The Prognosis of Early Recurrence in Patients with Colorectalcancer and Risk Factors for Early Recurrence

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Abstract

Background: Because predicting recurrence intervals and patterns would allow for appropriate therapeutic strategies, we evaluated the clinical and pathological characteristics of early recurrence of colorectal cancer and the survival in the recurrence patients. Methods: Patients who developed recurrence after undergoing curative resection for colorectal cancer stage I-III between July 2017 to june 2020 were identified. Analyses were performed to compare the clinicopathological characteristics in the recurrence patients followed by detecting the overall prognosis. Subjects and Methods: Four patients had cancer recurrence of consecutive 48 patients who underwent surgical resection for colorectal cancer from 2017 to 2018. Patients who underwent curative resection were enrolled in this study. The mean follow-up period of the patients was 26+-7 months. Among 4 patients with early relapse, All four were advanced T-stage, 03 (75%) had elevated postoperative CEA and 03 (50%) had venous invasion. T-Stage, postoperative CEA levels and venous Invasion were statistically significant. Among four recurrence patients, three (75%) recurrences were within 9 months. Among these patients, metastasis alone within the liver was one patient (25%), metastasis to peritoneum and liver was one patient (25%), and local recurrence in two patients (50%) respectively. The initial diagnosis of patients with early recurrence was done by CEA tumor marker as it rose (75%) and clinical parameters. Definite diagnosis was done by CT, and by alternative methods like PET-CT. two patients underwent surgery for recurrent lesions, two patients received chemotherapy only. In the follow up period two patients with distant metastasis died and one patient with Low anterior resection who had recurrence was followed by chemoradiation and APR. Result: In this study, only four (04) patients (8.3%), including two (02) with colon cancer (6.6%) and two (02) with rectal cancer (11.1%) had post operative recurrence within the time period. Among four patients with post operative recurrence, All patients were advanced T - Stage, three(75%) had elevated post operative CEA levels and three (50%) had venous invasion. We found no differences in the factors like sex, age, primary tumor site, operative method, tumor size, type of histopathology, the degree of lymphatic or neural invasion, preoperative CEA levels in the patients with recurrence. Conclusion: patients with high postoperative CEA levels, advanced T-Stage and venous Invasion after surgery should be examined by the abdominal CT scan or as early as possible after surgery as the prognosis of these patients is not good.

Keywords: Acute cholecystitis, GB calculi, Jaundice, wound infection

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Introduction Colorectal cancer (CRC) is one worldwide. It is the third most the second most common cance incidence rates are found in A Western Europe, while the low countries. ^[2] In India, the annu cancer and rectal cancer in men respectively. The number of col accounts for 8% of all cancer d	of the most common cancers common cancer in men and eer in women. ^[1] The highest ustralia, North America and vest are found in developing al incidence rates for colon are 4.4 per lac and 4.1 per lac lorectal cancer related deaths eaths worldwide and making	colorectal cancer the fourth most to cancer. Colorectal Cancer is th in both men and women in Kas strategy in the treatment of colo remains, complete surgical resec approximately 70–80% of patien surgical resection at the time of dia survival is only 50–60%. ^[4] Two undergo curative resection will ex distant metastases. In 85%, relapse	common cause of death due as 3^{rd} most common cancer shmir. ^[3] The only curative rectal cancer is, and so far etion. Despite the fact that this are eligible for curative agnosis, the five year overall b, out of three patients who perience local recurrence or e is diagnosed within the first

2.5 years after surgery.^[5]

Many factors have been studied and correlated for the early recurrence of colorectal cancer which include advanced stage, presence of metastatic disease, perforated or obstructed primary tumors, high CEA (Carcinoembryonic Antigen) levels, involvement of lymph nodes, histological subtype, histological grade and differentiation, venous and lymphatic invasion, perineural invasion, lymphocytic infiltration and status of surgical resection margins (free or involved). Some of these factors have been found to be significant.^[6,7]

Subjects and Methods

After obtaining proper history, physical examination, clinical parameters, biochemical parameters and pathological results, 48 patients were selected for the study.

