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Short term outcome and predictors of response to neoadjuvant treatment in rectal cancer

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ORIGINAL ARTICLE

Short term outcome and predictors of response to neoadjuvant treatment in rectal cancer

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Abstract

Objective: To evaluate response to neoadjuvant chemoradiation in the treatment of rectal cancer and to see if it can be predicted whether a particular patient will benefit from such treatment.

Methods: The retrospective case series was done at the Aga Khan University Hospital, Karachi, and comprised data related to period from January 2005 to December 2014 of patients with rectal cancer who had received neoadjuvant treatment. They were divided into responders and non-responders on the basis of imaging. Pre-treatment factors were compared to identify differences in the two groups. SPSS 19 was used for statistical analysis.

Results: The median age of 35 patients whose records were studied was 44 years (interquartile range: 33-54). Response to neoadjuvant treatment was seen in 13(37%) patients with complete pathological response in 8(22.9%). There was no statistically significant difference in age, gender, pre-treatment tumour stage, tumour biology and distance from anal verge among the responders and the non-responders (p>0.05 each).

Conclusion: Response to neoadjuvant treatment in rectal cancer was low.

Keywords: Neoadjuvant chemoradiation, Rectal cancer, Karachi. (JPMA 65: 1065; 2015)

Introduction

Rectal cancer is the third most common cancer after lung and prostate cancers in males, and breast and lung cancers in females worldwide. In 2009 in the United States more than 40,000 cases of rectal cancer were diagnosed.[1]

Despite histological and behavioural similarities between rectal and colonic cancers, there are some important differences. Mesorectum is fat pad surrounding the rectum, and contains lymphatics and lymph nodes, separating it from surrounding structures even when tumour breeches the muscular layer. It remains surgically resectable when it is within this fat pad. This fat pad is not present in the rest of the colon. The second difference is the retroperitoneal location of lower rectum which gives fixity and, hence, radiation can be used as a treatment modality. The proximity of sphincter complex leads to issues related to sacrifice or preservation of continence. Drainage of lower part of rectum by systemic circulation rather than mesenteric circulation can result in direct metastasis to lungs and other sites of the body.

Preoperative staging can be done by endorectal ultrasound, which has good sensitivity of 87%[2] but it is an invasive test, not readily available and operator-dependent. Also, it cannot judge the metastatic nature of the disease. The staging can also be done with magnetic resonance imaging (MRI) or computed tomography (CT) scan but they have low sensitivity of 77% and 74%.[2] They are non-invasive, non-operator-dependent and provide information related to metastatic deposits of the disease.

Surgery followed by adjuvant chemotherapy is the treatment decided on final histopathology staging. The second option of treatment is neoadjuvant chemoradiation followed by surgery, which is usually offered to Stage-3 tumours.

Five-year survival of Stage-I is about 90% when treated surgically. For Stage II it is 75% when treated surgically. In Stage III with lymph node metastasis, the five-year survival is 50%. For Stage IV it is <5%.[3]

The objective of neoadjuvant treatment is down-staging of disease, with complete pathological response seen in 10-25% of cases,[4-8] sphincter preservation[9] for surgically unresectable tumours, and increased disease-free survival rate of 30% at 5 years.[10,11]

The downside of neoadjuvant therapy is chemotherapy side effects i.e. enteritis and, more seriously, neutropenia, theoretical possibility of progression of disease in non-responders, cost of neoadjuvant therapy which is equivalent to the cost of surgery, especially in a society where patients have to bear the cost, and no overall survival.[10,11]

The question arises; can it be predicted before

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neoadjuvant treatment whether a particular patient will benefit from it or not? As an answer to this question, work-up is being done to identify the predictors of response to neoadjuvant treatment, not only in rectal cancer but in all other cancers as well. Common work-up variables include age at diagnosis, gender, tumour biology, distance from anal verge and immunocytochemical predictors, but to date there are no definitive set of factors identified for prediction of good response.

The current study was planned to evaluate the response of rectal cancer to neoadjuvant treatment in our population and to compare the characteristics of responders with non-responders. The secondary objective was to compare characteristics of patients with complete radiological response to neoadjuvant treatment for resectable rectal cancer with those of the non-responders.

Patients and Methods

The retrospective study was done at the Aga Khan University Hospital (AKUH), Karachi, and comprised records related to the period between January 2005 and December 2014. Records included were of patients over 16 years of age who were diagnosed as surgically resectable rectal cancer at presentation, and who were given neoadjuvant treatment, pre-treatment and post-treatment imaging and surgical treatment. The exclusion criteria was T4 lesions, patients offered upfront surgery, and those with incomplete or missing records. By using International Classification of Diseases (ICD) code 153.9, medical records of colorectal cancer patients were retrieved.

After histopathological confirmation, pre-treatment imaging was done, followed by neoadjuvant treatment for 6 weeks 5 Fluorouracil infusion and concurrent radiation 5 days a week for 6 weeks. Post-treatment imaging was done after which the patient underwent surgery and final histopathological staging was achieved.

Recorded variables included demographics, date of diagnosis, pre-treatment and post-treatment 'tumour, node, metastasis' (TNM) as recorded by a consultant radiologist especially for this study, days from diagnosis to surgery, surgical procedure, histopathological diagnosis and histopathological TNM.

Response to neoadjuvant treatment was divided into three groups on the basis of pre-treatment imaging compared with post-treatment imaging. The first groups was Regression Group in which down-staging was achieved. This group included patients with partial and complete pathological response. Second was the Static Group in which the stage remained the same. There was also the Progression Group in which there was increase in the stage of tumour. The study groups were responders and non-responders. Responders included complete pathological response plus partial pathological response, and non-responders included static disease and progression of disease.

