Original Article

Prognostic Factors for Locally Advanced Stage IV Colorectal Cancer

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Key Words
T4 colorectal cancer;
Neoadjuvant/adjuvant therapy;
Lymph node status

Purpose. The purpose of our study here was to analysis the prognosis of patients with locally advanced T4 colorectal cancer with distant metastasis, comparing those with lymph node negative and positive metastasis.
Methods. A retrospective review of patients who diagnosed with T4 colorectal cancer with distant metastasis from May 2002 to September 2018 was performed. A total 197 adult patients diagnosed with locally advanced T4 colorectal cancer with distant metastasis underwent curative surgery. Patients' demographic data, tumor stage, and follow-up data were collected for analysis.
Results. The overall survival of the lymph node negative status group is significantly better than N-positive status groups ($p = 0.0049$). The overall survival of the neoadjuvant/adjuvant group is significantly better than no curative operation group. The disease-free rate of adjuvant groups is slightly better than neoadjuvant groups ($p = 0.027$).
Conclusions. The prognosis of T4 colorectal cancer with distant metastasis is poor with high probability of recurrence and a dramatic reduction in OS. Based on our data for locally advanced stage IV colorectal cancer, patients in the N0 status group have a significantly better OS rate than in the N-positive status group.
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Colorectal cancer is the third most common cancer worldwide, with more than 1.8 million new cases estimated to have been diagnosed in 2018 alone.[1] It is also the second most frequent cause of cancer death, with 881,000 deaths estimated to have occurred in 2018.[1] In Taiwan, colorectal cancer is the most-frequently diagnosed malignancy among all cancers and represents the third leading cause of cancer-related deaths. The prognosis of patients with colorectal cancer depends mainly on tumor stage at diagnosis. The 5-year survival rate for stage I and II (localized disease) is 90%; whereas it is 71% in stage III (regional metastasis), and only 14% in stage IV (distant metastatic disease).[2]

T4 colorectal cancer is characterized by penetration of the visceral peritoneum (T4a), direct invasion by the tumor cells into adjacent organs, or tumor cells, which are histologically adherent to other organs/structures (T4b).[3] Several factors may be responsible for the poor prognosis of T4 colorectal tumors: the high incidence of lymph node metastasis, increased risk of distant metastasis, and local extension toward neighboring organs or structures, all of which may result in inoperable tumors.[5-8] The incidence of the T4 colorectal cancer is around 5%-8.8% of cases; among the advanced resected cases the incidence of T4 tu-

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mors is as high as 21%-43%.[4] The treatment choice colorectal surgeons face for T4 colorectal cancer is somewhat challenging because the adhesions between the cancer and the adjacent tissue have an unacceptably high risk of being malignant and the intraoperative assessment of the nature of adhesions is often inaccurate.[9]

Lymph node positivity affects the prognosis of T4 colorectal cancer. Gunderson et al.[10] reported that 5-year overall survival rates with lymph node metastases are poor, ranging from 55.0% for T4N0 (no lymph nodes involved), 39.6% for T4N1 (1 to 3 lymph nodes positive), and 21.7% for T4N2 (4 to 6 lymph nodes positive). The existence of metastatic lymph nodes represents a step toward systemic tumor spread and it is therefore a strong indicator of poor prognosis.[11] An adequate number of lymph nodes harvested is an important factor for the proper staging and subsequent therapy choices for colorectal cancer.[12]

For the purposes of this study, we analyzed the prognosis of patients in our hospital with locally advanced T4 colorectal cancer with distant metastasis, comparing those with lymph node negative (N-0) and positive (N-positive) metastases. We also compared the prognosis for those patients who only received adjuvant therapy against that for patients who received both neoadjuvant plus adjuvant therapy.

Materials and Methods

Patient selection

In this retrospective study, we collected data from the databank of National Chang Kung University Hospital for patients selected from a total 6481 patients diagnosed with colorectal cancer between May 2002 and September 2018. Locally advanced colorectal cancer was defined as T4 tumors, including T4a and T4b. The number of cases diagnosed as being in the pathologic tumor stage T4 was 735. Only 254 patients with distant metastasis were noted in the databank.