After proper preoperative workup patients had the following pre-operative routine investigations as per the protocol.

Complete blood count, Kidney function test, serum electrolytes, Blood sugar, Liver function test, Ultrasound abdomen, serum CEA, X-ray chest, contrast enhanced computed tomography(CECT) abdomen and pelvis and chest. The clinical and pathological parameters included in this analysis were age, sex, preoperative levels of the tumor marker CEA, primary tumor site (colon or rectum), pathological results, date of diagnosis of the recurrence, and site of recurrence. The adjuvant chemotherapy administered to all patients consisted of a 5-fluorouracil-based chemotherapy regimen or oral anticancer drugs (capecitabine, or fluoropyrimidine). The standard postoperative surveillance program at our institute consisted of routine follow-up at 7^{th} post-operative day and then monthly for six months and then after three months for the first year, during which routine physical examination was performed. CEA was done on postoperative day 7 and at each visit after discharge. We also performed colonoscopy within 12 months following surgery and Chest radiography and abdomino-pelvic computed tomography at 6 months postoperatively for the first year. Univariate and multivariate analyses were performed on variables influencing the recurrence interval, and for the latter, we also applied logistic regression tests. Variables with an associated P-value of less than 0.05 in univariate analysis were entered into a multivariate logistic regression model.

Results

In our study Recurrent tumors were diagnosed in 04 patients (8.3%), including 02 with colon cancer (6.6%) and 02 with rectal cancer (11.1%). We found no differences in the factors like sex, age, primary tumor site, operative method, tumor size, type of histopathology, the degree of lymphatic or neural invasion, preoperative CEA levels in patients with recurrence.

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In our study Sex variable was not found to be significant factor (p-value>.005). In our study, the maximum patients were of age greater than 60 years (41.66%) and the least number of patients belonged to less than thirty years (58.33%). In our study, among patients who were of age greater than 60 years, two patients (7.1%) showed recurrence (one anastomotic and other with peritoneum and liver metastasis). The age factor was not significant against recurrence. In our study, thirty patients (65.22%) were operated for colon cancer and eighteen patients (34.78%) for rectal cancer. Among colon cancer patients, two patients (6.6%) showed postoperative recurrence within the time period of one year, one patient (3.3%) with metastasis to liver and another patient (3.3%) with peritoneum as well as liver metastasis. Among rectal cancer patients, two (11.1%) showed post-operative recurrence (both of which presented with anastomotic site recurrence). Although local recurrence was found mainly in rectal cancer patients, the overall post-operative recurrence was not significantly different in colon and rectal cancer patients, and the recurrence was not statistically significant for the site of the lesion.

In our study, among the patients who had recurrence with elevated preoperative CEA levels, one patient (5.5%) had anastomotic site recurrence and another patient (5.5%) with liver metastasis only. The raised preoperative CEA was not found statistically significant predictor of recurrence in our study. In our study, Out of forty-eight consecutive patients taken in the study, only four patients (8.4%) had elevated post-operative CEA levels with sequential increase from first to second visit, among which three patients (75%) had recurrence which included one anastomotic site recurrence and two with distant metastasis. This factor was found to be statistically significant predictor in both univariate and multivariate analysis (p-value 0.001) .Similarly lymphatic invasion was found to be insignificant factor. In this study, among patients with recurrence, two patients (7.1%) were N1, and rest two patients(10%) were N2 and the factor was found statistically insignificant. Similarly Size of Tumour and Grade of Tumour were found to be non-significant factors for recurrence.

In this study, Venous invasion was present in six patients (12.5%) on the histopathology examination, among which three patients (50%) showed post-operative recurrence. Among patients with negative venous invasion, which were 42 patients (87.5%), only one patient (2.3%) had recurrence and the factor was found statistically significant.

