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Cross Analysis of Recurrent Types after Radical Resection of Colorectal Carcinoma

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OBJECTIVE To provide the evidence of predicting and preventing the postoperative recurrence by investigating the relationship between the recurring types of colorectal carcinoma (CRC) after radical resection and clinicopathologic factors.
METHODS Data from 464 CRC patients in stage I-III, who were admitted to our hospital during a period from January 1998 to December 2002 and underwent radical surgery, were collected, and retrospective analysis of the clinicopathologic data from 90 out of the 464 CRC patients, who developed postoperative recurrence was conducted. The 90 patients were divided into 2 groups based on the recurrence time (RT). Those with a RT of ≤ 30 months were classified into the early recurrence (ER) group and those with RT of > 30 months were classified into late recurrence (LR) group. The χ^2 test was used for univariate analysis, and binomial logistic regression analysis for multivariate analysis.
RESULTS There were 78 patients (86%) in the ER group and 12 (14%) in the LR group. The median recurrence time (MRT) was 35.1 months, 13.6 months, and 12.9 months in CRC patients with stage-I, stage-II and stage-III, respectively. There were significant differences in RT among the groups (P = 0.001). In the 90 patients, the MRT was 17.4 months. The median time (MT) was 16.9 months in patients with regional recurrence, 13.3 months in patients with single recurrence, and 7.7 months in patients with multiple metastases. Univariate analysis indicated that the depth of tumor infiltration, the number of positive lymph nodes, and the macroscopic types of the primary tumor were the factors affecting the relapse of the tumor. The multivariate analysis revealed that the depth of tumor infiltration was the independent factor affecting the time of ER (P = 0.049).
CONCLUSION Most of CRC patients receiving radical surgery for colorectal cancer occur recurrence within 30 months after the first operation, nevertheless, LR occurs in some CRC patients over 30 months after the surgery. The time interval varies in different types of recurrence. Distant metastasis is seen mainly in the cases with postoperative ER, and regional recurrence in the cases with LR. The depth of tumor infiltration is an independent predictor affecting the postoperative RT of CRC, and the tumor infiltration into, or beyond the seromembranous layer is considered as independent factor affecting the ER of CRC.

KEY WORDS: colorectal neoplasms, digestive system surgical procedures,recurrence.

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Introduction

Colorectal carcinoma (CRC) is one of the most common malignant digestive tract tumors, with morbidity and mortality rates in both the males and females ranking the third in the world[1]. The 5-year survival rate of the patients remains about 34%-65%[2], and the postoperative recurrence is the major cause of death in these patients. A meta-analysis[3] indicated that, with CRC patients in stage-II and III, the postoperative 5-year disease-free survival rates were respectively 55% and 67% in the groups of the simple surgery and the surgery plus adjuvant chemotherapy. This showed a rather high postoperative recurrence rate regardless of whether, or not there was postoperative chemotherapy. Most of the CRC relapses occurred within 5 years after surgery[4], among which 80% of the relapses occurred in 2 years following surgery, and 90% of them developed recurrence within 4 years postoperatively[5]. It remains controversial in present studies on the types of the postoperative recurrence in CRC patients, including how the time and site of the recurrence affect the prognosis of these patients[6]. However, at present, most authors believe that[7-11] early recurrence (ER) is a predictor of an unfavorable prognosis. The aim of this cross-check analysis is to investigate the clinicopathologic factors, which are related to the recurrence type of CRC.

Materials and Methods

Clinical data

A total of 464 CRC patients in stage-I to III, who underwent radical resection of colorectal cancer in the PLA General Hospital in Beijing during a period from January 1, 1998 to December 31, 2006, were selected and their case histories were used to set up a database. Among the selected patients, 90 with postoperative recurrence were analyzed. The standard of the tumor staging was based on the manual of TNM staging of the cancer developed by the American Joint Committee for Cancer (AJCC) in 2002. The inclusion criteria included that the patients received radical resection of colorectal cancer and occurring postoperative recurrence and metastasis were conformed. The exclusion criteria included the followings, i.e., patients with cancer of anal canal, case with preoperative radiotherapy and chemotherapy, cases with the canceration of familial polyposis, and inflammatory bowel diseases. In the 90 patients, 67 were male and 23 female, and their mean age was 58 ranging from 28 to 85 years. Among these patients, 4 of them were in stage-I, 26 in stage-II, and 60 in stage-III.

