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# Impact of Primary Tumor Site on the Prognosis in T4 Colorectal Cancer Patients

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## Abstract

**Objective:** To retrospectively analyze the prognostic differences between LCC and RCC, and to explore the occurrence of such differences in the relevant factors. Provide clinical basis for the individualization and precise treatment of CRC. **Methods:** The clinical and follow-up data of 155 T4 CRC patients who underwent surgery in the first Affiliated Hospital of Sun Yat-sen University between August, 1994 and December, 2005. The age, sex, family history, staging, pathologic features, DFS, OS and other information were collected. The survival of the LCC (Left colon cancer) and RCC (Right colon cancer) patients was analyzed by Kaplan-Meier method. The survival curves of the LCC and RCC patients were compared by log-rank test. **Results:** There are statistically significant differences in N stage, CCR, family history and histological grade between two groups. Gender, histological grade and CCR were factors associated with OS and DFS of the T4 LCC according to the univariate and multivariate analyses. In addition, only the CCR was found to be the factor associated with OS and DFS of the T4 RCC. The mean survival of the patients was 104.23 months (range, 87.32 - 121.15 months) in the T4 RCC and 76.96 months (range, 61.32 - 92.60 months) in the T4 LCC groups. The complete cytoreduction had significant survival benefit than the palliative surgery group. **Conclusion:** The T4 RCC patients with CCR had a relatively better prognosis than LCC. Compared with palliative surgery, the incomplete cytoreduction fails to improve the prognosis of patient.

*These authors have contributed equally to this work and should be jointly regarded the first.

**Keywords**

Colorectal Cancer, Surgery, Prognosis

## 1. Background

Colorectal cancer (CRC) is one of the most common malignant tumors in the world, with high mortality [1]. There are about 10% - 20% of patients with CRC with locally advanced disease, such as T4a and T4b [2]. T4 colon cancers have a significantly higher risk of peritoneal carcinomatosis (PC), which is the only metastatic site in some patients. The mean overall survival (OS) of T4 CRC is 12 - 15 months [3]. It can be a major histopathological indicator of poor prognosis in stage II and stage III cancer. The survival of patients has improved because of the multiple treatment strategies including perioperative chemotherapy and surgery.

A lot of studies associated with the difference between LCC and RCC from epidemiology, pathology and molecular genetics have been reported. In addition, for the difference of T4 left colon cancer (LCC) and left colon cancer (RCC), there are a few literatures that report the related problems, one of which found that the 5-year DFS, OS of pT4 RCC, LCC were 59.2% and 70.0% vs 61.1% and 71.8% [4]. However, some limitations existed, including heterogeneous populations, with a relatively small sample of T4 CRC patients.

The background knowledge was the impetus for this study which aimed to analyze the clinical data and survival of T4 CRC patients with different tumor site, and to explore the influence of different surgical methods and clinicopathological factors on the prognosis of patients with T4 CRC.

## 2. Materials and Methods

### General information

A retrospective analysis of 155 patients with operative treatment of T4 CRC patients who underwent surgery at the first Affiliated Hospital of Sun Yat-sen University between August, 1994 and December, 2005. Patients were divided in two groups: LCC group and RCC group. The age, sex, family history, staging, pathologic features, disease-free survival (DFS), overall survival time (OS) and other information were collected through medical records. Additionally, comparison of the effects of different surgical procedures on the prognosis of patients was done.

All patients and their families gave informed consent to the study and signed informed consent. The study was approved by the Ethics Committee of Sun Yat-sen University.

### Follow-up and review

The patients were followed up every 3 months for the first year, 6-monthly for the next 2 years and yearly after surgery. The first review was performed at the

hospital one month after the operation. Routine review of chest and abdomen CT, blood routine, liver and kidney function, tumor markers, colonoscopy and other examinations, if necessary, whole body bone scan and PET-CT to see if there is systemic metastasis.

