RESEARCH ARTICLE

# Outcome of Rectal Cancer in Patients Aged 30 Years or Less in the Pakistani Population

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## Abstract

**Background: The incidence of rectal cancer is increasing in younger age groups. Limited data is available regarding survival outcome in younger patients with conflicting results from western world. The goal of this study was to determine survival in patients with rectal cancer <30 years of age and compare it with their older counterparts in the Pakistani population. Materials and Methods: A retrospective chart review of patients operated for rectal adenocarcinoma between January 2005 and December 2010 was performed. Patients were divided into two groups, Group 1 aged ≤30years and Group 2 aged >30years. Patient characteristics, surgical procedure, histopathological details and number of loco-regional and distant failures were compared. Expected 5 year survival was calculated using Kaplan Meier curves and significance was determined using the Log rank test. Results: There were 38 patients in group 1 and 144 in group 2. A significantly high number of younger patients presented with poorly differentiated histology (44.7% *vs* 9.7%) (p=0.0001) and advanced pathological stage (63.1% *vs* 38.1%) (p=0.04). Predicted overall 5 year survival was 38% versus 57% in groups I and II, respectively (p=0.05). Disease free survival was 37% versus 52% and was significantly different (p=0.007). Conclusions: Early onset rectal cancer is associated with poor pathological features and a worse outcome in Pakistani population.**

**Keywords:** Rectal cancer - survival - young age - older age - Pakistani patients

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## Introduction

Colorectal cancer (CRC) remains the second leading cause of cancer death in 21st century (Heidarnia et al., 2013). A downward trend was observed in the incidence of rectal cancer with an annual change of 2.7 percent in men and 2.1 percent in women between 2004 and 2008 (Eheman et al., 2012). In addition, mortality decreased by 35% from 1990 to 2007. This has been attributed to early diagnosis through screening and improvement in treatment modalities (Siegel et al., 2011). Rectal cancer generally has been a disease of old age with an average age at diagnosis around 65 years (El Mernissi et al., 2009). In recent years, presentation at an early age has become more common. An annual incidence increase of 2.6% in the 20-40 year age group has been observed in comparison with only 0.2 percent increase in colon cancer (O'Connell et al., 2004). This trend has also been observed in Asia (Atrkar-Roushan et al., 2013). It was shown recently by Abdifard and colleagues that colorectal cancer was on a rise in Iran possibly due to elevation of risk factors in this characteristic population (Abdifard et al., 2013). Rectal cancer in younger patients is more aggressive, diagnosed late, presents at an advanced stage and has poor differentiation. Thus the outcome in these patients is expected to be poor when compared with older counterparts (Adloff et al., 1986; Smith and Butler., 1989; O'Connell et al., 2004). Results however are limited and conflicting (Smith and Butler., 1989; Cusack et al., 1996). Surprisingly, there is no consensus on how young age rectal cancer is defined and age cut-offs like 45, 40 and 35 years have been used previously. In Pakistan, a high number of patients are diagnosed with rectal cancer at a young age but their outcomes have not been reported so far.

The objective of the current study was to determine disease free and overall survival in very young patients (age≤30) with rectal cancer and compare it with their older counterparts in our population.

## Materials and Methods

A retrospective chart review of patients who underwent surgical resection for rectal cancer between January 2005 and December 2010 was performed. All patients with biopsy proven rectal adenocarcinoma were included in the study. Patients with squamous cell carcinoma, rectal gastrointestinal stromal tumors and metastatic disease

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were excluded. Patients with evidence of irresectable local disease on basis of clinical and radiological evidence were excluded from study.

Patients underwent extensive preoperative workup including colonoscopy, MRI pelvis for local and regional staging and CT scan chest, abdomen and pelvis for distant staging. All patients were discussed in multi-disciplinary team meeting and a treatment plan was formulated. Locally advanced resectable tumors were offered curative resection after neo-adjuvant induction chemotherapy with concurrent chemoradiotherapy or chemoradiotherapy alone. Pathological staging was performed based on American Joint committee on Cancer (AJCC) TNM classification. Patients were divided into two groups; Group I age≤30 years and Group II age 31 years and above.