Determination of the final number of lymph nodes was based exclusively on the final pathological report. All specimens were examined by the Pathology Department according to the 7th edition of the AJCC TNM classification. Lymph node metastases were identified by hematoxylin and eosin staining. Tumors located from the transverse colon to the cecum were defined as right-sided cancer, while tumors originating from the sigmoid colon to the left colonic flexure were defined as left-sided cancers.

Exclusion criteria were as follows: patients aged < 18 years, patients who did not undergo surgery to the primary lesion or only received palliative surgery, and patients who did not receive neoadjuvant and adjuvant therapy. Finally, a total 197 adult patients diagnosed with locally advanced T4 colorectal cancer with distant metastasis underwent curative surgery.

Data collection and outcome measures

Data collected included patient demographics comprising age, gender, and body mass index. Perioperative data collected included the carcinoembryonic antigen level when diagnosed or before operation, the location of the primary tumor, the size of the primary tumor, the site of distant metastasis at initial presentation, the TNM stage of the case, the procedure performed, the number of harvested lymph nodes, the status of surgical margins, the length of follow-up, vital status, and the use of neoadjuvant or adjuvant chemotherapy. The date of diagnosis was defined as the date of the first histological confirmation of malignancy, most often the day of endoscopic biopsy.

Overall survival (OS) was defined as the survival interval from the time of cancer diagnosis to the time of death, recorded under vital status in the databank of the NCKUH. Disease-free survival was defined as the time from diagnosis to recurrence of tumor or death.

Statistical analysis

A descriptive statistical analysis was performed for all variables, where the confidence interval of 95% was defined as $p < 0.05$. Patient characteristics were summarized using median (interquartile range (IQR)) and frequency (percentage) for continuous and categorical variables, respectively. The X^2-test, an independent t test, Kruskal-Wallis Test and Kaplan-Meier

curves were selectively used to study qualitative/quantitative variables and survival curves. The analyses were performed using the MedCalc Statistical Software version 19.1.6 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020).

Results

Table 1 represents the descriptive statistics of demographic and clinical features of these patients. A total of 197 adult patients, diagnosed with locally advanced T4 colorectal cancer with distant metastasis, underwent curative surgery. Of those, 36 patients received neoadjuvant therapy and 161 patients received adjuvant therapy. We divided them into four groups: group A included patients who received neoadjuvant therapy with lymph node status negative (N0). Group B included patients who received neoadjuvant therapy with lymph node status positive (N-positive). Group C included patients who received adjuvant therapy with lymph status negative. Group D included patients who received adjuvant therapy with lymph node status positive. We selected a further 150 patients who were also clinically diagnosed with locally advanced T4 colorectal cancer with distant metastasis, but did not undergo curative surgery. These patients were defined as group E. All treatment plan of these patient would undergo discussion by our Multidisciplinary team conference. The members of Multidisciplinary team included colorectal surgeon, hepatobiliary surgeon, chest surgeon, radiologist, oncologist and radiation oncologist. If assessment of locally advanced colorectal patients with metastasis is not suitable for operation, neoadjuvant therapy would be arranged.

Age was not significantly different between each group, median ages in group A to D were 49, 58, 53, and 58 ($p = 0.186$), respectively. Slightly more than half of the patients were men (50.8%), but there was

Table 1. Demographic and clinical characteristics of locally advanced stage IV colorectal cancer

	Group A	Group B	Group C	Group D	*p* value
Number	8	28	19	142	
Age*	49 (41-54)	58 (48-62)	53 (49-59)	58 (47-69.75)	0.186
Male	5 (62.5%)	12 (42.9%)	10 (52.6%)	73 (51.4%)	0.755
Survival time (months)*	20.8 (14.6-23.1)	19.0 (13.9-28.3)	42.0 (26.3-57)	21.4 (12.0-29.5)	0.00039
Tumor size (cm)*	5 (4.85-8)	4 (3.38-5.75)	4.8 (3-9)	5 (4-7)	0.358
Tumor location					0.06
Right-side colon	3	10	5	59	
Left-side colon	1	8	8	60	
Rectum	4	10	6	23	
Radial margin free	100%	84%	88.9%	91.9%	0.434
Initial metastasis location					0.156
Liver	4	21	5	71	
Lung	3	4	1	18	
Peritoneum	2	8	12	59	
Ovary, uterus	1	1	3	21	
Others	2	8	4	43	
CEA elevated at diagnosed					0.61
Normal (CEA < 5)	37.5%	37.5%	21.4%	26.2%	
Elevated (CEA > 5)	62.5%	62.5%	78.6%	73.8%	
Chemotherapy regimen					0.443
FOLFOX	5 (62.5%)	9 (32.1%)	7 (36.8%)	46 (32.4%)	
FOLFIRI	3 (37.5%)	17 (60.7%)	10 (52.6%)	86 (60.6%)	
Others	0	2 (7.1%)	2 (10.5%)	10 (7.0%)	
Recurrence	3 (37.5%)	13 (46.4%)	11 (57.9%)	47 (33.1%)	0.139

