Factors influencing outcome of surgery for stage I rectal cancer

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Stage I rectal cancer ($T_1N_0M_0$, $T_2N_0M_0$) carries excellent prognosis with up to 90% of long term survival rates and complete cure can be expected with curative surgery. However 10 to 15% of these patients show local recurrence and mortality seen in five years. The aim of this study is to analyze the prognostic factors that influence the overall and disease free survival in patients with stage I rectal cancer. Eighty-five patients with stage I ($T_1N_0M_0$, $T_2N_0M_0$) rectal cancer that had potentially curative surgery were entered into the study. The patients were evaluated according to age, sex, preoperative carcinoembryonic antigen (CEA) level, type of surgical procedure, tumor distance from anal verge, tumor size, depth of invasion, histological differentiation, presence of tumor ulceration, peritumoral vascular invasion, peritumoral lymphatic invasion and peritumoral perineural invasion. Five year overall and disease free survival rates for the patients were 88% and 74%, respectively. Multivariate analysis showed that independent predictors of recurrence were differentiation and peritumoral vascular invasion, and independent predictor of overall survival was only differentiation. Stage I rectal cancer patients with poor differentiation and peritumoral vascular invasion are at high risk for recurrence and should be evaluated for adjuvant therapies.

Key words: rectal cancer, stage I, prognosis, recurrence

Local or systemic recurrence of rectal cancer continues to be a common clinical problem despite potentially curative surgery. Especially patients, who have rectal cancer with transmural invasion or lymph node involvement (stage II and III) are at high risk for recurrence [5, 9, 12]. In order to improve surgical results, adjuvant chemotherapy plus radiotherapy has become the standard treatment of stage II or III rectal cancer [9, 11].

On the other hand patients with stage I rectal cancer ($T_1N_0M_0$, $T_2N_0M_0$) carry excellent prognosis with up to 90% of long term survival rates and complete cure can be expected with curative surgery. However, 10 to 15% of these patients show local recurrence and mortality seen in five years [1, 9, 11, 17]. Identifying this group of patients at risk for failure after radical resection may provide a guideline for postoperative adjuvant treatment.

In this study we analyzed prognostic factors that influence the overall and disease free survival in patients with stage I rectal cancer.

Patients and methods

Patients. Medical records of 1113 patients with primary adenocarcinoma of the rectum who had been admitted to Ankara Oncology Hospital between January 1990 to December 2000 were reviewed. Among these 85 patients with stage I ($T_1N_0M_0$, $T_2N_0M_0$) rectal cancer that had potentially curative surgery were entered into the study. All patients underwent routine preoperative evaluation including history and physical examination, routine laboratory evaluation, chest radiography and abdominal ultrasonography. None of the patients received preoperative or postoperative radiation therapy and/or chemotherapy. The patients were evaluated according to age, sex, preoperative carcinoembryonic antigen (CEA) level, type of surgical procedure, tumor distance from anal verge, tumor size, depth of invasion, histological differentiation, presence of tumor ulceration, peritumoral vascular invasion, peritumoral lymphatic invasion and peritumoral perineural invasion.

Statistical analysis. Statistical analysis was performed using SPSS 9.05 for Windows statistical software (SPSS Inc, Chicago, IL, USA). Survival times and curves were established according to the KAPLAN-MEIER method [6] and compared by means of log-rank test. Overall survival was estimated from the date of diagnostic biopsy to tumor related death as the endpoint by the end of follow-up, disease free survival was computed from the date of diagnostic biopsy to the first event of relapse (local, distant or both). The chi-square test and log-rank test were performed for univariate statistical analysis of each prognostic factor. In the univariate test, estimates of hazards ratios, their 95% confidence intervals (95% CI), and p values were calculated using the chi-square test. Multivariate analysis and calculations of hazards ratios, their 95% CI, p values in this analysis were carried out by the Cox's proportional hazards regression model [3]. In the multivariate analysis, only factors that proved to be significant in the univariate analysis were investigated. All p values were two-sided in tests and p values ≤0.05 were considered significant. Survival rates were given with their standard errors (± SE).

