Radical Treatment of Rectal Cancer in Elderly Is Feasible than Feared: Results from a Tertiary Care Centre

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Abstract The thought of subjecting an elderly patient with rectal cancer to protocol-based neoadjuvant chemoradiation (NACTRT), surgery and adjuvant chemotherapy is sought with fear due to their multiple comorbidities and impaired functional status associated with the process of ageing. Hence, many a times the treatment is compromised and it is a fact that this subgroup of patients is underrepresented in most of the clinical trials. This study was aimed at analysing the perioperative and oncologic outcomes after protocol-based treatment of rectal cancer in the elderly patients, defined here as those with age ≥ 70 years. Prospective analysis of medical records of rectal cancer patients was done who were ≥ 70 years of age and were diagnosed and treated at Regional Cancer Centre (RCC), Thiruvananthapuram from 2008 to 2012. In this 5-year period, a total of 339 rectal cancer patients underwent surgery as part of multimodality treatment with curative intent. Of them, 75 patients were ≥ 70 years of age. Half of them had one or more comorbidities (54%) and majority were locally advanced at presentation (77%). Forty-seven (62%) cases received NACTRT and all of them tolerated RT dose (50.4 Gy) without modification. Anterior resection (AR) was performed in 48 (64%) and abdominoperineal resection (APR) in remaining. Diverting stoma was made in four; of which three remained permanent. Two colostomies were per-

formed for delayed leaks. Three patients (4%) died within 30 days due to leak, sepsis and cardiopulmonary causes. Two thirds (49/75) received adjuvant chemotherapy (ACT) but only 55% of them (27/49) could complete all the cycles without dose modification. The median survival was 28 months. The 3-year disease-free survival (DFS) and overall (OS) were 80.1 and 83.9%, respectively. There were 11 distant recurrences including two locoregional recurrences. The morbidity and mortality of multimodality therapy is reasonable to proceed with radical treatment with curative intent in the elderly patients with rectal cancer.

Keywords Elderly · Rectal cancer · Surgery · Neoadjuvant chemoradiation · Morbidity · Mortality · Survival · Recurrence

Introduction

India accounts for 4.7% of colorectal cancer cases diagnosed worldwide annually. The estimated age standardized incidence rate of colorectal cancer in India is 6.1 per one lac population [1]. The incidence of rectal cancer in Thiruvananthapuram district of India was 4.4 per one lac population in 2012. Forty percent of the newly diagnosed rectal cancer cases were more than 65 years of age [2].

Elderly patients are a heterogeneous group as they have multiple comorbidities and have decreased body reserve compared to younger patients. Poor performance status and reluctance to treat them radically, by surgery and chemoradiation, makes their presence in clinical studies a rarity. Hence, this study was undertaken to assess whether multimodal radical treatment in elderly is feasible without compromising the oncologic safety.

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Patients and Methods

Data Collection Retrospective analysis of prospectively maintained database of all rectal adenocarcinoma patients who were ≥ 70 years of age and were undergoing treatment at RCC with multimodality approach was done from Jan 2008 to Dec 2012. Those patients undergoing part of their treatment outside RCC were excluded from this analysis. Pure sigmoid lesions were also excluded. Data regarding patient profile, tumour characteristics, neoadjuvant chemoradiotherapy (NACTRT), type of surgery, post-operative complications, mortality, survival and recurrence patterns were noted. Telephonic contact was made whenever feasible.

Treatment Protocol Patients with early stage disease underwent primary surgery followed by adjuvant therapy based on their histopathology. Locally advanced rectal cancers (T3/T4 and node positive on imaging) received protocol-based NACTRT followed by surgery (anterior resection (AR) or abdominoperineal resection (APR)). Prior to initiation of treatment, all patients underwent standard evolution in the form of full colonoscopy (except in case of obstructed patients), abdominal and pelvic imaging with CT scan or MRI (at the discretion of treating surgeon) and CEA. The dose of RT was 50.4 Gy in 28 fractions over 5 weeks with concurrent IV/Oral 5FU-based chemotherapy. Surgery was done after 6–8 weeks of NACTRT. Total mesorectal excision (TME) or partial mesorectal excision with autonomic nerve preservation was the standard surgical technique. Adjuvant chemotherapy (FOLFOX/CAPEOX) was started after 4 weeks and continued till 6 months of total treatment duration. Follow-up was done with regular clinical exam, CEA every 3 months for first 2 years and every 6 months for the next 3 years. Additional investigations were done depending on the situation.

