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Original research article

Predictors Of Survival After Curative Resection of Colorectal Carcinoma

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Abstract

Aim: The aim of the present study was to evaluate the predicting factors affecting the survival after curative resections in carcinoma of Colon and Rectum.

Methods: The Gujarat cancer Research Institute is well suited for studying the natural history of carcinoma of the colon and rectum because comprehensive cancer unit records are available and accessible. This includes the diagnoses made among outpatients or emergency room visits, as well as diagnoses recorded among hospital inpatients. Using this system, we studied prospectively all 133 patients with carcinoma of the colon or rectum newly diagnosed between August 1, 2014 and July31, 2015; the cases were confirmed either histologically or radiologically followed by histology e.g., in obstruction.

Results: Out of 133, 60% (n=80) of the patients were in the age group of <60 years, 31.5% (n=42) in 60-70 years age group and 8.5% (n=11) in 70+ years age group. The youngest and oldest patient was 16 years and 84 years old respectively. Emergency symptoms like intestinal obstruction and fistula were presenting symptoms in 18.80% (n=26) and 0.70% (n=1). After radiological investigations, mass lesions were noted in various parts of colon (cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon and sigmoid colon) in 50% (n=67) of the patients. In 6% (n=8) patients' lesions were noted in rectosigmoid while in 44% (n=58) it was in rectum.

Conclusion: There are multiple factors that can predict the survival – cure, recurrence free survival and overall survival at 2 years after curative resection in colorectal carcinoma. **Keywords:** Rectal, Colon, Carcinoma, Recurrence, Prognosis

Introduction

With an incidence of over 1.8 million new cases and almost 861,000 deaths in 2018 according to the World Health Organization, colorectal cancer (CRC) is the third most common cancer in the world.[1] Currently, the American Joint Committee on Cancer (AJCC) TNM classification is the most important determinant for treatment decisions and outcome. The standard treatment for stage I–III colon cancer is surgical resection of the primary tumor for patients, which is associated with a 5-year survival rate ranging from 92% in stage 1 to 53% in stage III.[2] Still, clinical outcomes of

individual patients with resectable tumors vary. Besides tumor characteristics, patient factors such as obesity, diabetes mellitus, smoking, and nutritional status have been associated with survival, yet much of the disparity in prognosis remains unexplained.[3 5]

Recurrence of CRC is chiefly a time-limited phenomenon, as 60–80% of recurrences becoming apparent within the first 2 years after resection and 95% within the first 4 years after resection.[6] The chances of recurrence remote after a 5-year recurrence-free period. Although recurrence is still possible after 5 years, the medical community considers many cancers "cured" when recurrence has not occurred within 5 years after diagnosis.[7]

Several patient-, tumor-, and treatment related prognostic factors are associated with the risk of recurrence of rectal adenocarcinoma. Some of these factors such as TNM stage[8], lymphatic and perineural invasion [8,9], and vascular emboli [10,11] have been found to affect recurrence-free survival in most studies. While the impact of other factors such as distal resection margin[12], tumor size [13,14], extracapsular spread [15], and neoadjuvant chemoradiotherapy [16,17] on recurrence remains controversial.

The principal aim of postoperative surveillance in patients with CRC is to improve survival. The recurrence of CRC is for the most part a time-limited phenomenon, with 60%–80% of recurrences becoming apparent within the first 2 years after resection and 90% within the first 4 years.[18] Survival in cases of early recurrence has remained persistently poor.[19] Both recurrent and metastatic disease, if detected early, might be amenable to a potentially curative surgical resection and this will improve the patient's chances of survival.[20,21]

This provides rationale for the follow-up strategy in patients at high risk of early recurrence, allowing the rational use of adjuvant therapy and the implementation of intensive follow-up regimes for those at increased risk. However, there are still no uniformly accepted follow-up programs after curative resection for CRC and very few studies have sought to identify factors that predict the time of recurrence or the pattern of recurrence.

The aim of the present study was to evaluate the predicting factors affecting the survival after curative resections in carcinoma of Colon and Rectum.