**Statistics method**

Using SPSS 17.0 software, Kaplan-Meier method was used to calculate OS, DFS and Log-rank method was used to test; Cox model was used for single factor and multifactor analysis, and $\chi^2$ test was used to analyze the effect of different treatment methods on survival rate. $P < 0.05$ was considered statistically significant.

## 3. Results

**Patients and tumor characteristics**

We've selected 155 cases of CRC patients out of 2948 patients, which accounted for 5.2% of all patients. Among them, there were 74 cases of LCC patients and 81 cases of RCC patients, which accounted for 2.50% and 2.70% of all patients respectively. The demographic and pathological characteristics of CRC are summarized in Table 1. The mean age of LCC and RCC patients was 57.18 months (range, 22 - 83 months) and 61.55 months (range, 19 - 87 months), respectively. There are statistically significant differences in N stage, CCR, family history and histological grade between two groups.

**Survival**

The mean survival of the patients was 104.23 months (range, 87.32 - 121.15 months) in the RCC and 76.96 months (range, 61.32 - 92.60 months) in the LCC groups ($P < 0.05$). We also observed that gender, histological grade and CCR were factors associated with OS and DFS of the LCC according to the univariate and multivariate analyses. However, certain factors, including age, PC, histological grade, N stage, family history and liver metastasis, were not found to affect survival of the LCC (Table 2, Table 3). In addition, only the CCR was found to be the factor associated with OS and DFS of the RCC according to the univariate and multivariate analyses (Table 4, Table 5).

Table 1. Characteristics on demographics, operations, and pathology in 155 patients of T4 CRC.

| Characteristics | Cases | T4 | | P |
|---|---|---|---|---|
| | | LCC | RCC | |
| Gender | | | | 0.175 |
| Female | 61 | 25 | 36 | |
| Male | 94 | 49 | 45 | |
| Age (years)[a] | | | | 0.082 |
| ≥65 | 57 | 22 | 35 | |
| <65 | 98 | 52 | 46 | |
| CCR | | | | 0.642 |
| No | 25 | 13 | 12 | |
| Yes | 130 | 61 | 69 | |

**Continued**

| | | | | |
|---|---|---|---|---|
| Histological grade | | | | 0.899 |
| Well + Moderately | 118 | 56 | 62 | |
| Poorly | 37 | 18 | 19 | |
| Family history | | | | 0.038 |
| No | 145 | 68 | 65 | |
| Yes | 10 | 6 | 16 | |
| Liver metastasis | | | | 0.098 |
| No | 135 | 61 | 74 | |
| Yes | 20 | 13 | 7 | |
| PC | | | | |
| No | 137 | 66 | 71 | 0.766 |
| Yes | 18 | 8 | 10 | |
| BMI | | | | |
| ≥25 | 104 | 53 | 51 | 0.252 |
| <25 | 51 | 21 | 30 | |

[a]Patients were divided according to the median values of age.

**Table 2.** Cox proportional hazards model univariate and multivariate analyses of individual parameters for correlations with overall survival (OS) variable of T4 LCC patients.

| Variable | Univariate analysis | | Multivariate analysis | | P |
|---|---|---|---|---|---|
| | 10 year-OS | P-value | HR | CL (95%) | |
| Gender | | 0.015 | | | 0.013 |
| Female | 20.0 | | 1 | | |
| Male | 40.3 | | 2.152 | 1.180 - 3.961 | |
| Age (y) | | 0.279 | | | |
| ≥65 | 23.8 | | | | |
| <65 | 40.2 | | | | |
| PC | | 0.758 | | | |
| No | 38.5 | | | | |
| Yes | 31.7 | | | | |
| Histological grade | | 0.001 | | | 0.000 |
| Well + Moderately | 39.1 | | 1 | | |
| Poorly | 16.7 | | 3.611 | 1.873 - 6.963 | |
| CCR | | 0.005 | | | 0.003 |
| No | 35.8 | | 1 | | |
| Yes | 16.7 | | 3.724 | 1.764 - 7.862 | |
| Family history | | 0.970 | | | |
| No | 35.5 | | | | |
| Yes | 33.3 | | | | |
| Liver metastasis | | 0.062 | | | |
| No | 37.8 | | | | |
| Yes | 11.1 | | | | |

