Original Article

Risk Factor Analysis on Distant Metastasis and Local Recurrence after Curative Resection in Early-stage Middle and Low Rectal Cancer

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Key Words
Early-stage rectal cancer;
Distant metastasis;
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Risk factor analysis

Purpose. The disease recurrence after curative surgery on early stage rectal cancer is frustrated and the patient number is scarce. This study aims to find out the risk factors in distant metastasis and local recurrence separately.

Methods. Patients who were diagnosed with pT1 or pT2 rectal adenocarcinoma and treated by local excision or radical resection between January 2005 and December 2016 were retrospectively recruited in this study. The risk factors for recurrence were identified by p value < 0.1 in Log-rank test from Kaplan-Meier survival analysis. Cox proportional hazard model was adopted individually to the risk factors for distant and local recurrences.

Results. There were 350 patients enrolled in this study. The length of follow up time was 73.8 [46.1-107.6] (months). "Pre-operative CEA ≥ 5 (ng/mL)" [hazard ratio = 4.02 (1.42-11.36)] (p = 0.009) and "Early post-operative morbidity" [hazard ratio = 3.22 (1.17-8.83)] (p = 0.023) were risk factors for distant metastasis; "Resection margin ≤ 0.1 (cm)" [hazard ratio = 6.12 (1.48-25.46)] (p = 0.013) was risk factors for local recurrence. "Lympho-vascular invasion" [hazard ratio = 2.51 (0.87-7.26)] and "Tumor Diameter ≥ 3 (cm)" [hazard ratio = 5.08 (0.90-28.57)] had borderline significance (p < 0.1).

Conclusions. For early-stage rectal cancer, recurrence rate is low after curative surgery. We suggest carefully follow-up plan for those who has high-risk factors. Further study on follow-up strategy and adjuvant treatment are needed to achieve better survival.

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Cancer remains top 1 of the most common 10 causes of death about 4 decades. In Taiwan, colorectal cancer has 1st incidence rate of all malignant disease, 3rd mortality rate in male and 4th mortality rate in female. As the implementation of occult blood test of stool for people above 50 years old, we screen out more and more early-stage colorectal cancer by diagnostic colonoscopy. For those resectable cancers, even advanced stage, en-bloc surgical resection remains the first priority of various treatment options.[1] However, bowel resection may bring peri-operative morbidity, or impact of long-term quality of life, especially for

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those patients with middle and low rectal cancer.

In the past, the treatment guidelines for rectal cancer suggested radical resection, which including various approaches. However, those treatment sometimes accompanied with long-term lifestyle modifications.[2-4] LAR syndrome, for example, is one of well-known term for those suffers from fragmented stool, defecatory urgency, frequent bowel movement, or stool incontinence the worst.[5] By the evolution of treatment on rectal cancer, anus-sparing surgery draws more and more attention. In the past, transanal excision, polypectomy, and transanal endoscopic microsurgery were reserved for pT1 tumor with low risk pathological factors. Precise pathological N stage is critical for colorectal cancer, as the adjuvant therapy is effective for those have high disease recurrent risk. Moreover, local excision with adjuvant chemoradiation brings less impact on anorectal function in comparison with radical resection.[6] Therefore, more and more studies focused on local excision combined with or without neoadjuvant or adjuvant chemoradiation.

To date, aggressive tumor biology and therefore poor prognosis were considered to present short disease-free interval to occurrence of distant metastases.[7,8] However, metastatic colorectal cancer still has low rates of complete cure and remains a therapeutic challenge.[9] Consequently, patients with early distant metastasis after primary tumor resection have less chance to receive intensive but potentially curative multimodality treatment because they might be considered to poor prognosis.[10]

Rectal cancer seems to have different metastasis mechanism to colon cancer. The most common site of distant metastasis for colon cancer is liver; isolated metastasis at lung and local recurrence were reported to be the most recurrence site for rectal cancer from the statistics of National Cancer Institute's Surveillance of America.[11] There were some studies focused on the risk factors of tumor recurrence. The number of lymph nodes, vascular invasion and perineural invasion (PNI), and low microsatellite instability have been shown to be important predictors of distant metastasis in a classic study.[12] A study reported that lymphatic invasion was a high-risk factor for disease recurrence and worse disease-free survival (DFS) in 433 patients with colon cancer and 86 patients with rectal cancer. T2 tumors were at risk with borderline significance ($p = 0.065$).[13]

Due to scarce patient number, there was no study focusing only on rectal cancer published before. The purpose of this study is separately to find out the risk factors for local or distant metastasis of early stage rectal cancer.