Data analysis was done using SPSS 19. Descriptive analysis of continuous variables was done with median and interquartile range (IQR) for skewed variables. Categorical variables were represented in frequencies and percentages. Comparative analysis of continuous variables was done with Mann Whitney U test or one-way analysis of variance (ANOVA) and that of categorical variables was done with Fisher Exact Test.

Results

Initially, medical records of 214 patients of colorectal cancer were retrieved. From these, 115(53.7%) patients had colonic cancer and 99(46%) had rectal cancer. From these 99 patients, 35(35.4%) matched the inclusion criterion, and comprised the stud sample.

The median age of these 35 patients was 44 years (interquartile range [IQR]: 33-54) and the male-female ratio was24:11. Overall, 33(94.3%) cases were T3 lesions and 20(57.1%) were N1. The median distance from anal verge was 4cm (IQR: 5-3cm). Besides, 12(34.3%) had

Table-1: Baseline characteristics.

Characteristic (n=35)	Frequencies
Age in years (Median)	44 (IQR 54-33)
Gender (male:female)	24:11:00
Tumour	
T2	2 (5.7%)
T3	33 (94.3%)
Nodal status	
N0	15 (42.9%)
N1	20 (57.1%)
Distance from anal verge in cms(Median)	4 (IQR 5-3)
Histopathology	
undifferentiated AdenoCA	10 (28.6%)
mod. differentiated AdenoCA	12 (34.3%)
well differentiated AdenoCA	7 (20%)
mucinous AdenoCA	6 (17.1%)
Surgical procedure	
LAR	11 (31.4%)
APR	24 (68.6%)
Diagnosis to surgery (days) (Median)	99 (IQR 110-93)

IQR: Interquartile range
AdenoCA: Adenocarcinoma
LAR: Low Anterior Resection
APR: AbdominoPerineal Resection.

Table-2: Comparison of factors between Responders and Non-responders.

Factors	Regression (n=13)	Static (n=20)	Progression (n=2)	P value
Age (years)	51.8±13.2	39.6±14.5	41±11.3	0.13*
Gender				0.651
Male	10	13	1	
Female	3	7	1	
Pre Treatment Tumour				0.157
T2	2	0	0	
T3	11	20	2	
Pre Treatment Nodal status				0.675
N0	6	7	2	
N1	7	13	0	
Histopathology				0.25
undiffer. AdenoCA	3	7	0	
mod. Diff. AdenoCA	6	6	0	
well diff. AdenoCA	3	2	2	
mucinous AdenoCA	1	5	0	

*One Way ANOVA
AdenoCA: Adenocarcinoma.

Table-3: Comparison betweenpatients with Complete Pathological Response (CPR) and Noresponse.

Predictive factors	CPR (n=8)	Non-responders(n=22)	P value
Age (years)	50.5±13.6	40.3±13.9	0.34
Gender	6	14	0.61
Male	2	8	
Female			
Pre-treatment Tumour status	1	0	0.08
T2	7	22	
T3			
Pre-treatment Nodal status	3	10	0.76
N0	5	12	
N1			
Distance from anal verge (Median)	4.6±1.79	4.28±1.75	0.656
Histopathology			
undifferentiated AdenoCA	0	9	0.159
mod. differentiated AdenoCA	3	6	
well differentiated AdenoCA	4	2	
mucinous AdenoCA	1	5	
Diagnosis to surgery (days) (Median)	110±32	111±40	0.949

AdenoCA: Adenocarcinoma.

moderately differentiated adenocarcinoma followed by poorly differentiated adenocarcinoma 10(28.6%). Further, 24(68.6%) patients had abdominoperineal resection (APR) done as a surgical procedure. Median days from diagnosis to surgery were 99 days (IQR: 110-93 days) (Table-1).

In terms of outcome, regression of tumour was seen in 13(37.1%) patients; and among them complete pathological response was seen in 8(22.9%). In 20(57.1%) patients the disease remained static, while progression of disease was seen in 2(5.7%). There was no statistical difference between age of patients, tumour status, nodal status, distance from anal verge and histopathological diagnosis in both groups (p>0.05 each) (Table-2).

There was no statistical difference between age, pre-treatment tumour status, nodal status, distance from anal verge and histopathological diagnosis in both groups (Table-3).

Discussion

To summarise, most of patients undergoing neoadjuvant treatment were T3 (94.3%). The regression of disease was seen in 37.1% of patients. Complete pathological response was seen in 22.9% of cases, while 5.2% patients had progression of the disease. There was no factor found significant to predict whether a particular patient will benefit from neoadjuvant treatment for rectal cancer. Some research work has been done on this topic in the last few years. The first such study[12] included 242 patients who presented from 1997 to 2007. The intervention was similar to our study and it saw complete pathological response of 24%. Another study[13] included 562 patients in 15 years and treatment was 5 Fluorouracil (FU) or Capecitabine and radiation. The response was 57% and circumferential involvement of < 60% was predictive for good response. A study[14] included 51 patients from 2005 to 2012. The treatment regimen was slightly different from ours but it showed regression in 55% cases and in 12% there was complete pathological response. It also failed to ascertain any predictive factors for this good

response. In our study we had 35 patients and intervention was 5FU with radiation. The response was 37.1%, which is lower than rest of the studies, but complete pathological response is almost equal or better than the other studies. We were unable to find any statistically significant factor to predict good response of treatment.

Our study is the first local research conducted on this topic, and imaging details were reviewed by a consultant radiologist.

The limitations of our study are its small sample size, retrospective nature, and most of the imaging was CT scanning, which has low accuracy for staging of rectal cancer.

Conclusion

Response to neoadjuvant treatment was lower in our population than other populations. Younger patients had relatively poor response to the treatment than the older one though it was statistically insignificant. There is need to study causes of lower response rate in our population. A prospective study is needed to confirm the findings.

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