* Median (IQR); IQR, interquartile range.

no difference between the gender distributions in each group, $p = 0.755$. The percentage of tumor location was 39.1%, 39.1%, and 21.8% in right-side colon, left-side colon, and rectum, respectively. The patients in the neoadjuvant groups (group A and group B) had significantly more tumors located in the rectum than the adjuvant group (38.9% vs. 28.0%, $p = 0.006$). The patients in the adjuvant group had slightly more tumors located in the left-side colon than the neoadjuvant group (42.3% vs. 25%, $p = 0.054$). The rate of CEA elevation before operation was 71.5%. There was no difference in the proportion of CEA elevation in group A to D, $p = 0.61$. The regimen of chemotherapy included FOLFOX, FOLFIRI, and others. A total of 67 patients (34%) received FOLFOX and 116 patients (58.9%) received FOLFIRI. The distribution of these treatments within the neoadjuvant group was 38.9% FOLFOX and 55.6% FOLFIRI, whereas within the adjuvant group it was 32.9% FOLFOX and 59.6% FOLFIRI. There was no difference in chemotherapy regimen for each group.

All patients in four groups received colon tumor resection; there are 95 patients (48.2%) that received metastasis lesion excision. Among the neoadjuvant group, 21 patients (58.3%) received metastatic lesion excision, and 74 patients (46.0%) received metastatic lesion excision in adjuvant group. There is no statistically significant difference between two groups, p valve = 0.18. The patient who didn't receive metastatic lesion excision had kept post-operative adjuvant chemotherapy.

The mean rate of whole cancer-free radial margins was 90.8%, and did not differ significantly between groups ($p = 0.434$). The median number of lymph nodes examined in each group were 13, 17, 17, and 19, respectively. The rate of harvested lymph nodes > 12 in each group was not significantly different: 75%, 78.6%, 73.7%, and 90.1% ($p = 0.086$), respectively. The most common sites of distant metastasis in these patients were: liver (51.3%), peritoneum (41.1%), ovary and uterus (13.7%). The proportion of liver metastasis in the neoadjuvant group was significantly greater than in the adjuvant group (69.4% vs. 47.2%, $p = 0.016$). There are a total 36 patients in neoadjuvant groups, 3 patients (8.3%) didn't complete adjuvant therapy. One patient refused post-operative adjuvant therapy; and the other 2 patients did not complete adjuvant chemotherapy due to mortality during chemotherapy.

The OS of each group is summarized in Fig. 1 to Fig. 4. The median survival time of groups A-D differed significantly: 19.6, 19.0, 42.0, and 21.4 months ($p = 0.00039$), respectively. The median survival time in group C is significantly longer than in the other groups, and the OS of group C is significantly better than other groups (Fig. 1). The median survival time in the no operation group was 7.3 months (interquartile range: 3.1-13.3 months). The OS of group A to group D were all significantly better than for group E. Fig. 3, shows that there was no difference in the OS between the neoadjuvant groups (A and B) and the adjuvant groups (C and D) ($p = 0.506$). Fig. 4 shows the OS of the lymph node negative status groups (A and C) is significantly better than N-positive status groups (B and D) ($p = 0.0049$).