**Table 3.** Cox proportional hazards model univariate and multivariate analyses of individual parameters for correlations with overall survival (OS) variable of T4 RCC patients.

| Variable | Univariate analysis | | Multivariate analysis | | P |
|---|---|---|---|---|---|
| | 10 year-OS | P-value | HR | CL (95%) | |
| Gender | | 0.398 | | | 0.310 |
| Female | 47.5 | | 1 | | |
| Male | 55.4 | | 1.424 | 0.720 - 2.815 | |
| Age (y) | | 0.034 | | | |
| ≥65 | 37.6 | | | | |
| <65 | 62.4 | | | | |
| PC | | 0.004 | | | 0.429 |
| No | 56.4 | | 1 | | |
| Yes | 20.0 | | 1.495 | 0.552 - 4.048 | |
| Histological grade | | 0.376 | | | |
| Well + Moderately | 52.9 | | | | |
| Poorly | 46.7 | | | | |
| CCR | | 0.000 | | | 0.000 |
| No | 60.0 | | 1 | | |
| Yes | 0 | | 14.965 | 3.541 - 63.257 | |
| Family history | | 0.764 | | | |
| No | 52.6 | | | | |
| Yes | 33.3 | | | | |
| Liver metastasis | | 0.000 | | | 0.712 |
| No | 56.8 | | 1 | | |
| Yes | 0 | | 1.294 | 0.330 - 5.073 | |

**Table 4.** Cox proportional hazards model univariate and multivariate analyses of individual parameters for correlations with DFS variable of T4 LCC patients.

| Variable | Univariate analysis | | Multivariate analysis | | P |
|---|---|---|---|---|---|
| | 10 year-OS | P-value | HR | CL (95%) | |
| Gender | | 0.013 | | | 0.016 |
| Female | 20.0 | | 1 | | |
| Male | 40.1 | | 2.102 | 1.115 - 3.842 | |
| Age (y) | | 0.272 | | | |
| ≥65 | 17.9 | | | | |
| <65 | 40.2 | | | | |
| PC | | 0.778 | | | |
| No | 34.2 | | | | |
| Yes | 38.5 | | | | |

**Continued**

| | | | | | |
|---|---|---|---|---|---|
| Histological grade | | 0.001 | | | 0.000 |
| Well + Moderately | 38.9 | | 1 | | |
| Poorly | 16.7 | | 3.882 | 1.982 - 7.602 | |
| CCR | | 0.036 | | | 0.008 |
| No | 23.1 | | 1 | | |
| Yes | 35.8 | | 2.942 | 1.321 - 6.551 | |
| Family history | | 0.926 | | | |
| No | 37.1 | | | | |
| Yes | 22.2 | | | | |
| Liver metastasis | | 0.044 | | | 0.102 |
| No | 32.1 | | 1 | | |
| Yes | 11.1 | | 2.060 | 0.867 - 4.896 | |

**Table 5.** Cox proportional hazards model univariate and multivariate analyses of individual parameters for correlations with DFS variable of T4 RCC patients.

| Variable | Univariate analysis | | Multivariate analysis | | P |
|---|---|---|---|---|---|
| | 10 year-OS | P-value | HR | CL (95%) | |
| Gender | | 0.399 | | | 0.390 |
| Female | 47.6 | | 1 | | |
| Male | 55.5 | | 1.355 | 0.678 - 2.706 | |
| Age (y) | | 0.032 | | | |
| ≥65 | 37.8 | | | | |
| <65 | 62.4 | | | | |
| PC | | 0.004 | | | 0.205 |
| No | 56.4 | | 1 | | |
| Yes | 20.0 | | 1.840 | 0.716 - 4.728 | |
| Histological grade | | 0.562 | | | |
| Well + Moderately | 57.8 | | | | |
| Poorly | 50.0 | | | | |
| CCR | | 0.000 | | | 0.003 |
| No | 59.1 | | 1 | | |
| Yes | 0 | | 8.450 | 2.054 - 34.755 | |
| Family history | | 0.307 | | | |
| No | 53.4 | | | | |
| Yes | 25.0 | | | | |
| Liver metastasis | | 0.000 | | | 0.154 |
| No | 56.8 | | 1 | | |
| Yes | 0 | | 2.775 | 0.682 - 11.292 | |