Materials and Methods

Detailed data of 990 patients who were diagnosed with pT1 or pT2 rectal adenocarcinoma and treated by curative surgery between January 2005 and December 2016 were retrospectively recruited from the Colorectal Section Tumor Registry at the Chang Gung Memorial Hospital. This study was approved by the Institutional Review Board. Clinical staging was determined using computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET). Patients were excluded from this study for the following reasons: having synchronous colon cancer (n = 116); having rectal cancer 8 cm above anal verge (n = 381); receiving neoadjuvant CCRT (n = 132) for rectal cancer; with clinical evidence of distant metastases (n = 3); pathology data loss or proved to be melanoma, NET (neuroendocrine tumor), or GIST (gastrointestinal stromal tumor) (n = 8) (Fig. 1).

The available medical records included data on age, sex, body mass index (BMI), family cancer history, tumor location (centimeter away from the anal verge), maximal tumor diameter, preoperative carcinoembryonic antigen (CEA), albumin level, and hemoglobin level. All preoperative laboratory parameters were measured within 24 hours after admission. Tumor location was confirmed from anal verge with rigid sigmoidoscopy. Operation types were recorded as trans-abdominal resections or local excision. Pathological reports including tumor diameter (cm), resection margin (cm), pT and pN stage, tumor differentiation, lympho-vascular invasion (LVI), and peri-neural invasion (PNI) were examined. Operative records included operation method and the creation of a temporary or permanent ostomy. Adjuvant therapy included

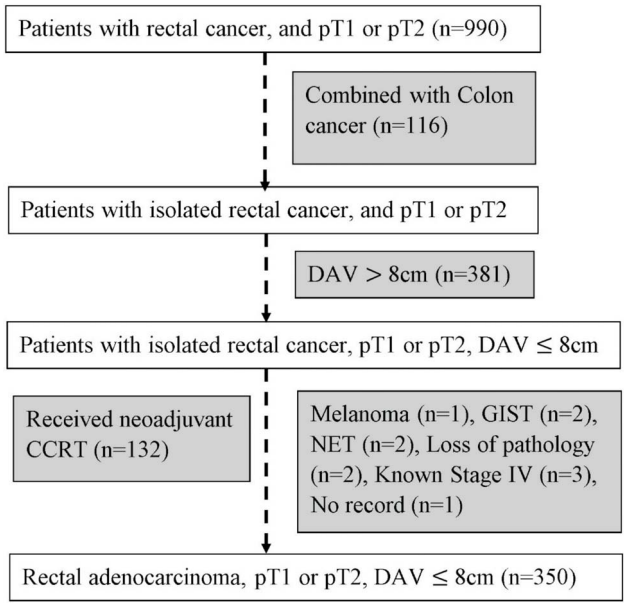

Fig. 1. Patient selection: 2005-2016. DAV: distance from anal verge; CCRT: concurrent chemoradiation; GIST: gastro-intestinal stromal tumor; NET: neuro-endocrine tumor.

chemotherapy or CCRT. Several chemotherapy regimens were adopted, including oral form combining tegafur and uracil, intravenous form fluorouracil and leucovorin (5-Fu/LV), and oxaliplatin plus intravenous 5-Fu/LV (FOLFOX). Adjuvant radiotherapy with long-course radiotherapy (5040 cGy delivered in 28 fractions) was implemented.

Postoperative complications were classified as early morbidity and late morbidity. Early morbidity was defined as postoperative complications occurring within 30 days, including wound-related (wound infection or wound dehiscence), pulmonary (atelectasis or pneumonia), cardiovascular (myocardial infarction, stroke or embolism), urinary (urinary tract infection or neurogenic bladder), gastrointestinal (obstruction, ileum or bleeding), and anastomosis-related (leakage, stenosis) complications. The late morbidity was defined as complications occurring after discharge and any event of readmission. Postoperative mortality was defined as death occurring within 30 days after operation.

