RESEARCH ARTICLE

Response of various histological types of locally advanced rectal cancer to neoadjuvant multimodality therapy

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Abstract

Objective: To determine the response of various histological types of locally advanced rectal cancer to neoadjuvant multimodality therapy.

Method: The non-randomised, quasi-experimental retrospective cohort study was conducted at the Combined Military Hospital, Rawalpindi, Pakistan, and comprised data of patients treated between January 1, 2020, to September 30, 2021. The data retrieved related to histologically proven and locally advanced rectal cancer patients aged 18-70 years receiving neoadjuvant chemoradiotherapy. Radiotherapy dose was 45 gray to pelvis with a boost to gross tumour of 5.4 gray in 3 fractions by using volumetric arc therapy concurrently with capecitabine 625mg/m^2 daily. A magnetic resonance imaging scan of pelvis with contrast was done at 5-10 weeks before surgery. Histological response to neoadjuvant treatment of various histological types was evaluated using the Rectal Cancer Regression Grade. Data was analysed using SPSS 22.

Results: Of the 182 patients evaluated, 108(59.34%) were included; 64(59.3%) males and 44(40.7%) females. The overall mean age was 45.4±5.2 years. Regression status was grade 1 in 24(22%) patients, grade 2 in 43(40%) and grade 3 in 41(38%) (p=0.074). There were 12(11.11%) patients with signet ring cell and 10(83.3%) showed pathological tumour regression. There were 17(15.74%) patients with mucinous variant, and 12(70.5%) had tumour regression. There were 79(73.15%) patients with adenocarcinoma, and 59(74.6%) of them showed tumour regression. .

Conclusion: There was less tumour regression in mucinous and signet ring cell variants of adenocarcinoma. Modification and intensification of neoadjuvant therapy may be required in such histologies.

Keywords: Chemoradiation, Colorectal cancer, Neoadjuvant, Rectal cancer pathology. (JPMA 74: 1240; 2024)

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Introduction

Colorectal carcinomas (CRCs) are the third most predominant cancers internationally and account for 8% of all cancer-related deaths.[1] Rectal cancer represents 30% of all CRC cases. Pakistan is a country with low CRC incidence. There was a rise in CRCs from 1.2% to 7.9% per year in European population from 2004 to 2016, especially in population aged <40 years.[2] Similar trends have been noted in Asian countries, including Pakistan.[3-5] According to a recent local study, CRC is among the top five malignancies in Pakistan. Change in dietary habits, Westernisation of food and certain genetic mutations can be the causes behind the change in trend.[3,6] Syndromes associated with colorectal cancers are usually associated with poor response to therapy, leading to onset of disease at an early age, higher incidence of local recurrence and distant metastasis, higher grade, proximal location and mucinous variant of histology.[7-9]

Over the last few decades, the treatment of rectal carcinomas is revolutionised with the use of magnetic resonance imaging (MRI) scans that provide more detailed and precise information of T stage, mesorectal fascia invasion, circumferential resection margin (CRM), lymph nodal (LN) involvement and extra-mural vascular invasion (EMVI).[10] There is a paradigm shift in treatment algorithm. Now neoadjuvant chemoradiation and better surgical technique of total mesorectal excision (TME) lead to much better outcomes. Currently, in many countries, neoadjuvant chemoradiotherapy (nCRT) followed by TME or short course radiotherapy is considered the standard treatment for locally advanced rectal cancer. But these treatments still failed to improve survival after more than 10 years of follow-up in Dutch[11] and German[12] TME trials.

The nCRT is used to obtain maximum local control and to decrease local recurrences. It can also lead to tumour size reduction and thus altering surgical approach to lower anterior resection (LAR) with sphincter preservation from planned abdomino-perineal resection (APR), providing stoma-free life. That would lead to improved quality of life (QOL). The response of tumour can vary. This variation in response has an established association with prediction of overall survival (OS) and disease-free survival (DFS).[13]

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To the best of our knowledge, there is no study from Pakistan which may have demonstrated response to nCRT in the local population. The current study was planned to fill the gap by determining the response of various histological types of locally advanced rectal cancer to neoadjuvant multimodality therapy.