Definition of the recurrence types

The category of recurrence in our study meant that the recurrent cancer was secondary to the primary cancer after radical surgery of CRC, including metastatic carcinoma, such as liver, lung, and bone metastasis etc., and local recurrence (RR). The recurrence had to be confirmed by at least one of the following examinations: pathology, CT, MRI, type-B ultrasonic, and X-ray, etc. In all the examinations, pathologic diagnosis was regarded as the gold standard, which included for example surgical, biopsy and body-fluid cytological examinations. The imaging diagnosis required several imaging examinations to verify the progression of tumor. The "RR" here indicated the recurrence occurring in the abdomino-pelvic areas, apart from distant metastasis to other organs in the body, including the anastomotic stoma, abdomino-pelvic peritoneum, retroperitoneum, uterine appendages, and the surgery incision, in which the retroperitoneal relapse involved the recurrence in the retroperitoneal lymph cells and the organs, as well as the tumor bed. "Single metastasis (SM)" was the distant metastasis (DM) to a single organ, such as SM in liver or in lung etc., while the "multiple metastases (MM)" was the metastases to 2 or more other distant organs, or the RR and DM occurred progressively within a month. The recurrence time (RT) $\leq$ 30 months was defined as ER, and that > 30 months was defined as late recurrence (LR).

Statistical analysis

The statistical description and analysis were conducted using SPSS15.0 software, with the P value of < 0.05 being regarded as statistically significant. The χ^2 test was used for the univariate analysis, and the binomial logistic regression analysis for multivariate analysis.

Results

Analysis of recurrence sites

All 90 cases in the study were confirmed to have recurrence, among which RR occurred in 41/90 cases (45.6%), SM in 33/90 (36.7%), and MM in 16/90 (17.8%). In these cases, hepatic metastasis was found in 17 cases, pulmonary in 10, osseous in 7, the renal in 2, the adrenal in 3, distal lymphatic in 2, brain in 1, and spinal metastasis in 1.

Analysis of the time when different recurrence types occurred

In our data, 78 was the ER cases (86%) and 12 the LR (14%). Fig.1 shows that there was a sharp rise of the cumulative relapse frequencies (CRF) within 30 months. Then, the CRF change gradually became stable 30 months later. The median recurrence time (MRT) was 17.4 months in the 90 patients, in which the median time (MT) of RR was 16.9 months (0.8-82.1 months), the MT of SM 13.3 months (1.4-59.7 months) and the MT of MM 7.7 months (3.3-29.3 months). There were statistical differences in the RT among the 3 groups (P = 0.018). It was found, after a multiple comparison, that

there were statistically significant differences in the time of relapse between the RR and MM groups ($P = 0.009$), i.e., the time of MM was obviously earlier than that of RR. The MRT of CRC patients in stage-I was 35.1 months, and that of CRC patients in stage-II and III was respectively 13.6 months and 12.9 months, showing the significant differences in the RT among the groups ($P = 0.001$).

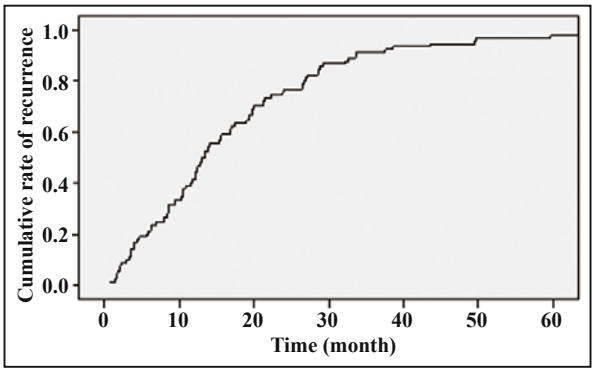

Fig.1. Relationship between the cumulative relapse frequencies and the corresponding time.

Univariate analysis of factors influencing RT

It was found after the univariate analysis that infiltration depth of the primary tumor, number of metastatic nodes, and macroscopic types of the tumor correlated with the RT ($P < 0.05$), see Table 1. However, age and gender of the patients, tumor sites, differentiation degree of the tumor, preoperative S-CEA level, and whether or not postoperative chemotherapy being applied didn't cause significant differences in the RT of CRC patients ($P > 0.05$).