In our study of forty-eight consecutive patients, 10 patients (20.83%) were of T2 Stage (defined as per 7^{th} edition of TNM), out of which none had recurrence in the postoperative study period, 31 patients (64.58%) patients were T3 Stage, out of which none had recurrence and rest 07 patients (14.58%) patients were T4 Stage, out of which 04 patients (57.1%)

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Table 1: Comparison of clinicopathological characteristics between patients with tumor recurrence and no recurrence.						
Variable		Recurrence(no.)	No recurrence (no.)	p-value		
Age	<60 yrs	10%(02)	90%(18)	0.369		
	>60 yrs	7.1%(02)	92.9%(26)			
Sex	Male	7.6%02	92.4%24	0.386		
	Female	9%(02)	91%20			
Tumour location	Colon	6.602	93.428	0.342		
	Rectum	11.1%(02)	88.916			
Pre-operative	Normal	6.2%(02)	93.828	0.306		
	Elevated	12.1%(02)	87.916			
Postoperaive	Normal	2.2%(01)	97.843	0.001		
	Elevated	75%(03)	2501			
Venous Invasion	Present	50%(03)	50%(03)	0.004		
	Absent	2.3%(01)	7.7%(41)			
Lymphatic	Present	09%(02)	91%(20)	0.386		
	Absent	7.6%(02)	92.4%(24)			
Neural Invasion	Present	9.6%(03)	90.4%(28)	0.321		
	Absent	5.8%(01)	94.2%(16)			
Tumour Size	<5cms	11.1%(03)	88.9%(24)	0.316		
	>5cms	4.7%(01)	95.3%(20)			
	Well diff.	6.6%(01)	93.4%(14)	0.263		
	Mod. diff	9.1%(02)	90.9%(20)			
	Poorly dif	9.1%(01)	90.9%(10)			
Nodal Stage	N1	7.1%(02)	92.9%(26)	0.369		
	N2	10%(02)	90%(18)			
T-Stage	T2	None	100%(10)	0.0001		
	T3	None	100%(31)			
	T4	57.1%(04)	43.9%(03)			

showed postoperative recurrence .When the T- stage was correlated with recurrence, it was found to be statistically significant factor in our study (p-value 0.000).

Patterns of recurrence after resection

Among the patients who had early recurrence after resection, two presented with local recurrence, two with distant metastasis. The most common site of distant metastasis was liver [Table 2]

With a minimum follow-up time of two and half year's patients with recurrence, the median survival times (from operation to death) in the recurrence group was 15 months. In patients who underwent repeated resections for local lesions, prognosis was better. We found that survival rate after recurrence was significantly lower in patients with metastatic lesions than with local recurrence lesions. Repeated resection for recurrence was feasible in only 50% of patient's recurrence group in our study.

ear's patients 80%

Discussion

however, because the definitions of early and late recurrence vary between studies as some defining it as early as within one year, and others within two or three years.^[8–10] A number of these studies analyzed risk factors associated with recurrence or the survival period after recurrence. Approximately 60%–80% of recurrences develop within the first 2 years after surgery and cases of recurrence 5 years after surgery are rare.^[11,12]In our study, we found the recurrence (local and distant metastasis) after curative resection in four patients (8.33%), which was lower as compared to previous studies, reason being exclusion of patients who were operated on emergency basis with obstructive or perforated lesions.^[13,14] Previous studies have identified a number of factors including

Recurrence after curative surgery in patients with CRC

remains a major clinical problem. Reaching a consensus on

the best treatment strategy has been made more difficult,

Table 2:				
Local recurrence alone	Distant metastasis	Distant metastasis		
02	01	01		
Rectum	1.liver	Peritoneum and liver		

advanced age, tumor stage, site of lesion, depth of invasion, the degree of vascular or perineural invasion, and serum levels of CEA and CA 19-9, some of which having statistically significant association with CRC recurrence.^[15,16]

In our study, majority of the patients were of age more than 60 years. Age factor was not found to be significant for recurrence in our study. Jong pil Ryuk et al. conducted a similar study in 2006, and correlated the early recurrence with advanced age, but the variable was found to be insignificant.^[17] The finding is also consistent with a study done by Dina et al. done in 2015, in which age factor was correlated with recurrence but no significant factor for recurrence as 7.6% of males and 9% of females had recurrence post operatively. Similarly, Fatemi et al. found no significant association between gender and risk of cancer recurrence.^[19]

In our study, no statistically significant association was found on the basis of site of lesion. However, local recurrence was found only in patients with rectal cancer in our study. Lese et al., found significant association between rectal cancer and local recurrence.^[20] Similarly, Sloothak et al, found significant association between site of tumor and local recurrence which is consistent with our study.^[21]However, the site of lesion was not found significant factor for the overall recurrence as 50% of the patients who had recurrence were operated for colon cancer.