Materials and Methods

The non-randomised, quasi-experimental retrospective cohort study was conducted October 1 to December 31, 2022, at the Department of Clinical Oncology of Combined Military Hospital (CMH), Rawalpindi, Pakistan, and comprised data of patients treated between January 1, 2020, to September 30, 2021. After approval from the institutional ethics review committee, data was retrieved using consecutive sampling technique. The data related to patients aged 18-70 years of locally advanced rectal cancer with histopathologically proven diagnosis who were receiving nCRT. Patients outside the specified age range and those receiving radiotherapy (RT) only were excluded.

Pre-treatment assessment included clinical history and physical examination, including digital rectal examination (DRE), colonoscopy and biopsy. Staging tools included pelvic MRI and contrast-enhanced computed tomography (CT) scan of chest and abdomen. Simulation CT scan of the pelvis with full bladder was done for RT treatment planning. Target volumes were delineated and organs at risk (OARs) were contoured by the use of planning system {Eclipse™ treatment planning software from Varian Medical Systems (NYSE: VAR)} Palo Alto, California. The treatment plans were approved after evaluating dose volume histograms (DVHs) and dose distribution. RT dose was 45 gray (Gy) to pelvis concurrently with capecitabine 625mg/m^2 with a boost to gross tumour of 5.4Gy in 3 fractions (total dose of 50.4Gy in 28 fractions) using volumetric arc therapy (VMAT). Patients had a gap of 6-8 weeks between nCRT and surgery because time to surgery can affect the response to RT. After publication of RAPIDO trial, we as a centre shifted to the Rectal Cancer and Preoperative Induction Therapy Followed by Dedicated Operation (RAPIDO) protocol,[14] which did not have long-term survival data at that time. Once long-term survival data of RAPIDO[15] was published, showing inferior treatment strategy for locoregional recurrence, adherence to the protocol was discontinued (Patients till 30 Sep 2021 were included in the study). Even during that period, all options were valid as per guidelines, including RAPIDO, the German rectal cancer trial protocol[12] and the PRODIGE trial protocol.[16]

Before surgery, the patients had preliminary baseline contrast-enhanced MRI of pelvis. The patients underwent LAR or APR depending on the location of the tumour, response to chemotherapy and surgeon's discretion. Some of the patients were also administered 3-4 neoadjuvant chemotherapy cycles consisting of oxaliplatin and capecitabine (CAPEOX). The primary end-point was pathological response post-CRT. A modified pathological staging system was used to evaluate the proportion of viable tumour and the number of involved LNs in postoperative specimen, and ypTNM stage (post-chemotherapy, pathological tumor, node, metastasis stage) was noted. The Rectal Cancer Regression Grade (RCRG)[13] was used to stratify patients to three levels where RCRG I and 2 represented significant regression, and RCRG 3 showed no significant fibrosis with the presence of abundant viable tumour.

Data was analysed using SPSS 22. Data was expressed as frequencies and percentages Or as mean ± standard deviation, as appropriate. Chi square test was used to determine pathological complete response (pCR) rates post-nCRT. P<0.05 was considered significant.

Results

Of the 182 patients evaluated, 108(59.34%) were included; 64(59.3%) males and 44(40.7%) females. The overall mean age was 45.4±5.2 years. Majority of the patients 62(57.4%) showed clinical stage III disease. The duration between the end of nCRT and surgery was 6-7 weeks in 60(55.6%) cases. Histological assessment after nCRT showed RCRG grade 1 in 24(22%) patients, grade 2 in 43(40%) and grade 3 in 41(38%) (p=0.074) (Table).

There were 12(11.11%) patients with signet ring cell, and 10(83.3%) of them showed tumour regression. There were 17(15.74%) patients with mucinous variant, and 12(70.5%) of them had tumour regression. There were 79(73.15%) patients with adenocarcinoma, and 59(74.6%) of them had pathological tumour regression (Figure).

