Negative prognostic factors in colorectal carcinoma: An analysis of 448 patients

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Abstract

Background and aims: Colorectal carcinoma (CRC) is the most frequent malignancy of the gastrointestinal tract. Prognostic researches are carried out for choosing the optimum therapy, evaluating therapy results and comparing multicentre results for better qualification in the therapy of the disease.

Patients and methods: In this study, 448 patients, whose surgery and follow-up was performed by the same correspondent surgeon between the years 1995 and 2003, were retrospectively analyzed.

Results Age, presence of comorbidity, weight loss, emergency admission, high serum CEA and CA 19–9 levels, neighboring organ invasion, operation type, major morbidity, tumor size and type, lymph node metastases, venous and perineural invasion, Dukes' classification and local recurrence and distant metastasis during follow-up are found to be significant negative factors affecting prognosis of the CRC patient.

Conclusion Therapy results of the CRC are evaluated by survival times regardless of the therapy method selected for each individual. In our study we tried to find out negative prognostic factors by researching possible factors affecting disease free survival time for CRC. Since our understanding of factors that have an impact on prognosis increases, we are hoping to improve survival.

Keywords Colorectal cancer · Prognosis · Survive

Introduction

Colorectal carcinoma (CRC) is the most frequent malignancy of the gastrointestinal tract [1]. It is the third most frequent malignancy after prostate and lung malignancies in men and after breast and lung malignancies in women [1]. It covers 10% of whole malignancies in both sexes and is the second most reason of death from cancer in the United States. The frequency of the disease rises with the fifth decade and reaches a maximum at the age of 80. According to WHO's (World Health Organisation) report, 800.000 new patients are diagnosed yearly. Nearly 70% of the diagnosed CRC patients have the chance to undergo curative resections. In 10% of the patients, resection is impossible due to local invasion and 20% of the patients have distant organ metastasis at the time of diagnosis. Total remission can be achieved in 75% of surgically resected patients who have no distant organ metastasis at the time of surgery. This cure ratio is markedly better when compared to other gastrointestinal system malignancies [2]. The curative attempts are hoped to be more elective with the understanding of the prognostic factors [2].

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Materials and method

In the current study, 448 patients, whose surgery and follow-up was performed by the same correspondent surgeon between the years 1995 and 2003, were retrospectively analyzed. Studied parameters were age, presence of comorbidity, weight loss, emergency admission, serum CEA and CA 19–9 levels, adjacent organ invasion, operation type, major morbidity, tumor size and type, lymph node metastasis, venous and perineural invasion, Dukes' classification, local recurrence and distant metastases during follow up. A CRC database was formed. All statistical tests were carried out two-tailed by the "SPSS for Windows 11.5" (SPSS, Chicago, USA). Survival was investigated by Kaplan-Meier analysis. Cox proportional hazards model, done by forward stepwise method, was used to investigate the independent contributions. A *p* value of less than 0.05 was considered statistically significant.

Results

Using the Cox regression test; age, presence of comorbidity, weight loss, emergency admission, high serum CEA and CA 19–9 levels, neighboring organ invasion, operation type, major morbidity, tumor size and type, lymph node metastases, venous and perineural invasion, Dukes' classification and local recurrence and distant metastasis during follow-up were found to be significant negative factors affecting prognosis of the CRC patient.

Kaplan–Meier survival test gave no difference between the survival rates of the patients who were older and younger than 40 years. Patients between the ages 41 and 50 and between 51 and 60 showed longer survival when compared to patients between the ages 61–70 ($p < 0.05$) and patients older than 71 ($p < 0.05$) (Table 1). Survival time of the patients without co-morbidities was found to be longer than patients with co-morbidities ($p = 0.026$). There was significant difference between the 45 months average survival time of 131 patients with weight loss and 71 months average survival time of 317 patients without weight loss ($p < 0.05$). The average and median survival times of the electively operated 398 patients were 68 and 48 months. Respectively, these were 36 and 26 months for 50 patients

who were operated under emergency conditions. Survival times of the electively operated patients were longer than those patients who had undergone emergency surgery ($p < 0.05$).