Statistical Analysis

The chi-square test or Fisher's exact test was used for comparison of categorical variables between the same groups. Disease-free survival (DFS) and overall survival (OS) were the primary endpoints of this study. DFS was defined as time from the date of diagnosis to the date of progression or recurrence. OS was calculated from the date of diagnosis to the date of either death or last follow up. Survival curves were obtained by using the Kaplan-Meier method and were compared with the log-rank test. All statistical tests were two-sided, and $P \leq 0.05$ was considered to be statistically significant. Analyses were performed with SPSS software, version 11.0.

Results

A total of 339 rectal cancer patients were treated with multimodality approach with curative intent during this period. Seventy-five patients were ≥ 70 years of age. The demographic characteristics of these 75 cases are summarized in Table 1. The median age at diagnosis was 73 years (70–85). Forty-one patients (54%) had one or more medical comorbidity (diabetes, hypertension, coronary artery disease, stroke or asthma). Majority of the cases (77%) were locally advanced at presentation (stage II and III). Twenty-six patients (35%) had disease in the lower rectum.

Treatment-related factors are summarized in Table 2. Forty-seven (63%) patients were planned for NACTRT and all of them tolerated radiation without any dose reduction or modification. The remaining 28 cases underwent primary surgery. All patients underwent curative surgery, either upfront or after NACTRT. Among the 48 patients who underwent AR, only four had a diverting stoma.

One case had suspicious liver lesion at diagnosis. The patient was planned for staged surgery, but died within 2 months after surgery for the primary. Another case had enlarged paraaortic nodes in imaging at diagnosis, completed multimodality treatment and survived for 2 years thereafter.

The pathological factors are summarized in Table 3. As a result of NACTRT, downstaging was seen in 43% of cases. Complete pathological response was present in one patient (1/47). The sterilization effect of NACTRT on regional nodes was seen on 62% of specimens. The concordance between the initial stage of diagnosis and pathological stage was 33% in upfront surgery group where as it was 23% in post NACTRT group respectively. Three patients (4%) were found to have distal margin positive, but none of the patients had a positive circumferential resection margin (CRM). The median

Table 1 Patient characteristics

Variable	Subtype	No. (%)
Age (years)	70–80	67 (89%)
	>80	8 (11%)
Sex	Male	42 (56%)
	Female	33 (44%)
Comorbidity	None	34(45%)
	Single	28 (37%)
	Multiple	13 (17%)
Clinical Stage	I	15 (20%)
	II	10 (13%)
	III	48 (64%)
	IV	2 (2.6%)
Tumour location	Upper	17 (23%)
	Middle	32 (42%)
	Lower	26 (35%)

Table 2 Treatment characteristics

Neoadjuvant chemoradiation (NACTRT)	Not received	28 (37%)
	Received	47 (63%)
Type of surgery	AR	48 (64%)
	APR	27 (36%)
AR with covering stoma	Ileostomy	1
	Colostomy	3 (1 reversed)
Adjuvant therapy	None	26/72 (36%)
	Chemotherapy alone	38/47 (81%)
	CTRT followed by CT	11/25 (44%)

numbers of nodes retrieved were 8.5 for upfront surgery and 3 in post neoadjuvant setting respectively.

After surgery, 72 (96%) patients were due for adjuvant therapy. But only 49 (68%) patients proceeded for adjuvant therapy (including chemo or radiation or both). During adjuvant treatment, 44 (61%) patients required dose modification or stoppage of chemotherapy. Haematological toxicity was the major reason for stoppage of chemotherapy. Severe hand foot syndrome and diarrhoea were the reason for dose modification in elderly patients.