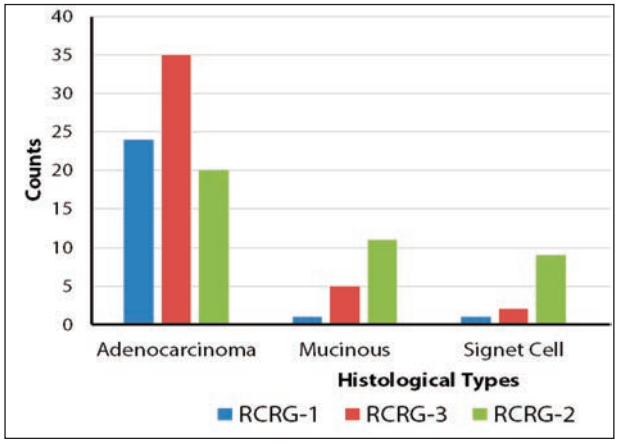

Figure: Pathological response in various histological types of rectal cancer.

Table-1: Patient characteristics.

Characteristics	n (%)
Gender	
Male	64 (59.3)
Female	44 (40.7)
Age (years)	
<40	46 (42.6)
>40	62 (57.4)
Stage at Presentation	
Stage II	46 (42.6)
Stage III	62 (57.4)
Distance from anal verge	
>5 cm	28 (25.9)
5-10 cm	54 (50.0)
>10 cm	26 (24.1)
Surgery	
Abdominoperineal resection (APR)	74 (68.5)
Low anterior resection	34 (31.5)
Histology	
Adenocarcinoma	79 (73.1)
Mucinous adenocarcinoma	17 (15.7)
Signet ring cell adenocarcinoma	12 (11.2)
Grade	
Well Differentiated (G-I)	33 (30.5)
Moderately Differentiated (G-II)	53 (49.1)
Poorly Differentiated (G-III)	22 (20.4)
Interval from Neo-adjuvant CRT to surgery	
5th week	10 (9.2)
6th, 7th weeks	60 (55.6)
8th, 9th weeks	38 (35.2)
RCRG group	
1	24 (22.2)
2	43 (39.8)
3	41 (38.0)

RCRG: Rectal cancer regression grade.

Discussion

Colorectal cancer is considered amongst top five malignancies in Pakistan. It has a male-to-female ratio of 1.8:1.0 worldwide[3,4] which was also the case in the current study where >60% of patients were males. In the present study, 42% patients were aged <40 years, which was in line with literature.[7]

Utilisation of multimodalities for the treatment of locally advanced rectal cancer has opened new horizons in the territory of management of rectal carcinomas. Despite the modifications, the reported 5-year survival in locally advanced rectal cancer (LARC) is 45-75% with failure occurring in 5-15% of these patients.[17] The standardised approach of nCRT causes remarkable tumour shrinkage with 15-27% of participating rectal cancer patients achieving pCR on histopathological examination of postoperative specimens. The pCR gained by nCRT leads to increased OS, which is a great clinical gain and is highlighted in a meta-analysis comprising 3,105 patients. If we can get a better pCR with novel therapies, then we should think of definitive CRT in selected population, sparing a good responding sub-group from surgery. Patients achieving pCR after nCRT had a 5-year survival of 83% versus 66% in those patients who had not achieved pCR.[17]

Response to nCRT can show variable pathological responses in various histologies of rectal cancer and thus affect prognosis and survival outcomes accordingly. Classical adenocarcinomas comprise more than 90% fraction of distal colorectal carcinomas. As per the World Health Organisation (WHO) classification, rare histologies include mucinous, adeno-squamous, medullary, signet ring cell, micro-papillary, serrated, cribriform, comedo type, undifferentiated and spindle cell types.[18,19] In the current study, significant number of rectal tumours showed mucinous and signet ring cell histology. Signet ring cell adenocarcinomas comprise 1-13% of total rectal cancers, and this was coherent with the current study in which 11% patients showed signet ring cell histology.[18-20]