The average and median survival times of the 150 patients whose CEA levels were high were 49 and 17 months, respectively, while these were found to be 77 and 120 months in 219 patients whose serum CEA levels were normal. Survival times of the patients whose CEA levels were normal were significantly longer than patients with high CEA ($p < 0.05$). The average and median survival times of the 89 patients whose serum CA 19–9 levels were high were 45 and 15 months, respectively, while these were found to be 71 and 64 months in 249 patients whose serum CA 19–9 levels were normal. Survival times of the patients whose serum CA 19–9 levels were normal were longer than patients with high CA 19–9 levels ($p < 0.05$). The average and median survival times of 107 patients with neighboring organ invasion were 28 and 14 months, respectively, while these were found to be 74 and 63 months in 341 patients without neighboring organ invasion. Survival times of patients with neighboring organ invasion were longer than patients without invasion ($p < 0.05$). Survival time of the patients who had undergone curative resections was found to be longer than the patients who had undergone palliative and/or combined surgical procedures ($p < 0.05$) (Table 2).

Major morbidities were sepsis and acute respiratory distress syndrome (ARDS) in 9 patients, acute myocardial infarction in 6 patients, deep vein thrombosis in 3 patients, anastomosis leakage in 3 patients, pneumonia in 3 patients, intraabdominal hematoma and hemorrhage in 2 patients, evisceration in 1 patient, massive ascites in 1 patient, acute renal failure in 1 patient, pulmonary embolism in 1 patient and intestinal ischemia in 1 patient. The average and median survival times of the patients with

Table 1 Average and median life time

Age	n	average life time (months)	median life time (months)
0–40	35	52, 20	36
41–50	63	62, 93	84
51–60	101	66, 59	50
61–70	141	44, 25	31
71 and older	108	71, 65	31

Table 2 The relation between operation type and average and median survival times

Operation type	N	Average survival time (months)	Median survival time (months)
Radical procedures	393	50, 07	44
Right hemicolectomy	65	66, 96	*****
Miles Operation	62	72, 27	50
Low anterior resection	109	55, 23	48
Anterior resection	78	57, 32	56
Total colectomy	6	57, 92	*****
Sigmoid resection	34	47, 83	35
Left hemicolectomy	36	58, 72	84
Transverse colectomy	9	34, 38	40
Palliative operations	46	16, 68	9
Combined operations	9	11, 62	12

major morbidity and patients without major morbidity were 21, 1, 68 and 48 months, respectively. Survival time of patients without major morbidity were significantly longer than those with major morbidity ($p < 0.05$).

The best prognosis was found to be in the “carcinoma in-situ” type tumors. There was no significant difference in survival times between the good differentiated adenocarcinoma and moderately differentiated adenocarcinoma groups ($p > 0.05$). These two tumor types had better survival times when compared to poorly differentiated adenocarcinoma, indifferntiated adenocarcinoma, mucinous and signet ring carcinoma tumor types ($p < 0.05$). There was no significant difference in survival times between the poorly- indifferntiated adenocarcinoma and signet ring carcinoma tumor types ($p > 0.05$). A better survival time was noted in the mucinous adenocarcinoma group, when compared to indifferntiated adenocarcinoma tumor group ($p < 0.05$). There was no difference between the mucinous adenocarcinoma and signet ring carcinoma groups ($p > 0.05$) (Table 3).

Table 3 Relation between tumor type and average and median survival time

Tumor type	N	Average survival (months)	Median survival (months)
Good differentiated adenocarcinoma	59	61, 86	50
Moderately differentiated adenocarcinoma	251	77, 61	84
Poorly differentiated adenocarcinoma	50	24, 76	14
Indifferntiated adenocarcinoma	6	17, 17	10
Carcinoma in situ	9	85, 87	*****
Mucinous adenocarcinoma	63	44, 88	25
Signet ring carcinoma	10	22	16

Survival time tend to shorten as the tumor size increased, but there was no difference between tumors of 6–10 cm in size and tumors of 11–15 cm in size ($p > 0.05$) (Table 4). Survival time also tend to shorten as the number of lymph node metastasis increased ($p < 0.05$) (Table 5). The average survival time of 252 patients with venous-perineural invasion was 27 months, while in 196 patients without venous-perineural invasion survival time was 124 months ($p < 0.05$). Survival time tend to shorten as Dukes’ stage progressed, but there was no difference between Dukes’ A and B tumors ($p > 0.05$) (Table 6).