Patient characteristics including age, gender, tumor grade, type, pathological variables and number of loco-regional and distant failures were compared. Operative information and details regarding neoadjuvant and adjuvant therapy were obtained from patient records. Chi square and Fischer's exact test were used for categorical variables. Disease free survival was calculated by subtracting date of recurrence from date of surgery. Overall survival was calculated by subtracting date of death or last follows up from date of surgery. Expected 5 year survival was calculated using Kaplan Meier curves and significance was determined using Log rank test.

## Results

*Patient characteristics*

A total of 182 patients with rectal cancer underwent surgical resection. Out of these 38(20.8%) were≤30 years of age while 144 (79.1%) were>30 years. No significant difference in demographics, clinical stage and treatments offered was observed between the two groups as shown in (Table 1).

**Table 1. Demographics and Treatment**

| | | AGE>30 N=144 | Percentage (%) | Age ≤30 (N=38) | Percentage (%) | Total | p value |
|---|---|---|---|---|---|---|---|
| Gender | Male | 96 | 66.6% | 24 | 63.0% | 120 | 0.685 |
| | Female | 48 | 33.4% | 14 | 37.0% | 62 | |
| Family history | Yes | 7 | 4.8% | 1 | 2.7% | 8 | 0.12 |
| | No | 136 | 95.2% | 37 | 97.3% | 171 | |
| Distance from anal verge(cm) | 0-5 | 100 | 69.4% | 25 | 65.7% | 125 | 0.6 |
| | 6 to 10 | 38 | 26.3% | 10 | 26.3% | 48 | |
| | More than 11 | 6 | 4.3% | 3 | 8.0% | 9 | |
| Tumor stage | 2 | 15 | 10.4% | 2 | 5.2% | 17 | 0.4 |
| | 3 | 97 | 67.3% | 25 | 65.7% | 122 | |
| | 4 | 32 | 22.3% | 11 | 29.1% | 43 | |
| Preoperative nodal stage | 0 | 21 | 14.5% | 7 | 18.4% | 28 | 0.18 |
| | 1 | 35 | 24.3% | 4 | 10.6% | 39 | |
| | 2 | 88 | 61.1% | 27 | 71.0% | 115 | |
| Clinical stage | 2 | 23 | 16.0% | 7 | 18.5% | 30 | 0.71 |
| | 3 | 121 | 84.0% | 31 | 81.5% | 152 | |
| Treatment | IC given | 70 | 48.0% | 23 | 60.0% | 93 | 0.19 |
| | IC not given | 74 | 52.0% | 15 | 40.0% | 89 | |
| Procedure | APR | 78 | 54.1% | 16 | 42.1% | 94 | 0.1 |
| | LAR | 45 | 31.2% | 18 | 47.3% | 63 | |
| | ULAR | 11 | 7.6% | 4 | 10.6% | 15 | |
| | Others | 10 | 7.1% | 0 | 0.0% | 10 | |
| Access | Lap | 80 | 55.5% | 25 | 65.7% | 105 | 0.44 |
| | Open | 49 | 34.0% | 11 | 28.9% | 60 | |
| | Lap to open | 15 | 10.5% | 2 | 5.4% | 17 | |

*LAR: Low anterior resection; APR: Abdominoperineal resection; ULAR: Ultra low anterior resection; IC: Induction chemotherapy