The disease-free rate of each group is summarized in Fig. 5 to Fig. 7. In our study, we found the group C had trend which had better outcome than group B in disease-free rate. However, p value was 0.1216. We may need more patients to distinguish this factor. There

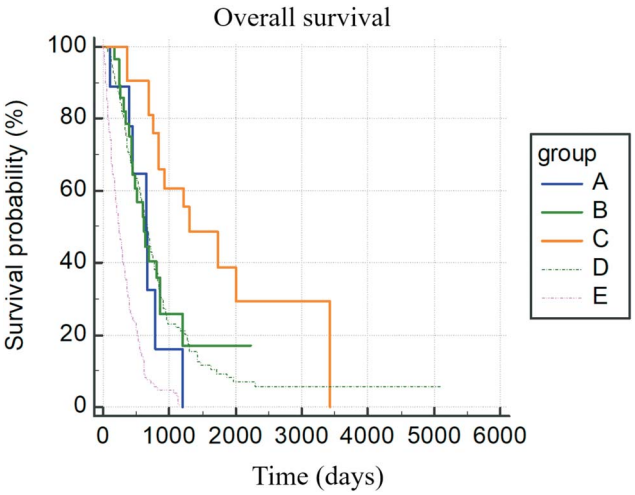

Fig. 1. Kaplan-Meier survival curves for all locally advanced colorectal cancer patients. Group A: N0 status with neoadjuvant therapy; Group B: N-positive status with neoadjuvant therapy; Group C: N0 status with adjuvant therapy; Group D: N-positive group with adjuvant therapy; Group E: no curative operation group.

is no significant difference between each group for disease-free rate. In Fig. 6, the disease-free rate of adjuvant groups (C and D) is slightly better than neoadjuvant groups (A and B) ($p = 0.027$). In Fig. 7, there is no significantly difference between N0 status group (A and C) and N-positive status groups (B and D) ($p = 0.448$).

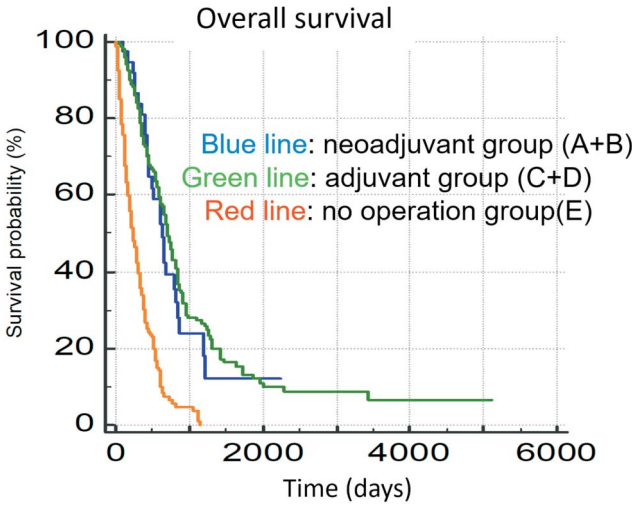

Fig. 2. Kaplan-Meier curve comparing overall survival rates of neoadjuvant group (blue line), adjuvant group (green line), and no operation group (red line). There is no significant difference between the neoadjuvant and adjuvant groups, whereas overall survival rates of neoadjuvant and adjuvant groups are both significantly better than those for the no operation group ($p < 0.05$).

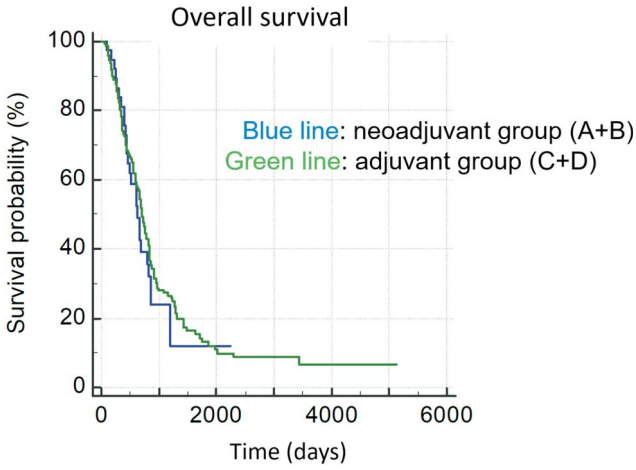

Fig. 3. Kaplan-Meier curve comparing overall survival rates of the neoadjuvant group (blue line) and adjuvant group (green line). There is no significant difference between the two groups ($p = 0.506$, $p > 0.05$).