Table 4 Relation between tumor size and average and median survival time

Tumor size	N	Average survival (months)	Median survival (months)
1–5 cm	282	76, 70	64
6–10 cm	147	37, 93	21
11–15 cm	13	26, 35	17
16–20 cm	6	6, 20	5

Table 5 Relation between lymph node metastase and average and median survival time

Lymph node metastases	N	Average survival (months)	Median survival (months)
None	238	87, 16	120
<4	119	46, 03	28
>4	91	19, 77	12

Table 6 Relation between Dukes stage and average and median survival time

Dukes’ stage	N	Average survival (months)	Median survival (months)	Estimated 5 years survival
Dukes A% 9, 8	4	81, 92 mts	*****	75%
Dukes B% 30, 6	137	94, 66 mts	120 mts	60%
Dukes C% 35, 3	158	53, 95 mts	43 mts	44%
Dukes D% 24, 3	109	11, 09 mts	10 mts	0%
Stage independent	448	65, 68 mts	41 mts	42, 50%

Survival time of the patients without local recurrence was longer than the patients with local recurrence ($p < 0.05$). The average and median survival of 51 patients with local recurrence in the follow-up period were 49 and 33 months, respectively. The average and median survival of 397 patients without local recurrence were 73 and 45 months, respectively. The average and median survival of 315 patients without distant metastasis was 84 and 120 months, respectively. The average and median survival of 133 patients with distant metastasis was 24 and 18 months, respectively. Distant metastasis were localized in liver in 45 patients, lung in 30 patients, brain in 6 patients, bones in 7 patients and in bone marrow in 1 patient.

Discussion

Prognostic researches for CRCs are carried out for choosing the optimum therapy, evaluating therapy results and comparing multicentre results for better qualification in the

management of the disease. In our study we tried to find out negative prognostic factors by researching possible factors affecting disease free survival time for CRCs.

However the incidence of CRCs in early decades is low, Moore et al. suggested that CRCs have poor outcomes in young individuals [3]. Many studies reported poor prognosis for CRC in individuals under the age of 40 [4, 5]. When stage-dependent survival times are analyzed, there was no significant difference in relative prognosis for young age groups. In a study covering 4430 CRC patients, Recio and Bussey found out those patients under the age of 30 resembled only 1%. The data derived from the study showed that the survival time of these patients was significantly shorter [6]. Köhler and his friends reported that there was no significant difference between the survival times of the young group and the older individuals. Common belief is that CRC is more aggressive in younger individuals [8, 9]. Dukes and Bussey reported that most of the old CRC patients do not represent an aggressive nature. In a study of 554 patients, Jensen et al. reported no difference between the 5-years survival of the patients who were older and younger than 70 [10]. In a study of 867 patients, Bokey et al. reported that the 5-years survival rate of patients older than 75 was significantly shorter than patients younger than 75 [11]. In our study the patients younger than 40 represented 7.8%, while patients younger than 30 represented 1.8%. When patients older and younger than 40 were evaluated, we found out those older than 40 had longer survival times. But there was no significant difference. Patients older than the age of 70 showed insignificant longer survival than those younger than 70.

Operative mortality and morbidity depends on patient selection and the underlying pathology. Mortality rate following resection is reported between 1–6% in many retrospective studies. These studies also cover the risk arising from accompanying comorbidities [12]. About 34% of our patients had comorbidities. Nearly 92% had diabetes, respiratory or cardiovascular disorders. Survival time of patients without comorbidities was found to be longer. The presence of weight loss is one of the negative prognostic factors in CRC [13]. There was weight loss in 29.2% of the patients and this group of patients had a significantly shorter survival than others.