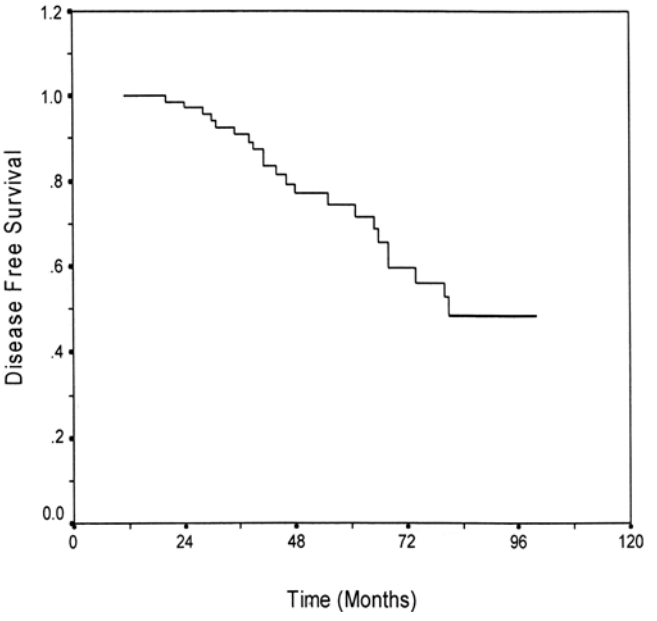

Figure 1. Disease free survival curves of the patients.

Results

Forty-three of the patients were female and 42 were male. The median age was 52 years (22–79 years) and the median follow-up time was 48 months (12–100 months). Surgical procedure was abdominoperineal resection in 55 patients and low anterior resection in 30 patients. Five year overall and disease free survival rates for the patients were 88% and 74%, respectively (Figs. 1 and 2). During the follow-up period 22 patients had recurrence. Of these 8 had local recurrence, 12 had distant recurrence and 2 had both local and systemic recurrences. Univariate analysis showed that preoperative CEA level (OR: 2.3, 95% CI: 1.4–3.8, p=0.003), tumor size (OR: 2.3, 95% CI: 1.4–3.6, p=0.002), differentiation (OR: 6.0, 95% CI: 3.2–11.3, p<0.0001), peritumoral vascular invasion (OR: 13.6, 95% CI: 5.2–35.6), p<0.0001), peritumoral lymphatic invasion (OR: 6.5, 95% CI: 3.1–13.8, p<0.0001) and peritumoral perineural invasion (OR: 4.3, 95% CI: 1.3–13.8, p=0.02) were closely related with recurrence (Tab. 1). Multivariate analysis identified differentiation (OR: 5.6, 95% CI: 1.3–24.6, p=0.02) and peritumoral vascular invasion (OR: 11.8, 95% CI: 2.7–52.0, p<0.001) as independent predictors of recurrence. The patients with well or moderately differentiated tumors had 95% 5-year disease free survival, whereas patients with poor differentiated tumors had 41%. The rates for negative and positive peritumoral vascular invasion were 100% and 27%, respectively.

For overall five year survival, univariate analysis showed that tumor size (OR: 1.7, 95% CI: 1.1–2.9, p=0.05), differentiation (OR: 5.8, 95% CI: 3.2–10.5, p<0.0001), peritumoral vascular invasion (OR: 7.4, 95% CI: 3.5–15.5), p<0.0001), peritumoral lymphatic invasion (OR: 6.0, 95% CI: 3.0–12.0, p<0.0001), peritumoral perineural invasion (OR: 3.2, 95% CI: 1.1–10.0, p=0.05) and depth of invasion (OR: 1.2, 95% CI: 1.1–1.5, p=0.05) were significant prognostic factors (Tab. 2). Multivariate analysis of these prognostic factors revealed that only differentiation (OR: 15.2, 95% CI: 1.9–120, p=0.009) was independent predictor of overall survival. The 5-year overall survival rates for well/moderately and poor differentiated tumors were 100% and 67%, respectively.