### Comparison of incomplete resection and palliative surgery case

The survival curves of patients with different surgical procedures in LCC and RCC were shown in Figure 1. The mean survival time were 82.0, 31.5 and 21.6 months in the LCC group, and survival rate were 36.7, 14.3 and 0 in 10nd years, and the patients in RCC group were 60.0, 0 and 0, respectively. The mean survival time of RCC were 119.2, 8.82 and 12.6 months, respectively. The above three groups of differences were statistically significant ($P < 0.001$). A pairwise comparison found that patients in the CCR group had a significant survival benefit compared with the palliative surgery group ($P < 0.05$), while patients in the incomplete resection group had no survival benefit.

## 4. Discussion

CRC is a common malignant tumor of the digestive tract. The mortality rate is ranked fourth in the world just after lung cancer, liver cancer and gastric cancer. The number of new cases and death case of CRC in China is a large cardinal and

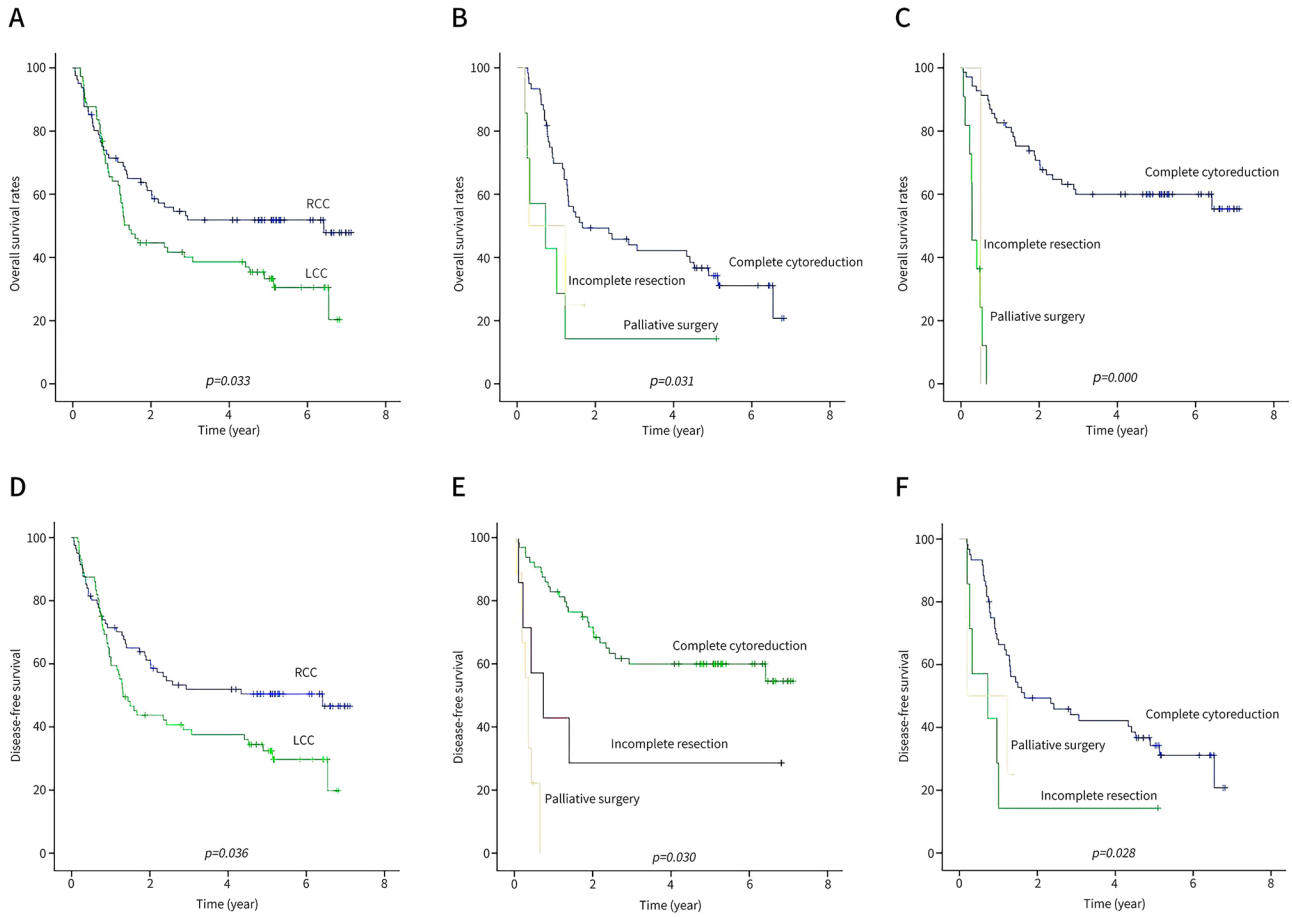


Figure 1. Survival curve for T4 CRC patients underwent different surgical procedures. (A) The OS of patients with T4 CRC in different sites after surgery. (B) The OS of patients with T4 RCC patients underwent different surgical procedures. (C) The OS of patients with T4 LCC patients underwent different surgical procedures. (D) The DFS of patients with CRC in different sites after surgery. (E) The DFS of patients with T4 RCC patients underwent different surgical procedures. (F) The DFS of patients with T4 LCC patients underwent different surgical procedures.

ranking first, accounting for 1% and 2% of the total number of cases of morbidity and occurrence in the world, respectively. As early as 1990, some study had confirmed the difference between LCC and RCC, according to the epidemiology, pathology, molecular genetics and so on. It was the first time to propose that the LCC and RCC were two distinct tumors [5].