In our study, pre-operative CEA elevation was not risk factor for predicting recurrence and outcome. Moertel C.G., et al., similarly found no association between recurrence and preoperative CEA.^[22] Our study is similarly consistent with previous study conducted by Corpelam-Holmstorm et al., in which they found no statistical significance between recurrence and preoperative CEA levels.^[23]

In this study, one of the most important factors influencing the recurrence was the post-operative CEA levels. Patients with elevated post-operative CEA had significantly higher risk of recurrence. This finding is consistent with previous study done by Pietra N. et al, in which they found that elevated post-operative CEA is associated with early recurrence.^[24] Similarly, Graham et al., in their study conducted in 1998 found post-operative CEA elevation as a significant factor for recurrence and prognosis.^[25] Recently Yakabe T et al, in a study on clinical significance of post-operative CEA on recurrence on colorectal cancer found the elevation of post-operative CEA to be significant for recurrence and outcome.^[26] McCall J.l., et al. found post-operative CEA elevation as independent and significant factor for recurrence after curative resection.^[27] In this study, Venous invasion was found to be an independent significant factor for recurrene as consistent with several previous studies.^[28,29]

A number of studies have been done in the past in which Perineural invasion was not found to be the significant factor similar to our study.^[30,31] At the same time ,many studies found it significant which is not consistent with our study. We did not found size of the tumor (categorised as <5cms and >5cms) to be significant factor for early recurrence as consistent with previous study. Our study did not find any association between early relapse and grade of the tumor. Aghili et al., in their study conducted in 2010 found no association between grade of tumour and recurrence.^[27]Similarly, Sloothak et al., found grade of tumor to be insignificant for recurrence as consistent with our study. Our study found tumor stage as an important prognostic factor. In addition, this study showed that tumor stage is associated with the risk of recurrence. In accordance to this finding, results of a study (Sloothaak et al., 2014) suggested that patients with colorectal cancer at stage III have worse prognosis and more chance for recurrence compared to patients with stage-I tumour.^[18] Dianatinasab et al., (2016) reported that higher tumor stage is significantly associated with worse prognosis of CRC.^[28] Westberg et al., (2015) reported that early local recurrence in patients with a stage III primary tumor were more common compared with the late local recurrence.^[29]

In our study, liver was the most common site for distant metastasis and the local recurrence was found mainly in rectal cases. Tsai HL et al., in their study, similarly found that the liver was the most common site of early recurrence and that local recurrence was more common in patients with rectal cancer than in those with colon cancer.^[30] However, the study has some limitations as it was a short period study, less number of patients (48), type of method applied whether laparoscopic or open was not taken into consideration, only Adenocarcinomas were taken into study,

With a minimum follow-up time of two and half years patients with recurrence, the median survival times (from operation to death) in the recurrence group was 15 months. In patients who underwent repeated resections for local lesions, prognosis was better. We found that both survival rates after recurrence were significantly lower in patients with metastatic lesions than with local recurrence lesions .This concurs with a previous study; in that, when patients can undergo curative resection for relapse, they receive a survival benefit. However, repeated resection for recurrence was feasible in only 50% of patients in recurrence group in our study.

Conclusion

From the observations we made in our study of predictive factors for the recurrence of colorectal cancer and their prognosis after curative resection, we conclude that the patients who have post-operative elevated CEA levels, who have positive venous invasion on histopathology and advanced T-Stage are significant and independent risk factors for colorectal cancer recurrence and the prognosis is not good in this subset of patients. We further conclude that these patients should have an intensive close follow-up including serial monitoring of post-operative CEA levels, which may help in early detection and resection of recurrent disease which in turn might offer a cure in this subset of patients.

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