**Table 2. Histopathological Variables**

| | | Age >30 (N=144) | Percentage (%) | Age≤30 (N=38) | Percentage (%) | Total | p value |
|---|---|---|---|---|---|---|---|
| Grade | Well | 30 | 20.8% | 5 | 13.0% | 35 | 0.001 |
| | Moderate | 95 | 65.9% | 15 | 39.4% | 110 | |
| | Poor | 14 | 9.7% | 17 | 44.7% | 31 | |
| | Undifferentiated | 5 | 3.6% | 1 | 2.9% | 6 | |
| Mucinous | Yes | 43 | 29.9% | 26 | 68.5% | 69 | 0.001 |
| | No | 101 | 70.1% | 12 | 31.5% | 111 | |
| Pathological nodal stage | 0 | 89 | 61.8% | 14 | 36.8% | 103 | 0.01 |
| | 1 | 25 | 17.3% | 8 | 21.0% | 33 | |
| | 2 | 30 | 20.9% | 16 | 42.2% | 46 | |
| Pathological Tumor Stage | 0 | 39 | 27.0% | 6 | 15.7% | 45 | 0.33 |
| | 1 | 7 | 4.8% | 2 | 5.2% | 9 | |
| | 2 | 24 | 16.6% | 4 | 10.5% | 28 | |
| | 3 | 64 | 44.4% | 24 | 63.1% | 88 | |
| | 4 | 10 | 7.2% | 2 | 5.5% | 12 | |
| Pathological overall Stage | 0 | 36 | 25.0% | 6 | 15.7% | 42 | 0.04 |
| | 1 | 22 | 15.2% | 2 | 5.2% | 24 | |
| | 2 | 31 | 21.5% | 6 | 15.7% | 37 | |
| | 3 | 55 | 38.3% | 24 | 63.4% | 79 | |

**Table 3. Pattern of Recurrence**

| | | AGE >30 (N=144) | Percentage (%) | Age≤ 30 (N=38) | Percentage (%) | Total | p value |
|---|---|---|---|---|---|---|---|
| Overall recurrence | Yes | 51 | 35.5% | 22 | 57.8% | 73 | 0.01 |
| | No | 93 | 64.5% | 16 | 42.2% | 109 | |
| Pattern of recurrence | None | 93 | 64.5% | 16 | 42.1% | 109 | 0.1 |
| | Local | 15 | 10.4% | 6 | 15.7% | 21 | |
| | Regional | 2 | 1.3% | 1 | 2.8% | 3 | |
| | Locoregional | 5 | 3.8% | 4 | 10.5% | 9 | |
| | Distant | 29 | 20.0% | 11 | 28.9% | 40 | |
| Status | Alive | 79 | 54.8% | 15 | 39.5% | 94 | 0.09 |
| | Dead | 65 | 45.2% | 23 | 60.5% | 88 | |

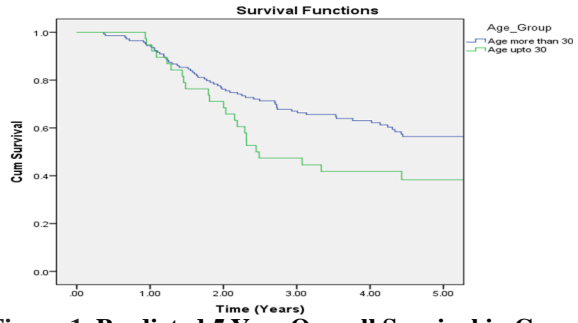


**Figure 1. Predicted 5 Year Overall Survival in Group 1 and 2 (p=0.05), 38% *vs* 57%**

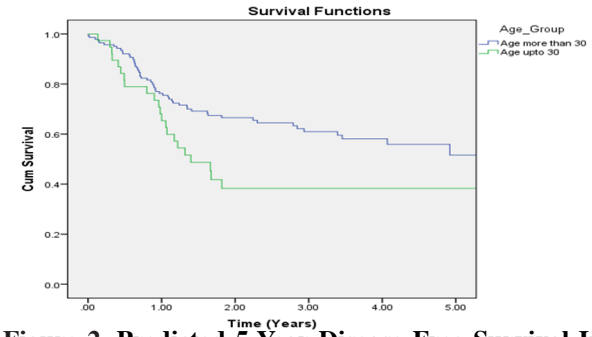


**Figure 2. Predicted 5 Year Disease Free Survival In Group 1 and 2 (p=0.007), 37% *vs* 52%**

*Histopathological variables*

A significant difference between two groups was present with respect to histology and differentiation. Younger patients were more likely to have poorly differentiated 17 (44.7%) and mucinous 26 (68.4%) tumors when compared with older counterparts (p<0.0001). Younger patients were also more likely to have nodal involvement when compared with the older group (p=0.01). Majority of young patients had advanced pathological stage i.e. (63 versus 38%) (p=0.04) as shown in (Table 2).