This study analyzed the clinicopathologic data of 155 patients with CRC, and the survival analysis was done by follow-up. The CRC in males is more than females. At the same time, in terms of age, the morbidity of CRC has an aging trend, and its morbidity gradually increases with age [6]. The results of this study showed that males with colon cancer were more than females, while the incidence rate of RCC was slightly higher than LCC in women. But the P-value was not less than 0.05. So that, the statistical difference of incidence rate between the RCC and LCC does not have clearly determined, we need to increase the sample size for a further statistics. In addition, age groups were divided into ≥65 years old, and <65 years old. The results showed that there was no significant difference between LCC and RCC group. The possible reasons are as follows: 1) morbidity of colon cancer increases with age. Many studies [7] have shown that the probability of CRC incidence over 50 years old rises sharply. This may be related to changes in the diet structure, physiological function, endocrine function and internal environment homeostasis human body with the age growing into the middle age, and the definite factors need to study deeply. 2) This study was a monocentric small sample study. The lack of sample size resulted in no statistically significant results.

At the same time, the occurrence of colon cancer is related to familial inheritance factors. Among patients with a family history of cancer in close relatives, the incidence of RCC is higher than that of LCC, and the difference is statistically significant. This may be associated with hereditary nonpolyposis colorectal cancer. So, in the early screening of colon cancer, attention should be paid to screen young women with HNPCC-related tumors in primary or secondary relatives, especially those with chronic constipation, diarrhea, mental illness, positive in occult blood in stool and other clinical symptoms, who needs to be checked by colonoscopy regularly [8] [9].