The median follow-up in our study was 25 months (range 1–86 months). The perioperative morbidity and mortality data are summarized in Table 4. The overall morbidity was 20%

Table 3 Pathological characteristics

Variable	Subtype	No. (%)
p T and ypT	p T0	1 (1%)
	p T1	6 (8%)
	p T2	22 (29%)
	p T3	38 (51%)
	p T4	8 (11%)
p N and ypN	p N0	50 (67%)
	p N1	21 (28%)
	p N2	4 (5%)
Pathological AJCC stage ^a (seventh edition)	0	1 (1.3%)
	I	23 (32%)
	II	27 (36%)
	III	24 (32%)
Grade	Well differentiated (WD)	3 (4%)
	Moderately differentiated (MD)	67 (89%)
	Poorly differentiated (PD)	5 (7%)
Nodes retrieved (median)	Upfront surgery (28/75)	8.5 (1 to 1.5)
	Post NACTRT (47/75)	3 (0–7)
Margin	Negative	72 (96%)
	Positive	3 (4%)
CRM	Negative	73 (97.4%)
	Close	2 (2.6%)
ECS	Positive	NIL
	Negative	70 (93%)
	Positive	5 (7%)

^a The patients with liver metastasis and para-aortic node have been staged based on their pathological T and N status

Table 4 Perioperative morbidity and mortality

Surgical site infection (SSI)	8 (11%)
Wound Re exploration	2 (3%)
Secondary suturing	2 (3%)
Stoma for rectovaginal fistula (RVF) and delayed leak	2/44 (4.5%)
30-day mortality	3 (4%)
6-month mortality	6 (8%)

and the 30-day mortality was 4%. The incidence of anastomotic leak was 4.5%. One patient presented with a delayed leak after discharge and another patient presented with rectovaginal fistula (RVF). Both of them were salvaged with diversion stomas. Among the six patients who had a stoma (4 elective and 2 late), only one patient (16%) has undergone a stoma reversal till date. The remaining five patients are still on stoma.

There were two locoregional recurrences in the study group (2.6%). Eleven patients developed distant metastasis (14.67%). The most common site of distant metastasis was liver (5/75); followed by lungs (3/75); bones (2/75) and peritoneum (1/75). Of these 11 cases, only four patients had completed the multimodality treatment. The median survival in the study population was 28 months (1–75 months). The actuarial 3-year DFS and OS were 80.1 and 83.3%, respectively. There was one case of second primary tumour—basal cell carcinoma of nose. Details regarding the multimodality treatment and survival are as given in Table 5.

On multivariate analysis, no correlation was found between patient, treatment or pathologic factors listed in Tables 1, 2 and 3 and the post operative morbidity, survival or recurrence.

Discussion

Different authors have used various age limits to define elderly patients in the context of rectal cancer. Although the median age at diagnosis of rectal cancer is 65 to 70 years, majority of patients above 70 years are excluded from trials due to their antecedent comorbidities. Hence, the results of such clinical trials are actually applicable to the younger and healthier population. Review of literature shows that this is the group of patients in whom data regarding radical treatment of rectal cancer is lacking. In a comprehensive review published by

Table 5 Treatment modality and survival

Treatment	Numbers	Average survival
Surgery alone	17	20 months
Surgery + CT/RT	10	25 months
NACTRT + surgery	14	23 months
NACTRT + surgery + CT	34	35 months

Gilles Manceau et al. [3], the authors searched for all studies from 1985 to 2012 for rectal cancer surgeries in patients ≥ 70 years of age. A total of 48 studies including retrospective, case control and cohort studies were identified. Most of these had 65 years as a cutoff and only three had taken 70 years as defining age [4–6]. In our study, we have taken 70 years as a cut off to define elderly patients as this subgroup represents the real elderly.

Majority of the patients in our study presented in a locally advanced stage (77%). The absence of a national screening program or lack of awareness of the early symptoms may be a reason for this late presentation. Referral bias may also have contributed to the larger number of stage II and III patients in our analysis.

Locally advanced rectal cancer patients were subjected to NACTRT and radiation was given as 50.4 Gy in 28 fractions over 5 weeks, with concomitant oral/IV 5FU. Sixty-three percent (47/75) of patients received NACTRT protocol. A point worth mentioning here is that NACTRT tolerance was well tolerated in our study group as compared to that reported in literature (59 to 70%) [7, 8]. All the patients successfully completed the NACTRT protocol. This could be due to the different patient profile, better performance status and better compliance to oral capecitabine, which was used in majority of the patients. Another reason could be the lower dose of capecitabine used in our patients (750 mg/day).

