) (8). NSABP R-03 study showed a trend towards improved survival with preoperative RT (74.5% vs. 65.6%,p=0.065), the results have not been considereddecisive because of poor accrual of patients (12). In another Korean trial, significant differences did not exist in DFS, local control and OS, but preoperative RT facilitated sphincter preservation for low lying tumors (p=0.008) (13). Even in the German trial the beneficial effect in local control was restricted to the intention to treat analysis. Thus the effect of preoperative RT on long term survival still remains debatable.

In our retrospective analysis,we found higher distant metastases free survival in the postoperative chemoradiation group (38months vs. 17 months; p=0.039). There is a possibility that patients with more risk features at initial diagnosis might have higher tendency to undergo preoperative RT but similar observations have been made by Peng et al. who compared T3N0 rectal cancer patients who underwent surgery alone, preoperative RT followed by surgery, and surgery plus postoperative RT. They found that use of postoperative RT was associated with improved 10-year DSS rates compared with surgery alone (76.1% vs. 66.1%,p<0.001) whereas there was no survival benefit of preoperativeRT (p=0.127) (11). A meta-analysis of randomized controlled trials also came to the conclusion that as compared to postoperative chemoradiation, preoperative chemoradiation improves only locoregional control, not distant control and survival with similar chronic toxicity and sphincter preservation rate in rectal cancer patients (13). Moreover, staging discrepancies do exist between clinical and pathologic tumor status in analyzing patients who undergo preoperative chemoradiation.

There are marked geographic variations in usage of adjuvant and neoadjuvant chemoradiation regimes with variable outcomes. There are two general approaches in which RT has been used in the adjuvant treatment of resectable rectal cancer - post-operative treatment and pre-operative treatment. Until 1990, most patients in USA underwent surgery followed by adjuvant RT if needed. The advantage lies in availability of pathological staging and avoidance of overtreatment. Also if APR is done, perineal scar can be covered in RT field. Pre-operative RT was first used in Northern Europe and Scandinavia to a dose of 25Gy/5# in the form of short course RT (SCRT). The second way of delivering prolonged standard course of 45-50.4Gy /25- 28# with concurrent chemotherapy is more widely accepted and popular.

In USA, 55% of locally advanced rectal cancer patients received neoadjuvant chemoradiation in 2010-2012 period whereas the receipt of adjuvant chemoradiotherapy has declined from 16.7% in 2004-2006 to 6.7% in 2010-12 (9). The overall survival for trimodality therapy remains above 70% irrespective of the sequence. Similarly in Sweden, 68.3% of rectal cancer patients receive preoperative radiotherapy or chemoradiation based on the analysis of Swedish National Patient Register (14). In Sweden 80% of patients receive short course RT and only 20% receive long-course chemoradiation.

Over the past 3 decades, there have been improvements in the management of rectal cancer in terms of reduction in locoregional failure from 40% to <15% , sphincter conserving surgery increased from20% to 60%, post-operative death rates decreased from 10% to 2%, 5 year survival in stage II and stage III improved from 47% to 64%.

Our results show 30 (39.47%) locoregional recurrences in the cohort of stage III patients which is similar to the 46% local recurrences reported by Swedish Rectal Cancer Trial in node positive patients (15). One of the reasons

for higher number of local recurrences could be non-availability of MRI in District Hospitals to guide treatment selection and non-adherence to TME in patients operated in District Hospitals.TRUS and high resolution MRI are the two most common techniques for predicting T stage. Moreover MRI can identify patients likely to have close or positive CRM margin if they underwent upfront surgery. Accuracy in predicting T stage is 50-90% and in detecting positive lymphnodes is 50-75% and can be improved with the use of external and endorectal coil. A clear circumferential resection margins (CRM) is highly important because a positive margin increases the risk of local recurrence by 3-4 times. Normal rate of positive CRM in clinical practice ranges between 0-10%. Preoperative chemoradiation does not compensate for CRM positivity. Postoperative radiation has an equally limited ability to control local recurrence after CRM positivity.

Swedish Rectal Cancer Trial is the only one showing survival advantage for the preoperative short course radiotherapy but it was before the advent of TME era. Swedish Rectal Cancer trial randomized clinically T1-3 rectal cancers to pre-operative RT 25Gy/5# followed by surgery after 1 week versus surgery alone. Local recurrence was reduced from 27% to 12% (p=.001). 5-year overall survival (OS) was 58% versus 48% (p=.004). Updated results after 13 years,showed OS 38% vs. 30% (p=.008) (15). The Dutch Colorectal Cancer Group studied SCRT with TME and found it superior to TME alone in terms of local control, while overall survival remains similar. In Dutch CKVO 95-04 trial, 1805 patients with cT1-3 were enrolled for short course RT(SCRT) followed by TME, local recurrence observed were 2% vs. 8% (p<.0001). Five year local failure 11% vs 6%. Disease free survival 40% vs. 51%(p=.01). Death due to other causes increased by 11%. Overall survival remained equivalent (16,17). Positive CRM after preoperative chemoradiation is unfavourable, 44/460 patients with positive CRM had local recurrence 35% versus 11% and survival rate 27% versus 73%.In Dutch CKVO, 17% were CRM positive.Camma et al confirmed survival advantage of short course pre-operative RT in the meta-analysis (18). Colorectal Cancer Collaborative Group meta-analysis showed no survival advantage with short course RT (3,19). It is widely accepted that postoperative radiation also decreases incidence of local recurrence without improving survival. Whereas systemic chemotherapy further reduces local recurrences as well as improves survival by 10-15% approximately compared with surgery alone.However these adjuncts are not a substitute for a proper TME with poor surgery invariably leading to local recurrence. Additional evidence from the MRC of UK CR07 and NCI of Canada-CTG CO16(CR07) trial have highlighted the importance of good quality surgery and how inadequate surgery can only be minimally compensated by chemotherapy and radiotherapy (20,21). The EORTC 22921 trial showed similar reduction in local recurrence whether 5FU/ leucovorin chemotherapy was given with preoperative RT, after preoperative RT plus surgery, or both (22).

In Europe there is an ongoing debate regarding two different approaches to preoperative therapy – SCRT and long course chemoradiation. Polish Colorectal Study Group and TROG Australian trial comparing the two approaches reported no superiority for long course chemoradiation in local control or survival (23,24). The Berlin Rectal Cancer Trial aims to settle the optimal course of neoadjuvant chemoradiation but the results are awaited (25).

Conclusion

Our results are supportive of equivalent overall and locoregional recurrence free survival outcomes of the two combined approaches in stage III rectal cancer. The RT strategy in each case needs to be determined at the discretion of the radiation oncologist and surgeon with informed consent of patient, considering the need of sphincter preservation and compliance of surgery or RT at the institution. This study provides an insight into the long term prognostic implications of these two chemoradiotherapy strategies, suggesting that the sequence of radiotherapy does not lead to differential survival in stage III rectal cancer.A comparative prognostic assessment of these two different chemoradiation strategies is needed in contemporary clinical practices. The retrospective and non-randomized nature of our data and subsequent results of statistical analysis cannot be considered conclusive due to presence of various confounding factors and contamination by related selection bias.It should be our endeavor that all of rectal cancer patients receive appropriate individualized evidence based care using a multidisciplinary team of qualified doctors and offering appropriate MRI based imaging for staging. A structured intervention programme is needed to improve and assure the quality treatment for rectal cancer patients so that we can expect further reduction in local recurrence rates, lower permanent stoma rates and higher cure rates.

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