Methods

The Gujarat cancer Research Institute is well suited for studying the natural history of carcinoma of the colon and rectum because comprehensive cancer unit records are available and accessible. This includes the diagnoses made among outpatients or emergency room visits, as well as diagnoses recorded among hospital inpatients. Using this system, we studied prospectively all 133 patients with carcinoma of the colon or rectum newly diagnosed between August 1, 2014 and July31, 2015; the cases were confirmed either histologically or radiologically followed by histology e.g. in obstruction.

Inclusions Criteria:

- Patients should have biopsy proven colorectal carcinoma
- Disease should be operable – Early or Locally advance carcinoma.

- Patients must be willing for surgical treatments and thereafter follow up.
- ECOG Performance status must be upto 2.

Exclusion Criterias:

- Patients with inoperable colorectal carcinoma with noncurative or palliative resection.
- Previously treated patients with recurrence or distant metastasis.
- Patients not willing for surgery or regular follow up.

A series of clinical and pathological variables was then determined for each case. Clinical variables consisted of patient age, sex, history, presentations, site, duration of symptoms, presence or absence of abnormal liver function tests preoperatively and radiologically proven large or small bowel intestinal obstruction. Details of the operation (method of anastomosis, clinically apparent anastomotic leak), with all excised specimen reviewed histologically by pathologist with respect to the macroscopic& microscopic appearance of the tumour, the degree of tumour differentiation, the number of positive nodes lymphovascular invasion& TNM Staging. We also noted the presence of obstruction (clinically, radiologically, or at surgery) or perforation (free gas into the peritoneal cavity as noted at surgery). Postoperatively, patients analysed for adjuvant treatments. Outcome data included date of first recurrence, date of second primary colon cancer, survival status, together with date and cause of death. Factors affecting the final outcomes were analysed in details at minimum follow up of 24 months. The variables included in the survival analyses were sex, age, (<60, 60-69, 70+ years), site (colon, rectosigmoid, rectum), tumour markers, obstruction (yes, no), perforation (yes, no) stage (TNM), grade (1, 2, 3, and 4), and completeness of adjuvants therapies. For those with curative surgery, overall survival, survival free-ofrecurrence and mortality were calculated using life-table (Kaplan-Meier) methods. The significance (using P <0.05) of each variable upon survival was assessed univariately.

Results

Table 1: Age and Gender distribution

Age	**N %**
<60 years	80 (60)
60-69 years	42 (30)
70+ years	11 (10)
Gender	N %
Male	88 (66)
Female	45 (34)

A total of 133 patients were diagnosed and underwent curative surgical resection of colon and rectum in this study. Out of 133, 60% (n=80) of the patients were in the age group of <60 years, 31.5% (n=42) in 60-70 years age group and 8.5% (n=11) in 70+ years age group. The youngest and oldest patient was 16 years and 84 years old respectively. Majority, 66% (n=88) of the patients in this study were male while 34% (n=45) of the patients were females.

Table 2: Predisposing Factors, Presentations, Site distribution, Operative technique, Pathological gradings, Pathological stage, Pathological lymph node status

Predisposing Factors	**N %**
F/H + , P/H +	14 (10.5%)
SPORADIC	119 (89.5%)
Presentations	
Routine	107 (80.5%)
Obstruction	25 (18.80%)
Fistula	1 (0.70)
Site distribution	
Colon	67 (50%)
Rectosigmoid	8 (6%)
Rectum	58 (44%)
Operative technique	
Open	23 (17%)
Laparoscopy	110 (83%)
Pathological gradings	
G1	29 (22.5%)
G2	70 (56.5%)
G3	26 (21%)
Others	14 (12%)
Pathological stage	
Stage 1	22 (22.5%)
Stage 2	43 (34.7%)
Stage 3	63 (48.8%)
Pathological lymph node status	
N0	68 (52)
N1	51 (38.7%)
N2	10 (9.3%)