In obese patients (BMI ≥ 25), LCC is higher than RCC. The difference is not statistically significant. Meyerhardt *et al.* [10] found that among the 3759 subjects, the risk of LCC of obese people increased significantly. However, the mechanism is not clear, but obesity may be a potential independent risk factor for left colonic carcinoma. At the same time, Kabat GC *et al.* [11] pointed out that obesity is also an independent risk factor for postoperative recurrence in patients with colorectal cancer. From a prognostic point of view, domestic studies have shown that for colorectal cancer, the risk of death in the thinner group (BMI < 18.5) is increased, while the risk of death in the overweight group (BMI > 24) are lower. The reason may be related to the constitution of thinner patients were better than that of obese patients at the time of diagnosis, and the tolerance of subsequent treatment such as surgery and chemotherapy are better.

There are many factors affecting the prognosis of CRC. Domestic and oversea scholars had also carried out various researches, they were believed that the main cause of colon cancer is age, sex, smoking, location, depth of invasion, lymph node metastasis, distant metastasis and degree of differentiation, etc [12] [13]. The multivariate regression analysis of this study suggests that gender, histological grade and CCR are independent risk factors for the prognosis of CRC. Combined with the differences of pathological and immunohistochemical in LCC and RCC in this study, it is believed that the recurrence and prognosis of CRC may be the comprehensive result of the interaction of several potential risk factors mentioned above.

In the 10-year OS comparison of patients with colon cancer at stage T4, the survival rate of RCC was better than that of LCC, and the difference was statistically significant. Beside the strong invasiveness and transferability of LCC, the transfer site is also an important factor. Studies have shown that the LCC is mainly metastasized to liver, lung and bone, while the RCC is more likely to metastasize to peritoneal, mesenteric and retroperitoneal [14] [15]. Differences in metastatic places lead to differences in treatment strategies and outcomes, it may be one of the reasons for their survival. In addition, patients with LCC have poor nutritional status at the primary survey. Resulting in the patients with advanced LCC is more likely to occur cachexia, so that, the survival rate is reduced.

This study found CCR was an independent factor influencing the prognosis of patients with T4 CRC patients, consistent with previous studies [16]. The results of this study also showed that the survival time of CCR group was significantly longer than incomplete resection and palliative surgery ($P < 0.05$). In addition, there is no survival benefit between the incomplete resection and palliative surgery. This finding is similar to the result of a previous study, in which patients with incomplete resection had a median survival of 5.0 months, whereas systemic chemotherapy with or without palliative surgery had a median survival of 12.6 months [17].

Our study has several limitations. One the main limitation includes the single center design and its retrospective nature which might decrease the ability to generalize the results. A second limitation is that we compares LCC with RCC from a macro perspective, the mechanism of some statistical results should to be further studied.

## 5. Conclusion

To sum up, this study showed that CCR and liver metastasis were independent factors influencing T4 CRC patients' survival with PC. Patients who performed CCR have a relative good prognosis. The incomplete cytoreduction fails to improve the prognosis of patient, compared with palliative surgery. Individualized treatment of patients can prolong their survival time and improve their quality of life.

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## Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Authors' Contributions

WC and XPT study design, data collection, data analysis and interpretation, draft of the manuscript, approval of final manuscript, supervision. JWY study design, data collection, data analysis and interpretation, draft of the manuscript, approval of final manuscript, supervision. JLL study design, data collection, data analysis and interpretation, draft of the manuscript, approval of final manuscript, supervision. MJH study design, data collection, data analysis and interpretation, revision of the manuscript, approval of final manuscript. All authors approved the final version of the manuscript.

## Ethics Approval and Consent to Participate

The study was conducted in compliance with all national and international ethical standards for research with humans. All study procedures were approved by the Research Ethics Board of the Six Affiliated Hospital, Sun Yat-sen University and patients gave written informed consent before being enrolled.

## Consent for Publication

Not applicable.

## Conflicts of Interest

The authors declare that they have no competing interests.

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## Abbreviations

CRC: Colorectal cancer;
LCC: Left colon cancer;
RCC: Right colon cancer;
PC: Peritoneal carcinomatosis:
CCR: Complete cytoreduction;
OS: Overall survival.