Different physicians in the same department of this institute adopted similar follow-up routines. At the discretion of an individual physician, all patients were subjected to a follow-up program that included outpatient visits every 3 months in the first 1 year and 6 months in the second with physical examinations, including digital rectal exams, and CEA tests. Scheduled CT or MRI scans every 6 months in the first 2 years, and colonoscopies annually in the first 2 years. Recurrent disease was confirmed by histology of colonoscopy biopsy specimens, re-operation, or radiological studies.

All statistical analyses were performed with IBM SPSS version 24.0 in this study. The risk factors for distant metastasis or local recurrence were identified by p value < 0.1 in Log-rank test from Kaplan-Meier survival analysis. Cox proportional hazard model was adopted individually to distant metastases and local recurrences. The results were reported as hazard ratios (HR) with a 95% CI. Two-sided p values with $p < 0.05$ showed statistical significance in the results.

Results

Between 2005 and 2016, 350 patients were identified. The age was 63.6 ± 12.6 (mean ± SD, standard deviation), and the BMI was 24.3 ± 3.5. There were 189 (54.0%) males and 133 (38.0%) cases with family cancer history. Pre-operative CEA was 1.9 [1.1-2.9] (ng/mL) (median [25 percentile-75 percentile]). Tumor location was marked as distance from anal verge (DAV): 6 [5-8] (cm) (Table 1). In the peri-operative days, 153 (43.7%) patients received temporary ileostomy or colostomy, and 28 (8%) patients had permanent stoma. The patients received one of two operation types: (1) 292 trans-abdominal resections (including 266 low anterior resections with staple anastomosis, 2 subtotal coloprotectomy with staple anastomosis, 21 abdomino-perineal resections, and 3 Hartmann's procedures) by laparotomy or laparoscopy. (2) 58 Local excision (including trans-anal excision or polypectomy, and trans-anal endoscopic microsurgery). There were 76 (21.7%) patients had post-operative morbidity, which included 53 (15.1%) patients had early morbidity in post-operative 30 days, 35 (10.0%) patients had late morbidity after post-operative 30 days (Table 2).

The length of follow up time was 73.8 [46.1-107.6]

(months). 153 (43.7%) patients had temporary colostomy or ileostomy, and 28 (8.0%) patients had permanent colostomy or ileostomy. 83 (23.7%) patients received adjuvant therapy, including 57 (16.3%) of them received chemotherapy, and 26 (7.5%) received CCRT (Table 2).

There were 158 (45.1%) patients had T1 stage, while others were T2 stage. N stage was examined in 292 patients with trans-abdominal resection, and there were 62 (21.2%) patients had N+ stage (including 53 N1, and 9 N2). 47 (13.4%) patients had lympho-vascular invasion (LVI), while 21 (6%) patients had perineural invasion (PNI). There were 261 (74.6%) moderate-differentiated, 80 (22.9%) well-differentiated, and 9 (2.6) poor-differentiated cancers. The tumor diameter was 2.7 [2.0-3.9] (cm), and the resection margin was 1.2 [0.5-2.0] (cm) (Table 3).

In the analysis on distant metastasis, "Pre-operative CEA ≥ 5 (ng/mL)" had hazard ratio (HR) = 4.02 (1.42-11.36) (p = 0.009), "Early post-operative morbidity" had HR = 3.22 (1.17-8.83) (p = 0.023), and "LVI" had HR = 2.51 (0.87-7.26) with borderline significance (p = 0.090) (Table 4). In the analysis on local recurrence, "Resection margin ≤ 0.1 (cm)" had HR = 6.12 (1.48-25.46) (p = 0.013), and "Tumor diameter ≥ 3 (cm)" had HR = 5.08 (0.90-28.57) with borderline significance (p = 0.065) (Table 5).