89.5% (n=119) of the patients were having no personal or familial history of colorectal carcinoma and presented sporadically while 10.5% (n=14) patients had positive family or personal history. Majority of the patients 80.5% (n=107) were presented in OPD with the non-emergency symptoms

indicative of colorectal carcinoma. Emergency symptoms like intestinal obstruction and fistula were presenting symptoms in 18.80% (n=26) and 0.70% (n=1). After radiological investigations, mass lesions were noted in various parts of colon (cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon and sigmoid colon) in 50% (n=67) of the patients. In 6% (n=8) patients' lesions were noted in rectosigmoid while in 44% (n=58) it was in rectum. After work up, all patients underwent curative resection. 83% (n=110) of the patients operated by conventional open methods while 17% (n=23) patients operated by laparoscopy or laparoscopic assisted methods. After histopathological examination, Grade 1 (well differentiated) adenocarcinoma noted in 22.5% (n=29). Majority, 56.5% (n=70) patients had Grade 2 (moderately differentiated) while 21% (n=26) had Grade 3 (poorly differentiated) adenocarcinoma. 12% (n=14) patients had other varieties like Signet ring or Mucinous types of adenocarcinoma. In the histopathology, 22.5% (n=22) patients were noted to have Stage I (early) disease, 34.7% (n=43) patients had Stage II (early) disease while in 48.8% (n=63) Stage III (locally advance) disease were seen. Pathologically tumour free lymph node (N0) was seen in 52% (n=68) while N1 (upto 3 positive lymph node) noted in 38.7% (n=51) patients and N2 (4 or more positive Lymph node) noted in 9.3% (n=10).

Table 3: Margin of resection & Histology

Margin of resection	**N%**
Adenocarcinoma	93.2%
Squamous cell carcinoma	3.7%
Others	
Histology	
R0	126 (99.3%)
R1	1 (0.7%)
Adjuvant treatment status	
Taken	95 (82%)
Not Taken	21 (18%)
Follow Up Status	
Normal	109 (90%)
High	5 (4%)
Very High	7 (6%)

Histologically, adenocarcinoma noted in 93.2% patients while squamous cell carcinoma and others in 3.7%. Almost all, 99.3% (n=126) underwent R0 (microscopic negative margin) resection but in 0.7% (n=1) patient, R1 (microscopic positive margin) resection noted. After proper histopathological analysis, 116 patients advised to take adjuvant treatment. Out of 116 patients only 82% (n=95) completed the adjuvants while 18% (n=21) didn't take adjuvants even after it

was indicated and advised. In the Follow up analysis, CEA level noted to be NORMAL (upto 3ng/ml) in 90% (n=109) patients. CEA level noted to be HIGH (3- 20ng/ml) in 4% (n=05) patients and VERY HIGH in 6% (n=7) patients.

Table 4: Survival statistics after 2 years

Survival statistics after 2 years	N%
Disease free survival (rfs)	83.2% (n=104)
Overall survival (os)	98.4% (n=123)
Mean duration of recurrence / mets	11.9 months
Mean duration of death	12.3 months

Survival statistics of this study at the minimum follow up of 2 years were as – 6% (n=8) patients were lost to follow up. Among those who came for regular follow up Disease-free survival (clinical and biochemical no evidence of disease) were noted in 83.2% (n=104) patients while local or distant recurrence (metastatic) or second primary were seen in 16.8% (n=21) patients. Death was noted in only in 1.6% (n=02) cases. So, at the end of 2 year of our study, recurrence free survival was 83.2% and overall survival were 98.4% (n=123). Mean duration of recurrence or metastasis were 11.9 months while mean duration of death were 12.3 months.

Discussion

Colorectal cancer is one of the most frequently diagnosed cancers and a major cause of cancer deaths worldwide.[22] Recurrence after curative surgery is one of the major factors affecting the long-term survival and its frequency is estimated to be 22.5% at 5 years, of which 12% have a local recurrence. The overall survival in case of recurrence is about 11% at 5 years.[23]

Mehrkhani et al.[24] studied 1090 patients and described patients younger than 65 years had a longer survival than those over the age of 65. In our study, patients over 70 years had disease free survival significantly lesser than <60- or 60–70-year age group, which is supported by these and many others studies.