Discussion

The OS in locally advanced T4 colorectal cancer is greatly influenced by age and pre-existing co-morbidities of the patient, the therapeutic strategy (neoadjuvant or/and adjuvant treatment), and the possibility

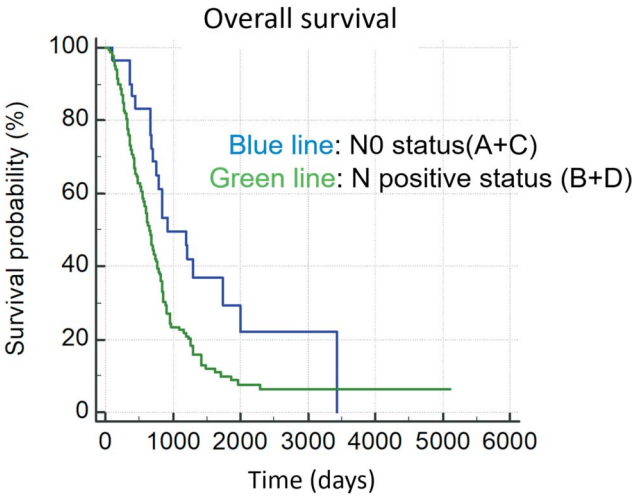

Fig. 4. Kaplan-Meier curve comparing overall survival rates in the N0 status group (blue line) and N-positive status group (green line). Overall survival of N0 group is significantly better than that of the N-positive group ($p = 0.0049$, $p < 0.05$).

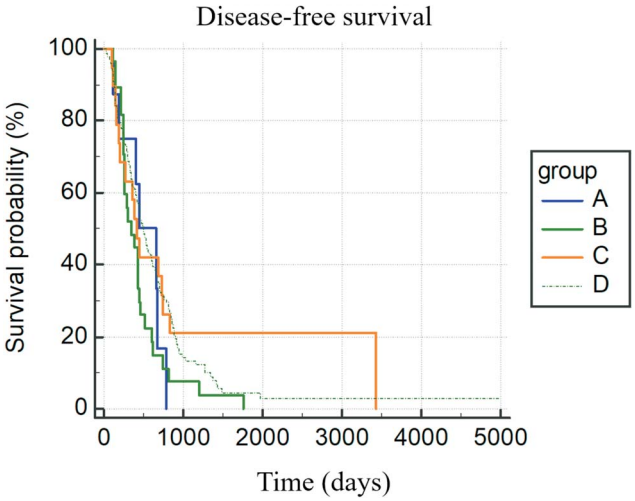

Fig. 5. Disease-free curve for all locally advanced colorectal cancer patients. Group A: N0 status with neoadjuvant therapy; Group B: N-positive status with neoadjuvant therapy; Group C: N0 status with adjuvant therapy; Group D: N-positive group with adjuvant therapy; Group E: no curative operation group.

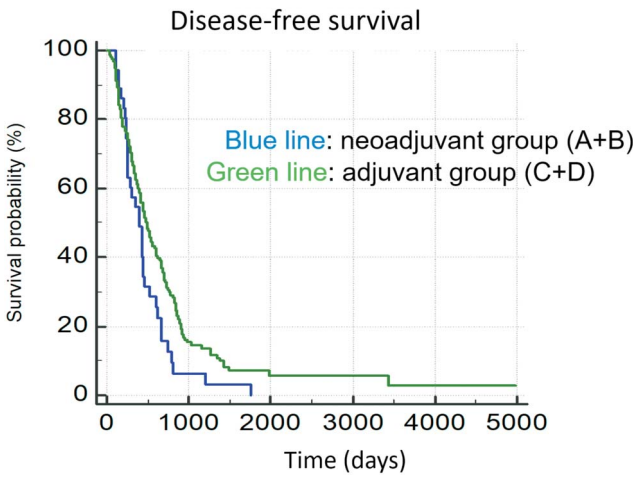

Fig. 6. Kaplan-Meier curve comparing disease-free rate (DFR) by neoadjuvant group (blue line) and adjuvant group (green line). The DFR of the adjuvant group is slightly better than that of neoadjuvant group ($p = 0.027$, $p < 0.05$).