*Survival*

At 3.6 years of median follow up, 22(57.8%) patients experienced a recurrence in Group I while 51(35.4%) recurrences were observed in Group II (p=0.01) as shown in (Table 3). Median disease free survival was 1.8 (0.01-6.6) years and 1.2 (0.1-5.6) years for Group I and II respectively. Median overall survival was 3.8(.37-8.53) years and 2.46 (0.93-9.07) years for young and old groups. Predicted overall 5 year survival was 38% versus 57% in group I and II respectively. Although it was not statistically significant, a trend towards significance was observed (p=0.05). Disease free survival was 37% versus 52% in Groups I and II respectively and was significantly different (p=0.007) (Figure 1 and 2).

## Discussion

Despite its frequent occurrence, little is reported about outcomes of rectal cancer in young patients from developing countries. The current study highlights significant differences in histopathology and adverse events between young and old age patients. A trend is observed for poor survival in younger patients. Limitations of the current study include its retrospective design and small number of patients in the age group less than 30.

The incidence of rectal cancer in the young is vastly variable and geographically tailored. It is as high as 10-23 percent in Asia and as low as 2.8-5.5 percent in the West (Adloff et al., 1986; Isbister., 1992; Chen et al., 1999; De silva et al., 2000; Alici et al., 2003; Keating et al., 2006).

However, studies have not used 30 years as the age cut-off. In most of the published studies age limit for young onset rectal cancer is 40 years (Domergue et al., 1988; Liang et al., 2003; Amin et al., 2012; You et al., 2012). Kansakar and colleagues attempted to determine changing trends in etiopathology in colorectal cancer patients in Nepal. Rectum was the most common site of primary and 28% patients belonged to 20-39 year age group. This distribution did not change over time (Kansakar and Singh, 2012). A 40 year cut-off is used since rectal cancer is predominantly a disease of old age and screening recommendations are generally developed for patients 40 years and above. We have used an age cut-off of 30 years. A close look at our data shows that 38.4% of our patients are 40 or younger. It has already been shown that around 30 percent patients in Pakistan are under 40 when diagnosed with rectal cancer (Bhurgri et al., 2011). The average life in Pakistan is low when compared to the west and would potentially make significant conclusions on survival difficult with higher age cut-offs.

In the current study, a high number of tumors in younger patients were poorly differentiated and of mucinous histology validating results of previously conducted studies (Smith and Butler., 1989; Chen et al., 1999; Liang et al., 2003). As reported by National Cancer Database, mucinous and signet ring histological subtypes occurred more commonly in patients with young-onset CRC (12.6% versus 10.8%)(You et al., 2012). Tumors were poorly differentiated in 27.3% of patients 20 to 40 years old versus 17.2% in patients in 60-80 years age group (p<0.001). In the current study, younger patients were more likely to present in stage III. This is also consistent

with previously conducted studies (O'Connell et al., 2004; Endreseth et al., 2006).

Variable outcomes have been reported for rectal cancers presenting at young age. Predicted survival of 38% at five years in the current study in younger patients is slightly low and can be due to high percentage of poorly differentiated, mucinous adenocarcinomas with advanced pathological stage. Studies with similar histopathological distribution in young age cancers have reported survival as low as 30% (Domergue et al., 1988, Smith and Butler., 1989). Recently, Haroon and colleagues reported on 23 patients with rectal cancer aged less than 40 years from Pakistan. Overall survival was not calculated and there was no comparison group (Haroon et al., 2013).

To our knowledge, this is the first study from Pakistan reporting 5 year disease free and overall survival in patients less than 30 years of age and comparing it with their older counterparts. Young age rectal cancer is a significant problem in our population and merits attention. This can be partially attributed to low average expected life in certain parts of Asia. Only 7.5% population in sub-continent was reported to be 60 years or above in comparison with 21% population in UK (Census of India., 2001; Census of England and Wales., 2001) We need to develop screening protocols designed to meet challenges of our characteristic patient population. There is a dire need to increase awareness in the community regarding significance of trivial signs and early presentation when disease is not advanced. This study highlights the characteristic age distribution and prognostic variables in young patients.

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