The overall postoperative morbidity in our series was 20% which is listed in Table 4 and is similar to that reported in literature (12–27%) [4, 6]. The 30-day mortality has been reported in literature to be 3.6% for ≥ 70 years [4], 54% for ≥ 75 years [9] and 13% for ≥ 80 years [10]. Advanced age, poor ASA score and need for emergency surgery being the contributing factors. In our study, the 30-day mortality was 4% and was well within acceptable limits. The lower morbidity and mortality can be attributed to proper patient selection, preoperative optimization and adequate perioperative care in a high volume tertiary centre.

Preoperative radiation is considered to be one risk factor for anastomotic leak and many institutes follow a policy of routine faecal diversion in such cases. Despite the fact that 63% of our patients underwent surgery after NACTRT, the rate of creation of diverting stoma during AR in our series was only 4/48 (8.3%). But 3 out of these 4 elective stomas remained permanent. Previous studies also have shown higher incidence of permanent diverting stomas in elderly patients (19–33%) [11, 12]. This is generally attributed to the reluctance of the patients to undergo another surgical procedure. Probably keeping this fact in mind, the surgeons in our institute had a very high threshold for creation of a stoma even in post irradiated patients. This is well justified by the fact that there were only two cases of delayed leaks in our series (4.5%), which is lesser than what is reported in retrospective studies (7.5%) [5].

In spite of the fact that NACTRT was tolerated by all the patients, adjuvant therapy was not well accepted in our study population. Among 28 patients who underwent upfront surgery, 25 patients had indications for adjuvant therapy. Among these patients, 56% (14/25) did not take adjuvant therapy even though it was indicated. Similarly 19% (9/47) patients did not take adjuvant therapy in the NACTRT group even though it was indicated. Among the patients initiated on adjuvant chemotherapy, only 22 (45%) were able to complete the planned 6 months of therapy. The most common indication for alteration of chemotherapy dose was gastrointestinal toxicity and myelosuppression. The National Cancer Comprehensive Network (NCCN) Colorectal Cancer Database analysis [13] shows that there were 1193 patients of stage 2/3 colorectal cancers, who had received NACTRT. Among them, 24% patients were more than 65 years of age and 17% did not receive any adjuvant treatment. They found that patients more than 50 years of age were less likely to receive the planned chemotherapy.

The oncological outcome of our study seems to be similar to other published data. In the literature available, the locoregional recurrences in elderly patients have been reported to be in the tune of 8–22% [14–17] where as in our study it is only 2.6%. The standardized treatment protocol of NACTRT and TME might have contributed to the low incidence of local recurrence rates. The 3-year DFS and OS were 80 and 83%, respectively. The published data being 66.1% and 76.3% respectively [18].

The strength of this study is that it comes from a very high volume tertiary care centre with 6–12 rectal cancer surgeries every month. The surgical technique has been standardized at our institute with TME as the standard. Our oncological results are in harmony or even better than what has been published earlier. The tolerance of NACTRT protocol and surgery was associated with good locoregional control. However, on the other hand, the poor acceptance of adjuvant chemotherapy puts the patients at a risk of systemic relapse which is clearly reflected in our recurrence pattern. The treating team has to strike a balance between the commitment to complete the treatment regimen like in younger patients and the survival gained versus the treatment related toxicity which will equally affect their quality of life. This is a research topic but definite randomized trial might not come owing to reasons cited above.

Conclusion

Radical treatment of rectal cancer in elderly patients is much feasible than is feared. This study brings about the data from the South Asian region from a tertiary care centre and clearly demonstrates that protocol-based NACTRT is tolerated by elderly patients. Adjuvant chemotherapy is not well tolerated

by this group of patients and should be given only in well-preserved selected patients. The perioperative mortality and morbidity are within acceptable limits and the long-term oncological outcome is as good as any other ethnic group or age group. The findings of our study indicate that the biological age rather than the chronological age should be considered for these patients before planning radical treatment.

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