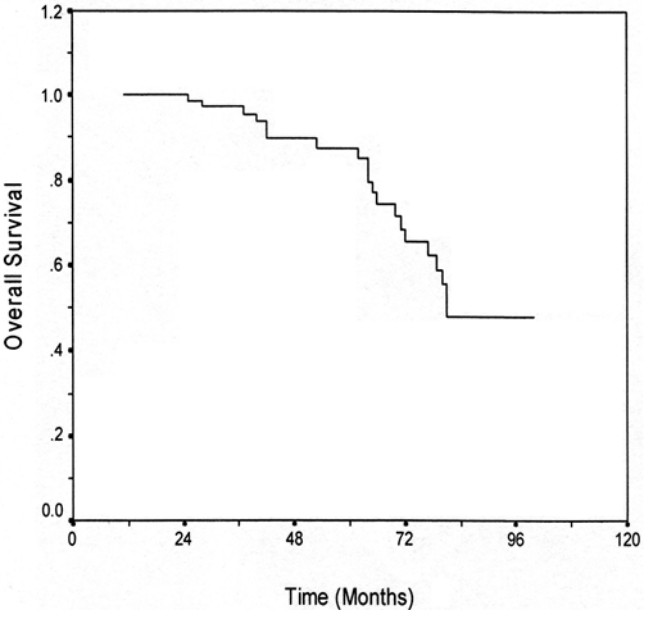

Figure 2. Overall survival curves of the patients.

Table 1. Univariate and multivariate analysis of the prognostic factors and Disease Free Survival (DFS)

Features	n	5-year DFS ± SE	Univariate p value	Multivariate p value
Sex				
Male	42	0.69 ± 0.09	NS	NS
Female	43	0.79 ± 0.08		
Age				
≤ 50	34	0.79 ± 0.08	NS	NS
>50	51	0.71 ± 0.09		
Distance from anal verge				
≤5cm	55	0.71 ± 0.08	NS	NS
>5cm	30	0.82 ± 0.10		
Preoperative CEA level				
>5ng/dl	29	0.88 ± 0.09	0.003	NS
≥5ng/dl	34	0.42 ± 0.12		
Undetermined	22			
Type of surgery				
APR	55	0.71 ± 0.08	NS	NS
LAR	30	0.82 ± 0.10		
Tumor size				
≤5cm	51	0.84 ± 0.08	0.002	NS
>5cm	34	0.62 ± 0.10		
Depth of invasion				
T1	18	1.0	NS	NS
T2	67	0.66 ± 0.08		
Ulceration				
Negative	19	0.68 ± 0.14	NS	NS
Positive	66	0.76 ± 0.07		
Differentiation				
Well/moderate	57	0.95 ± 0.04	0.0001	0.002
Poor	28	0.41 ± 0.11		
Peritumoral vascular invasion				
Negative	62	1.0	0.0001	0.001
Positive	23	0.27 ± 0.10		
Peritumoral lymphatic invasion				
Negative	60	0.87 ± 0.06	0.0001	NS
Positive	25	0.51 ± 0.12		
Peritumoral neural invasion				
Negative	75	0.76 ± 0.06	0.02	NS
Positive	10	0.54 ± 0.20		

Table 2. Univariate and multivariate analysis of the prognostic factors and Overall Survival (OS)