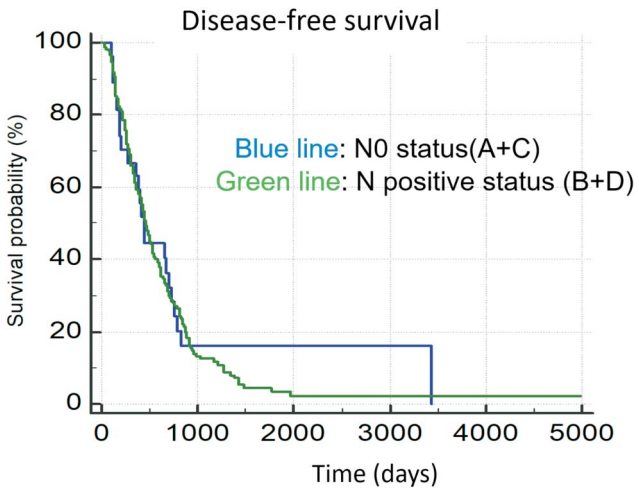

Fig. 7. Kaplan-Meier curve comparing disease-free rate of the N0 status group (blue line) and N-positive status group (green line). There is no difference between N0 and N-positive status groups ($p = 0.448$).

to achieve an R0 resection.[4] The OS among these high-risk patients who had locally advanced T4 colorectal cancer was poor, especially in node-positive patients.[13]

Ahmed et al.[13] suggested that lymph node status and lymph node ratio are important prognostic factors and correlate with survival independent of systemic therapy and other patient- and tumor-related factors in patients with locally advanced tumor with distant metastasis. Macari et al.[14] found that the OS of locally advanced T4 cancer was associated with age, positive lymph node involvement, and positive margins. These findings are consistent with our results. We found no significant difference in the OS rates between adjuvant and neoadjuvant groups ($p = 0.506$) (Fig. 3). However, compared to the no curative operation group (group E), both the neoadjuvant and adjuvant groups had significantly better OS rates ($p < 0.0001$) (Fig. 2).

Many past articles support that regional lymph node status is not only an important predict prognostic factor in early-stage colorectal cancer but also in stage IV colorectal cancer. Colorectal cancer could spread by both lymphatic and hematogenous dissemination. Although the detailed mechanism is not clear, it suggested that colorectal tumor cells spread through the lymphatic system from primary tumor site to the lymph nodes, to the next distant organ. Therefore, regional lymph node metastasis is an important point in tumor cell spreading in colorectal cancer.[20] Ahmed et al. assumed that a greater host immune response account for good survival in the stage IV colorectal cancer patient who had N0 status.[13] A previous literary review article indicates different prognoses for T4 tumors (including T4a and T4b) with or without lymph node metastasis.[10] In T4a the observed survival at five years was 60.6% for N0, and 26.6-47% for N-positive cases, whereas in T4b the observed survival at five years was 45.7% for N0, and 15.8-27.9% for N-positive cases. Our data confirmed this as it showed that the OS of the N0 status group was significantly better than that of the N-positive status group ($p = 0.0049$) (Fig. 4). The median survival time in the N0 status group was 27.7 months (interquartile range: 22.6-48.3 months), and the median survival time in the N-positive status group was 21.0 months (interquartile range: 12-28.7 months). There was also a significant difference between each group, $p = 0.0006$.

In a review of past literature, many articles established neoadjuvant chemotherapy as the gold standard for the treatment of locally advanced tumors, located in the rectum. De Gooyer et al.[15] illustrates that preoperative chemotherapy is safe, results in significant tumor and nodal downstaging, and yields excellent long-term outcomes in patients with locally advanced colon cancer. Patients treated with neoadjuvant che-

motherapy had similar long-term survival rates compared to patients treated with adjuvant chemotherapy.[16] Krishnamurthy et al.[16] also illustrated that neoadjuvant radiation therapy in locally advanced T4 colon cancer was safe and associated with increased downstaging. Dehal et al.[17] reported that patients with clinical T4b colon cancer treated with neoadjuvant chemotherapy may have an improved survival rate compared to those who receive adjuvant chemotherapy. Neoadjuvant therapy should be considered in patients with locally advanced rectal cancer with or without metastasis, as it is associated with a lower risk of local recurrence and improved functional results, compared to adjuvant therapy.[18,19]