According to our analysis, female sex had significantly lower recurrence free survival than male counterpart though, female sex has generally been considered a favorable prognostic factor, but data is limited and inconclusive. Cheung et al.[25] performed a prospectively planned, pooled analysis of 33,345 patients participating in the ACCENT database of randomized trials. The authors found a significant but very modest survival advantage for women with early-stage disease that persisted across all ages, stages, and types of adjuvant therapy.

In our study, there is significantly lower recurrence free survival among positive family or personal history patients and this is due to the fact that survival analysis is done only after curative resection. This negative impact of survival is supported by Utah Population Database[26], though even in this study survival is counted after screening and surgery. Data obtained from 1,021 patients with CRC, who were entered into randomized clinical trials of the National Surgical Adjuvant Breast and

Bowel Project (NSABP) showed that the presence of bowel obstruction strongly influenced the outcome.

Though, favorable postoperative results in terms of less pain, less consumption of analgesia, early return of bowel function, and shorter hospital stay in patients who underwent laparoscopic colorectal surgery have been persistently reported in series with malignant colorectal diseases.[2730] Our study also concluded that site of the lesion (colon or rectum) and nature of surgery (open vs laproscopic) doesn't predict the recurrence free survival after curative resection.

Greene et al.[31] demonstrated that WHO pathological gradings has important prognostic significance. "Signet ring" morphology carries an adverse prognosis. The prognostic significance of the finding of mucinous (>50% mucinous) carcinoma remains controversial. In our study, gradings and pathology like signet ring and mucinous varieties didn't appear to predict the recurrence free survival, though the finding is statistically not significant (p=0.2).

Staging is the most critical factor to define survival. According to the National Cancer Institute Study that looked at 120,000 people diagnosed with colorectal cancer between 1991 and 2000, survival for Stage I colon or rectal cancer is about 93 percent. Survival for Stage II is between 72 and 85 percent and for Stage III, 44 and 83 percent. In our study, the recurrence free survival in Stage I, II and III was 90%, 86% and 77% respectively which is almost consistent with this study.

The R0 (microscopic negative margin of resection), R1 (microscopically positive), and R2 (macroscopically positive) carry strong prognostic implications. In three studies, the local recurrence rate after resection of a rectal cancer was 29%, 78%, and 85% for cases with margins positive for disease compared with 3%, 8%, and 10%, respectively, for cases with margins negative for disease.[32-34] In our study contrary to available literature recurrence free survival is 83.3% in R0 patients while 100% in R1 patient. This is because in this study there was only one patient with R1 resection that too survived disease free at 2 years follow up.

Moertel and colleagues (104) reported a sensitivity of 34%, specificity of 84%, and median lead time of 4.5 months from detection of clinical recurrence. Interestingly, the sensitivity of CEA depends on the site of recurrence, with sensitivities exceeding 70% for liver and retroperitoneal metastases and lower than 50% for lung, peritoneal, and locoregional recurrences. Solitary lung recurrence was detectable by CEA in only 15% of instances. In our study, postoperative CEA level was 91%, 20% and 0% in normal (<3ng/ml), high (3-20) and very high (>20) respectively. CEA is very strong determinant of survival.

The knowledge of the prognostic factors for recurrence of rectal adenocarcinoma after curative surgery could calculate a predictive risk score. This score will define a profile of patients at very high risk of recurrence who need a surveillance protocol that differs from the recommended guidelines.

Conclusion

There are multiple factors that can predict the survival – cure, recurrence free survival and overall survival at 2 years after curative resection in colorectal carcinoma. The recurrence interval of CRC is a prognostic factor, and that a shorter interval between resection and recurrence of the primary

tumor was associated with a poorer prognosis. Longer follow up is also needed to validate our study more strongly.

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