Features	n	5-year OS ± SE	Univariate p value	Multivariate p value
Sex				
Male	42	0.89 ± 0.06	NS	NS
Female	43	0.76 ± 0.07		
Age				
≤50	34	0.92 ± 0.05	NS	NS
>50	51	0.84 ± 0.07		
Distance from anal verge				
≤5cm	55	0.86 ± 0.06	NS	NS
>5cm	30	0.92 ± 0.06		
Preoperative CEA level				
<5ng/dl	29	0.96 ± 0.04	NS	NS
≥5ng/dl	34	0.72 ± 0.11		
Undetermined	22			
Type of surgery				
APR	55	0.86 ± 0.06	NS	NS
LAR	30	0.92 ± 0.06		
Tumor size				
≤5cm	51	0.92 ± 0.05	0.05	NS
>5cm	34	0.82 ± 0.08		
Depth of invasion				
T1	18	1.0	0.05	NS
T2	67	0.83 ± 0.06		
Ulceration				
Negative	19	1.0	NS	NS
Positive	66	0.85 ± 0.05		
Differentiation				
Well/moderate	57	1.0	0.0001	0.009
Poor	28	0.67 ± 0.10		
Peritumoral vascular invasion				
Negative	62	0.98 ± 0.02	0.0001	NS
Positive	23	0.67 ± 0.11		
Peritumoral lymphatic invasion				
Negative	60	0.95 ± 0.03	0.0001	NS
Positive	25	0.73 ± 0.11		
Peritumoral neural invasion				
Negative	75	0.90 ± 0.05	0.05	NS
Positive	10	0.71 ± 0.17		

Discussion

Approximately 10% of all patients with rectal cancer have stage I tumors [7, 17] and although 80 to 90% will be cured by radical surgery, 10–25% go on to develop recurrent disease [1, 8, 17].

In the presented study, among 85 stage I rectal cancer patients, 22 patients had local or systemic recurrences with 5-year disease free survival rate of 74% and 5-year overall survival rate of 88%. These were similar with the literature.

We found that patients with peritumoral vascular invasion had increased incidence of recurrence rate. In 1940 Dukes was the first to report the clinical significance of peritumoral vascular invasion. Since than, a lot of studies investigated the prognostic significance of vascular invasion

[4, 10, 15, 16]. DIONNE in an analysis of 1376 rectal carcinomas, observed that microscopic venous invasion was associated with 47% incidence of blood-born metastasis, in comparison with a 27% incidence in the absence of venous invasion [4]. SUNDERLAND was the first to correlate vascular invasion with poorer long term survival [15]. Later TALBOT et al [16] has shown that venous invasion results in a lower survival rate independent of lymph node status or Dukes' stage. Survival was worse with a greater degree of lymph node involvement in the presence of blood vessel invasion. RICH et al [13] showed that all patients with blood vessel invasion, regardless of nodal status had higher chance of local failure. In a series of 64 patients with stage I rectal cancer treated by abdominoperineal resection, WILLET et al [17] reported that 6-year actuarial disease free survival, local control and freedom from distant metastases rates for seven patients with vascular/lymph vessel involvement were 48%, 56% and 86%, respectively. In contrast, these rates were 89%, 91% and 90%, respectively, for 57 patients without this feature [17]. In another study of stage I rectal cancer BLUMBERG et al [1] stated that blood vessel invasion was independent predictor of recurrence and tumor related mortality.

In the presented study, patients with poorly differentiated tumors had higher rates of recurrence and poor survival. The influence of differentiation on survival has been shown to be associated with poor prognosis in several reports and Dukes originally referred to it as "the pace of growth" of the tumor when the relationship between stage and grade was estaplished [16]. In a study, BRODSKY et al [2] investigated the correlation of differentiation with lymph node metastases. They reported a high risk of lymph node metastases (50%) for poorly differentiated T_1/T_2 lesions. In the studies of GRIFFIN et al [5], McDERMOTT et al [9] and RICH et al [13], differentiation was found to be an independent predictor of disease free survival. In a recent study, BLUMBERG et al [1] reported that poorly differentiated stage I rectal cancers have a worse prognosis.