Obstruction and perforation worsens the survival and in some studies these are found to be the major prognostic factors. There are distant metastasis in many of these patients at the time of diagnosis and operative mortality and morbidity is higher in these [6, 12, 14–16]. Cure is impossible in the presence of free perforation in the peritoneal cavity, because of implantation of tumor cells. In some studies, 5-years survival rate of this group of patients is reported as 7–33% [6, 14]. More than 11% of our patients were operated under emergency conditions. Survival time of the electively operated patients was significantly longer.

Preoperative CEA levels >5 mg/dl is shown to have a

negative effect on survival. Higher CEA levels are usually correlated with Dukes' stage, however there are some authors suggesting that they are irrelevant. It is used to monitor the efficacy of the treatment and diagnosing recurrences [17, 18]. In 40.7% of our patients, serum CEA level was higher than 5 mg/dl and 74% of these were Dukes' C and D patients. Survival time of patients with normal CEA levels was longer than patients with high CEA levels. In a retrospective study of 495 patients, Reiter et al. found out that high CA 19–9 levels have a significant negative effect on prognosis. However, only 42% of the CRC patients have high CA 19–9 levels. It is useful for postoperative follow up [19]. Nearly 26% of our patients had high CA 19–9 levels and 76% of these were classified as Dukes' C or D. Patients with normal serum CA 19–9 levels had longer survival times.

Patients with neighboring organ invasion have shorter survival. The incidence of neighboring organ invasion in CRC patients is 5.5–16.7%. Neighboring organ invasion is among the most important negative prognostic factors affecting prognosis and brings about obligatory resection of all suspected neighboring tissues in an "en bloc" fashion (20). As a result, the resection of the tumor with the involved neighboring tissues is very important [14, 21]. In our study, 24% of the patients had neighboring organ invasion and these patients had significantly shorter survival times.

Seventy percent of CRC patients undergo curative resections. Resection is impossible in 10% due to local invasion and 20% of CRC patients have distant organ metastasis at the time of diagnosis. As a rule in surgery, the main goal is to carry out a complete anatomic resection of the involved segment with surrounding lymphatic tissues and clean surgical borders and establish a tension free anastomosis. This is the most important factor positively affecting the prognosis. The risk of residual tumor and local recurrence rises if the gap between the tumor and resection border is shorter than 1 mm. For this reason, some staging systems classify the patients with residual tumor as stage IV (Dukes' D1). In our study there was no difference in survival between curative operation types. The survival times of patients undergoing curative procedures were longer than patients receiving palliative and combined procedures. According to our data 90% of our patients received curative procedures and this ratio was higher than reported in the literature.

In a study covering 5833 patients, the hospital mortality rate for 30 days was reported as 5.7%. There was a 28% complication rate among the same group of patients. The most serious complication were reported as coma lasting more than 24 hours, cardiac arrest, acute renal failure, pulmonary embolism and progressive renal failure. The least serious complications were reported as urinary system infections, superficial wound infections, deep vein thrombosis and phlebitis [12]. Our 30 days mortality was found to be 4%. There were postoperative complications in 13% of our patients. The complications that have the

most 30 days mortality were ARDS, myocardial infarction, anastomosis leakage, pulmonary embolism, intestinal ischemia. Major morbidity was found to be a negative prognostic factor.

Adenocancer resembles about 90% of CRCs. Some subtypes has worse prognosis compared to classical type adenocarcinoma. Nearly 10–30% of the CRC patients have the diagnosis of mucinous adenocarcinoma. Signet ring carcinoma resembles 1%. Mucinous and signet ring carcinomas are represented with more advanced stage [6, 13, 14]. There are studies suggesting the signet ring subtype to be more aggressive than mucinous type. Distant organ metastases are more frequent and appear earlier in these types of tumors [22, 23]. Indifferentiated cancers resemble about 1% and have poorer prognosis than typical adenocarcinomas [6, 13]. In our study 14,1% of the patients had mucinous adenocarcinoma, 2,2% had signet ring carcinoma and 1,3% had indifferentiated cancer. Seventy percent of mucinous and all of signet ring carcinomas were classified as Dukes' C and D. Similar as stated in the literature, we found out that mucinous cancers, signet ring cancers and indifferentiated cancers had poor outcomes than the typical adenocarcinoma.