Multivariate analysis of influencing factors of RT

The binomial logistic regression analysis was used in multivariate analysis. The inclusion criterion of the variables was 0.05, and exclusion criterion was 0.1. It was shown in the analysis of the above 3 significant univariates that the depth of tumor infiltration was an independent factor affecting the RT, and tumor infiltration to seromembranous layer and to extramembranous was the independent correlation factor in the ER of CRC ($P = 0.049$).

Table 1. Comparison of clinicopathologic factors between the ER and LR groups.

Factors	ER $n = 78$ (%)	LR $n = 12$ (%)	P
Sex			
Male	60 (66.7)	7 (7.8)	0.17
Female	18 (20.0)	5 (5.6)	
Age (years)			
≤ 40	10 (11.1)	3 (3.3)	0.54
40-60	27 (30.0)	3 (3.3)	
≥ 60	41 (45.6)	6 (6.7)	
Site of primary tumor			
Proximal colon	15 (16.7)	3 (3.3)	0.45
Distal colon	19 (21.1)	1 (1.1)	
Rectum	44 (48.9)	8 (8.9)	
Tumor size (max) (cm)			
≤ 5	52 (57.8)	5 (5.6)	0.09
> 5	26 (28.9)	7 (7.8)	
Differentiation degree			
Well-differentiated	52 (57.8)	6 (6.7)	0.26
Poorly differentiated	26 (28.9)	6 (6.7)	
pT			
pT1 + pT2	8 (8.9)	4 (4.4)	0.029
pT3+ pT4	70 (77.8)	8 (8.9)	
pN			
pN0	23 (25.6)	7 (7.8)	0.048
pN1+ pN2	55 (61.1)	5 (5.6)	
Macroscopic types			
Protrude type	10 (11.1)	6 (6.7)	
Ulcerative type	55 (61.1)	4 (4.4)	0.008
Ulcer-protrude type	7 (7.8)	2 (2.2)	
Infiltrating type	6 (6.7)	0 (0)	
Vascular cancer embolus			
Found	6 (6.7)	1 (1.1)	0.93
Not found	72 (86.7)	11 (12.2)	
Preoperative S-CEA (ng/ml)			
≤ 5	36 (45.0)	3 (3.8)	0.32
> 5	35 (43.8)	6 (7.5)	
Postoperative adjuvant chemotherapy			
Yes	61 (68.5)	7(7.9)	0.28
No	17 (19.1)	4 (4.5)	

Discussion

Recurrence is the most important factor influencing the postoperative survival rate of CRC[12], and various recurrence time and types have considerable effect on the prognosis of the CRC patients. Kaiser et al.[13] found, after their analysis of the 212 CRC patients with relapse, that the earlier the relapse was, especially with a RT interval of less than 12 months or with a distant metastasis, the poorer the prognosis would be. Also, the RT was not affected by postoperative adjuvant chemotherapy. After a retrospective analysis, Weiser et al.[14] found that the site and type of the CRC recurrence could directly affect the post-recurrent reoperation rate and, as a result, affect the overall survival time of the patients. Concerning the RR in a single site, especially the relapse at the anastomotic stoma, the achievement ratio of salvage radical surgery is high. Therefore, effectively improve the survival rate of the CRC patients with recurrence. Some authors[15] conducted an investigation in the cancer of colon patients who underwent a salvage excision of

liver metastasis via follow-up. Their findings also demonstrate the feature that the earlier the RT is, the poorer the prognosis.