Mucinous histology of distal colorectal carcinomas comprises 10-20% of all rectal carcers.[21,22] Only 16% of the patients in the current study had the mucinous variant of adenocarcinoma. Mucinous signet ring cell variants of rectal carcinomas have been quoted to have meagre response to nCRT and worse surgical outcomes. Similar was the case in the present study where 83% of patients with signet ring cell histology showed very poor response to nCRT. Shin et al. reported that mucinous rectal cancers experience a lower rate of tumour downsizing after nCRT, as highlighted in the current study where 70% of patients with mucinous variants showed RCRG 3 pathological response to nCRT.[23,24] There are opposite and variable data about the clinical behaviour of mucinous histology. One study in Singapore did not support the consideration of mucinous histology as a poor prognostic factor.[25]

Utilisation of nCRT in causing shrinkage of tumour size has opened a new set of arguments about the timing of surgery after neoadjuvant therapy in order to get the most benefits from nCRT. One strategy is to intensify the therapy, and extending time duration between nCRT and surgery to get higher complete response on histopathology and indirectly improving oncological survivals. Time interval after completion of nCRT to response evaluation at 8 weeks for CRM-negative and at 10-12 weeks for CRM-positive patients. Many trials showed that the MRI assessed response of rectal cancers to neoadjuvant therapy was strongly related to OS.[26]

Complete tumour regression after nCRT leads to much better survival outcomes and also reduces local recurrence

rates significantly. Belluco et al reported pCR rates of 12 - 38% in patients who received nCRT, which is contrary to the current findings.[27] It may be because in the study region, rectal cancers have different behaviour than cancers from other parts of the world. Secondly, majority of participants were aged <40 years and had an aggressive pattern of disease, as mentioned in literature.[7] Thirdly, a significant number of specimens showed mucinous and signet ring cell histology which are notorious for poor response to nCRT.[19-22]

To find out the incidence of local recurrence and visceral metastasis, and to measure DFS (disease free survival) of such patients, there is a need to follow these patients for longer time. Most of the patients reported in data were primarily had adenocarcinomas, and there was very limited data regarding pathological response of other histologies.

Neoadjuvant CRT is mainly used to get maximum number of patients with pCR. Various factors are studied that predict pCR after nCRT in locally advanced rectal cancer, such as CRM, size of primary tumour, histopathological subtype and stage at initial presentation. One study used statin, CEA (Carcinoembyonic antigen) levels and closeness to the anal verge to predict pCR.[28] In the current study, results showed less tumour regression, which demands thorough investigation of the causes responsible for this resistant behaviour. The need is to change, enhance, improve and escalate nCRT and a different management strategy should be explored for such patients in randomised controlled trials (RCTs). American Joint Committee on Cancer (AJCC) tumour regression score can be used to document the clinical response to neoadjuvant therapy.[29]

Rectal cancers discovered in younger population have clear-cut association with genetic mutations. Pre-treatment intra-tumour epidermal growth factor and vascular endothelial growth factor mRNA (messenger ribonucleic acid) expression levels, K-RAS (Kirsten rat sarcoma virus) and B-RAF (B-rapidly accelerated fibrosarcoma) mutation status may act as predictive molecular markers of pathologic response to neoadjuvant therapy in locally advanced rectal cancer.[30]

The current study had limitations as the sample had a limited number of rarer histologies. A multi-centric study with larger sample size is recommended. Also, the patients only represented Pakistani population, and external validity of the findings may be limited.

Conclusion

There was less tumour regression in mucinous and signet ring cell variants of adenocarcinoma. Modification and intensification of neoadjuvant therapy may be required in such histologies. Utilisation of intense chemotherapeutics, radiation dose escalation, biological agents and targetted therapies are likely to open new pathways of scientific research.

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Author Contribution:

MSN: Synopsis and IRB approval, concept, data compilation, table making, final approval, responsible for accuracy of work.
UA: Study design, calculations, drafting and corrections, final proof reading, accountable for accuracy of data.
AK: Design, writing, data analysis, tables and figures, final proof reading, responsible for integrity of the work.
IW: Editing, data interpretation, reference writing, revision, final approval, accountable for accuracy of work.
OR: Concept, data analysis, writing, supervision, final approval, responsible for integrity of paper.