According to the National Cancer Institute Consensus Conference in 1990, the use of adjuvant chemotherapy combined with radiation is the standard treatment for patients with stage II and III rectal cancer [11]. Because of the success achieved by resection alone, adjuvant radiation therapy and chemotherapy have not been routinely advised for stage I disease [17]. There are very few studies regarding the identification of patients with stage I disease that should be considered for adjuvant therapy [1, 17]. This presented study showed that patients with poor differentiated tumors had 41% and the patients with positive peritumoral vascular invasion had 27% disease free 5-year survival rates. These rates are almost similar with stage II or even Stage III patient groups of several studies [14]. It is obvious that patients with these features have high risk of recurrence and tumor related mortality even in early stage. The use of adjuvant chemotherapy and/or radiotherapy might be considered for selected stage I patients. Further prospective randomized and multi-institutional trials are necessary to clarify the use of adjuvant therapies.

References

[1] BLUMBERG D, PATY PB, PICON AI, GUILLEM JG, KLIMSTRA DS et al. Stage I rectal cancer: Identification of high-risk patients. J Am Coll Surg 1998; 186: 574–579.

[2] BRODSKY JT, RICHARD GK, COHEN AM, MINSKY BD. Variables correlated with the risk of lymph node metastasis in early rectal cancer. Cancer 1992; 69(2): 322–326.

[3] COX DR. Regression model and life tables. J R Stat Soc 1972; B34: 187–220.

[4] DIONNE L. The pattern of blood-borne metastasis from carcinoma of the rectum. Cancer 1965; 18: 775–781.

[5] GRIFFIN MR, BERGSTRALH EJ, COFFEY RJ, BEART RW, MELTON LJ. Predictors of survival after curative resection of carcinoma of the colon and rectum. Cancer 1987; 60: 2348–2324.

[6] KAPLAN EL, MEIER P. Nonparametric estimation for incomplete observations. J Am Stat Assoc 1958; 53: 457–481.

[7] LE VOYER TE, HOFFMAN JP, COOPER H, ROSS E, SIGURDSON E, EISENBERG B. Local excision and chemoradiation for low rectal T_1 and T_2 cancers is an effective treatment. Am Surg 1999; 65: 325–630.

[8] MAINPRIZE KS, MORTENSEN NJM, WARREN BF. Early colorectal cancer: recognition, classification and treatment. Br J Surg 1998; 85: 469–476.

[9] McDERMOTT FT, HUGHES ESR, PIHL E, JOHNSON WR, PRICE AB. Local reccurrence after potentially curative resection for rectal cancer in a series of 1008 patients. Br J Surg 1985; 72: 34–37.

[10] MICHELASSI F, BLOCK GE, VANNUCCI L, MONTAG A, CHAPPELL R. A 5- to 21-year follow-up and analysis of 250 patients with rectal adenocarcinoma. Ann Surg 1988; 208: 379–389.

[11] NIH Consensus Conference. Adjuvant therapy for patients with colon and rectal cancer. JAMA 1990; 264: 1443–1450.

[12] PILIPSHEN SJ, HEILWEIL M, QUAN SHQ, STENBERG SS, ENKER WE. Patterns of pelvic recurrence following definitive resections of rectal cancer. Cancer 1984; 53: 1354–1362.

[13] RICH T, GUNDERSON LL, LEW R, GALDIBINI JJ, COHEN AM, DONALDSON G. Patterns of recurrence of rectal cancer after potentially curative surgery. Cancer 1983; 52(7): 1317–1329.

[14] SKIBBER JM, HOFF PM, MINSKY BD. Cancer of the rectum. In: DeVita VT, Hellman S, Rosenberg SA, editors. Cancer. Principles and Practice of Oncology. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2001: 1271–1319.

[15] SUNDERLAND DA. The significance of vein invasion by cancer of the rectum and sigmoid. Cancer 1949; 2: 429–437.

[16] TALBOT IC, RITCHIE S, LEIGHTON MH, HUGHES AO, BUSSEY HJ, MORSON BC. The clinical significance of invasion of veins by rectal cancer. Br J Surg 1980; 67(6): 439–442.

[17] WILLETT CG, LEWANDROWSKI K, DONNELLY S, SHELLITO PC, CONVERY K et al. Are there patients with stage I rectal carcinoma at risk for failure after abdominoperineal resection? Cancer 1992; 69: 1651–1655.