Clinically, the difference in the tumor RT among the groups not only includes the frequency of the follow-up, but also various mechanisms of the tumor relapse. It was shown in our data that the MRT of tumor was 17.4 months. There was a sharp rise of the CRF within 30 months. Then, the CRF change gradually became stable 30 months later. Concurrently, the RT is related to the staging of primary tumor, i.e., the earlier the staging of the tumor, the later is the recurrence. The MRT of CRC patients in stage-I, II and III was respectively 35.1, 13.6 and 12.9 months. Chmielarz et al.[16] confirmed the above-mentioned points of view in their study. Our multivariate analysis has also revealed that "ER" is mainly in relation to the depth of tumor infiltration, which agrees without prior consultation to the findings of quite a few authors[17-19]. Greene et al.[20] analyzed the survival status of over 50000 CRC patients in stage-III reported by AJCC and UICC during the year 1987-1993. It was found in their analysis that stage-III CRC was divided into the stage-IIIA, IIIB and IIIC, and the 5-year survival rates in these sub-stages were respectively 59.8%, 42%, and 27.3%. The differences in the survival rates among the sub-stages were statistically significant. It was mentioned in the 2002 TNM Staging (6th Ed) that as the depth of tumor infiltration was considered an important prognostic indicator equal in importance to metastatic lymph nodes. Therefore, the previously defined stage-II and stage-III have been subdivided respectively into stage-IIA and IIB, and into stage-IIIA, IIIB and IIIC. We also found in our study that the RT was apparently related to the relapse type, where the DM mainly occurred in ER, and RR mainly occurred in late recurrence. That is why ER indicates unfavorable prognosis. Liang et al.[21] found, after a retrospective analysis of 692 CRC patients who underwent the radical surgery that the depth of tumor infiltration was the key prognostic factor of postoperative DM, which was in accord with the conclusion of our study. Yonenaga et al.[22] believed that the metastasis of CRC correlated to the tumor angiogenesis, and profuse blood vessels could increase the opportunity for tumor cells to break into circulatory system, especially when the vessels in the sub-serous layer was invaded. Therefore, DM, especially the hematogenous metastasis, correlates to the depth of invasion in intestinal wall. We propose based on the above ideas that the main reason of "ER" is because there is remaining tumor tissues that has not been completely removed in surgery, or the metastasis was not found during the surgery, where the residual cancer cells continue to proliferate postoperatively. That is, "ER" can only be regarded as the residue, and surgery as a palliative resection. "LR" is the true recurrence and most of them result from an intraoperative pressurization and a stimulus on the tumor, which causes the cancer cells to break away from its primary site. It has been revealed in some studies that the regimen of current adjuvant chemotherapy has limited lethal effect on the residual tumors, and these cancer nests are the major reason of "ER". It is well known that the growth of tumor meet the Gompertzian curve[23], that is, there is a rapid tumor cell proliferation at the initial phase of tumor growth. The speed of the cell proliferation slows down after reaching a definite volume, which is in relation to the factors, such as control of cell proliferation and apoptosis etc. Based on this, Norton et al.[24] put forward the hypothesis of Norton-Simon intensive dosage. The basis of this hypothesis is that after chemotherapy, the speed of tumor volume shrinking is directly proportional to that of the tumor re-growth. This means that before chemotherapy, the smaller the tumor load, the stronger is the logarithm lethal effect.

However, if the cancer cells are not completely removed, the speed of tumor cell re-growth compared to that of the original tumor size is faster, i.e., the speed of the growth of residual tumor cells accelerate. This hypothesis requires the intensive therapy and shortened interval of chemotherapy, which is the dose-intensified chemotherapy. This hypothesis explains from the other hand that the current postoperative adjuvant chemotherapy may probably reduce the incidence of "LR", but limits prevention of "ER". Ni et al.[25] found after an endoscopic follow-up of 71 postoperative CRC patients, that there were 14 cases with relapse in anastomotic stoma, 5 with metachronous carcinoma, and 33 with recurrent adenoma. The authors pointed out that as the high-risk population, the opportunity of re-suffering CRC was 3 to 6 times higher in the postoperative CRC patients than in the normal persons. Therefore, concerning the postoperative CRC patients, especially some patients with the tumor recurrence but without homologous character of the clinical symptoms[26], regular enteroscopic check ups after surgery are very necessary[27]. It was reported[28] that the mean survival time was 29.9 months in the CRC patients who relapsed after the initial surgery and received salvage surgery again (6-125 months). The survival time was only 7 months in the recurrent CRC patients with natural progression of disease (4-72 months), suggesting that the reoperation can obviously extend the survival time. It was reported by Guyot et al.[29] that concerning the CRC patients with RR who underwent salvage radical operations, the 5-year survival rate was increased up to 36.1%, while the 5-year survival rate was 24.0% in the patients who received salvage radical surgery for DM after their initial surgery. If the patients failed to undergo a radical reoperation, their survival time was very limited[30]. It was shown in our study that LR occurred in 14% of the total patients. Therefore, the long-term follow-up and regular check up for the postoperative CRC patients is important for early detection of residual cancer, thus making it possible to further prolong the postoperative survival time and to improve the quality of life for CRC patients.

Conflict of interest statement

No potential conflicts of interest were disclosed.

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