Table 1. Patient characteristics

Variable	All 350 patients (% or [Q1 - Q3])
Age	63.6 ± 12.6*
BMI (kg/m^2)	24.3 ± 3.5*
Male gender	189 (54.0)
Family cancer history	133 (38.0)
Pre-operative CEA (ng/mL)	1.9 [1.1-2.9]**
Pre-operative CEA ≥ 5	39 (11.1)
DAV (cm)	6 [5-8]**
DAV < 5	86 (24.6)

BMI: body mass index; CEA: carcinoembryonic antigen; DAV: distance from anal verge.
* Mean ± SD (standard deviation). ** Median [25 percentile-75 percentile].

Table 2. Treatment and follow-up characteristics

Variable	All 350 patients (% or [Q1-Q3])
Operation type	
Trans-abdominal resection	292 (83.4)
Local excision	58 (16.6)
Post-op morbidity	76 (21.7)
Early	53 (15.1)
Late	35 (10.0)
Ostomy	
Temporary	153 (43.7)
Permanent	28 (8.0)
Adjuvant therapy	83 (23.7)
Chemotherapy	57 (16.3)
CCRT	26 (7.5)
Follow up length (month)	73.8 [46.1-107.6]*
Distant metastasis	18 (5.1)
Local recurrence	8 (2.3)

CCRT: concurrent chemoradiation.
* Median [25 percentile-75 percentile].

Discussions

In this retrospective study to 350 patients receiv-

Table 3. Pathological characteristics

Variable	All 350 patients (% or [Q1-Q3])
Resection margin (cm)	1.2 [0.5-2.0]*
Tumor diameter (cm)	2.7 [2.0-3.9]*
T stage	
T1	158 (45.1)
T2	192 (54.9)
LVI	47 (13.4)
PNI	21 (6)
Differentiation	
Poor	9 (2.6)
Moderate	261 (74.6)
Well	80 (22.9)
N stage +	62 (21.2)**

LVI: lymphovascular invasion; PNI: peri-neural invasion.
* Median [25 percentile-75 percentile]. ** From 292 patients received trans-abdominal resection.

Table 4. Hazard ratio for distant metastasis

Variable	Hazard ratio (95% CI for Exp(B))	p value
Pre-operative CEA ≥ 5 (ng/mL)	4.02 (1.42-11.36)	0.009*
Early post-operative morbidity	3.22 (1.17-8.83)	0.023*
LVI	2.51 (0.87-7.26)	0.090
Tumor Diameter ≥ 3 (cm)	2.34 (0.80-6.85)	0.120
Resection margin ≤ 0.1 (cm)	1.98 (0.62-6.30)	0.248

CEA: carcinoembryonic antigen; LVI: lympho-vascular invasion.
* p value < 0.05.

Table 5. Hazard ratio for local recurrence

Variable	Hazard ratio (95% CI for Exp(B))	*p* value
Resection margin ≤ 0.1 (cm)	6.12 (1.48-25.46)	0.013*
Tumor diameter ≥ 3 (cm)	5.08 (0.90-28.57)	0.065
DAV < 5 (cm)	3.42 (0.79-14.76)	0.099

DAV: distance from anal verge.
* *p* value < 0.05.

ing curative surgery for early stage rectal cancer, we found "Pre-operative CEA ≥ 5 (ng/mL)" and "Early post-operative morbidity" as high-risk factor for distant metastasis. In the separate analysis, we found "Resection margin ≤ 0.1 (cm)" as a high-risk factor for local recurrence.

Pre-operative CEA

There were some studies found that pre-operative or pre-chemotherapy CEA elevation is related to disease recurrence or disease-free survival.[14-19] However, there were some studies reported non-significant results of CEA elevation for disease recurrence and/or disease-free survival.[20] Besides, shorter time to recurrence was reported in patients with stage I colon cancer in a retrospective study.[21]

Post-operative morbidity

Our study showed 53 (15.1%) patients had early morbidity in post-operative 30 days. Eighteen of the 53 patients were favored with anastomotic leakage from both image study and clinical observation. A systematic review containing 14 studies and 11,353 patients, anastomotic leakage was associated with higher local recurrence rate but not distant metastasis rate.[22] In our study, four of the 18 patients with anastomotic leakage had recurrence (3 distant metastases and 1 local recurrence).