Data available in the literature for primary tumor size and prognosis is not reliable. There was no correlation found between tumor size and lymph node metastasis in studies. There was no significance for prognosis found in these studies researching the correlation between tumor size and survival [11, 14]. The tumor size was 1 to 10 cm in 95% of our patients. The survival was decreasing as the tumor size increased, but there was no difference in survival of tumors of 6–10 cm and 11–15 cm in size. Eight percent of our patients having 1–5 cm tumors were classified as Dukes' A, 39% as Dukes' B, 36% as Dukes' C and 17% as Dukes' D. Three percent of the patients with 6–10 cm tumors were classified as Dukes' A, 23% as Dukes' B, 38% as Dukes' C and 36% as Dukes' D. All of the patients bearing 11–15 and 16–20 cm sized tumors were classified as Dukes' C and D. This data suggests that the stage increases with the tumor size. Although results of our study are not similar to other reports, we believe that tumor size is a negative prognostic factor.

Lymphatic invasion is still one of the prognostic factors affecting survival. The rationale for cure decreases with increasing number of involved nodes, nodal invasion of the nodes running along the major vascular structures and the nodes placed in the origin of the main vasculature. Five years survival of the patients with more than 4 involved nodes is reported as 6%, while patients with less than 4 nodes has a survival of 44% [6, 11]. In our study 53,1% of our patients had no nodal invasion. 26,6% had less than 4 involved nodes and 20,3% had more than 4 involved nodes. The 5 years survival in these patients was 58% 38% and 5%, respectively. Conclusively the survival seems to decrease as the lymph node involvement increases.

Invasion of the extramural veins in the perirectal and pericolic areas is obviously related with poor prognosis and presence of perineural invasion is related with higher recurrence rates and lower survival rates. Venous and perineural invasion are found to be negative prognostic factors in some multivariable studies [6, 11]. Fifty-six percent of our patients had venous and perineural invasion and survival times of the patients with invasion were significantly shorter than the patients without invasion.

Dukes' classification remains the most used classification in CRC, because of its simpleness. The lowest and the highest survival rates reported in the literature is 81–100% for Dukes' A, 45–78% Dukes' B, 15–43% in Dukes' C, and 0–10% in Dukes' D [6, 11, 24]. When our data was analyzed, the rate of Dukes' A and B patients was found to be lower than it is was reported in literature, but 5 years survival rates were similar to the literature. We are hoping that our early diagnosis ratios will increase with the increasing socioeconomic level of our country. In our study we found out that, as stated similarly in the literature, the most important prognostic factor is clinicopathologic staging.

Recently, it is accepted that the survival in CRC is affected from local recurrence and treatment modalities [25]. Eleven percent of our patients had local recurrence. The average survival time of these patients was 48 months and 5 years survival rate was 25%. In our study we found out that survival time of the patients without local recurrence was longer than the patients with local recurrence. Thirty-five percent of resectable patients are expected to have local recurrence or distant metastases. Survival time significantly shortens in the patients with distant metastases [6]. Nearly 30% of our patients had distant metastases during the postoperative period. The survival time of patients without distant metastases was found to be longer than patients with distant metastases.

To conclude; age, presence of comorbidity, weight loss, emergency admission, high serum CEA and CA 19–9 levels, neighboring organ invasion, operation type, major morbidity, tumor size and type, lymph node metastases, venous and perineural invasion, Duke's classification, local recurrence and distant metastases during follow-up are found to be significant negative factors affecting prognosis of the CRC patient. Since our understanding of factors that have an impact on prognosis increases, we are hoping to improve survival.

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