In our study, the OS of those patients who received neoadjuvant and adjuvant therapies was not significantly different. But the disease-free rate of the adjuvant group was better than that of the neoadjuvant group. We suspect that this might be due to patients in the neoadjuvant therapy cohort having more serious distant metastases than those in the adjuvant therapy cohort. A total of 52.8% patients who had neoadjuvant therapy had unresectable liver metastasis prior to neoadjuvant therapy (Table 2). The proportion of unresectable liver metastases in the N-positive status group was not significantly greater than the proportion in the N0 status group (57.1% vs. 37.5%, p = 0.32). After neoadjuvant therapy, those patients who had unresectable liver metastasis could receive curative colon surgery. However, in our study, patients in the neoadjuvant therapy cohort, still had higher postoperative recurrence rates than the patients in the adjuvant therapy cohort.

Diaconescu et al.[4] reported that surgical resection of T4 colorectal tumors and invaded organs represented the preferred method of treatment; however, most T4 tumors are nonresectable. Adding neoadjuvant or adjuvant therapy could therefore improve therapeutic results, including increasing resectability, decreasing locoregional and distant recurrences, and improving the functional outcome. In our study, the OS rate of operation groups (group A to group D) was significantly better than those of the no curative operation group (group E), in both the adjuvant and neoadjuvant groups (Fig. 1 and Fig. 2). The median survival time in the no curative operation group was just 7.3 months — much worse than the other groups (Table 1).

The limitations of our study were as follows: first, it consisted of a retrospective study involving only one single hypothesis, and it included patients treated by many different colorectal surgeons. Second, the numbers of patients who received neoadjuvant treatment and formed part of the N0 status group were relatively small (only 36 patients), which reduced the statistical power to determine the OS and disease-free rates. Three, the variables and criteria which determine the use of adjuvant or neoadjuvant therapy for these locally advanced colorectal patients with metastasis is not clearly stated and will be obvious heterogeneous. It would cause our result to be weak.

Conclusions

The prognosis of T4 colorectal cancer with distant metastases is poor, with high probability of recurrence and a dramatic reduction in OS. Based on our data for locally advanced stage IV colorectal cancer, patients in the N0 status group have a significantly better OS rate than in the N-positive status group. Patients who had adjuvant therapy had a significantly better disease-free rate than those who had neoadjuvant therapy. For OS, curative resection with neoadjuvant or adjuvant therapy was better than the no curative operation group for locally advance stage IV colorectal cancer.

Sources of Financial Support

None.

Table 2. The reason for these patients who underwent neoadjuvant therapy

	Group A	Group B	
Unresectable liver metastasis	3	16	19 (52.8%)
Peritoneal seeding	4	6	10 (27.8%)
Pre-operative CCRT[a]	1	6	7 (19.4%)

[a] CCRT, concurrent chemoradiotherapy.

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原　著

T4 大腸直腸癌合併遠端轉移的預後因子分析

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國立成功大學附設醫院　外科部　大腸直腸外科

目的　從回溯性研究去分析局部晚期第四期大腸直腸癌的預後因子。

方法　從 2002 年 5 月到 2018 年 9 月，收集所有 T4 腫瘤分期合併有遠端轉移的大腸直腸癌個案，進行回顧性的分析。總共有 197 位 T4 合併遠端遠移的病人有接受治癒性的手術。將所有病人資料、腫瘤分期和術後數據收集做統計。

結果　淋巴結陰性病人的總生存期明顯優於淋巴結陽性的病人 ($p = 0.0049$)；有接受前導性/輔助性化學治療病人的總生存期都明顯優於無接受根除性手術的病人；而接受輔助性化學治療的病人群的無疾病存活率略好於接受前導性化學治療的病人群 ($p = 0.027$)。

結論　具有遠端轉移的 T4 大腸直腸癌的預後差，復發機率高，存活率顯著降低。根據我們數據，淋巴結陰性病人的總生存期明顯高於淋巴結陽性病人。

關鍵詞　T4 大腸直腸癌、前導性化學治療/輔助性化學治療、淋巴結狀態。