Resection margin

In our study, we set distal margin from the tumor to the cutting edge of the specimen as "Resection margin". Among 97 patients with distal margin of ≤ 1 mm, higher 5-year local recurrence rate (24.1% vs. 12.0%, $p = 0.005$) and worse 5-year disease-free survival (45.5% vs. 69.5%, $p < 0.001$) were noted from a retrospective study including 6,574 patients underwent anterior resection for rectal cancer.[23] For oncologic safety, resection margin should be ≥ 1 cm. Nevertheless, there were various definitions of "Positive resection margin" from previous studies, with 0.1 cm to 2 cm in low anterior resection. With the reference, we set microscopic resection margin ≤ 0.1 cm to analysis.

Local excision vs. radical resection

Local excision is suitable for cT1 with low pathological risk factors.[24,25] There were some studies focused on local excision for T2 tumors, for example, a National Cancer Database Analysis in review of 4822 patients concluded that local excision with CCRT was not associated with worse overall survival in comparison to radical resection.[26] Another study use the same database concluded similar results in the comparison of 1,761 patients underwent transabdominal resection and 3,531 patients underwent local transanal excision with and without neoadjuvant chemoradiation.[27] A systematic review reported that local excision with adjuvant therapy for pT1 rectal tumors with high-risk pathologic factors can achieve acceptable long-term outcomes.[28] Another study also showed 5-year survival outcome from 53 patients with T1 lesions who treated with local excision and full-dose chemoradiotherapy.[29] A single-center experience for TEM with adjuvant therapy for early rectal cancer showed 98.6% disease-specific survival rate in 54 pT1 and 22 pT2 patients.[30] Though more and more patients were selected for local excision, higher local recurrence rate was reported in some studies.[31-34]

Nevertheless, by the evolution of adjuvant treatment, local excision with adjuvant treatment is gradually accepted by colorectal surgeons. In our survival analysis with Kaplan-Meier method, local excision had similar local recurrence rate ($p = 0.645$), distant metastasis rate ($p = 0.917$) and disease-free survival rate ($p = 0.740$ in Log Rank test) to radical resection. Therefore, our study did not exclude patients receiv-

ing local excision with or without adjuvant chemotherapy.

Concern of N stage

Local excision does not provide accurate regional lymphatic stage (N stage in TMN), which potentially indicates tumor spreading, so there are some studies trying to find out risk factors of regional lymph nodes metastasis.[35-38] Our study found out 62 patients with N stage positive from 292 radical resections. According to current guideline, N stage positive is a high-risk factor for disease-free survival, and adjuvant chemotherapy would be suggested to most of them. In our retrospective study, 7 of 62 patients with N stage positive did not receive adjuvant chemotherapy. Three of them died at post-operative 1st, 4th, and 7th year due to non-cancer related disease; four of them were still cancer-free for 1 to 7 years, but finally they were found with 4 distant metastases and 1 local recurrence. Old age and comorbidity were the reasons why they did not receive adjuvant therapy. We found that N stage positive was not significant to neither distant nor local recurrence, and this finding might be resulted from the retrospective design.

Miscellaneous

In a Danish population-based study with 21,152 patients, Holmes et al. reported that the recurrence risk of colorectal cancer was highest in the first three years of follow-up.[39] They also reported that patients had 55 years old or younger had increased risk of recurrence. In our study, age showed non-significant findings. Different cancer stages and populations at diagnosis might contribute this finding (the study include stage I-III colorectal cancers).

A cohort study with 1,857 patients reported that pre-operative anemia (Hemoglobin level < 7.5 mmol/L in women and < 8.0 mmol/L in men) was associated with poor 3-year overall survival and higher local recurrence rate in multivariable analysis model.[40] Regarding to BMI, a retrospective analysis showed more conversion to open surgery and higher rate of surgical complications in a large case series of 1464 patients.[41] Another retrospective study reported that patients had overweight (BMI ≥ 35 kg/m^2) or underweight (BMI < 18.5 kg/m^2) had reduced overall survival and higher rates of distant metastases in comparison to patients with normal bodyweight.[42] Due to the small sample size as well as non-significant hazard ratio, more studies should be reviewed. Due to different selected patient groups, our study showed non-significant findings on hemoglobin level or BMI.

Limitations

Our study had some limitations. Though we used cox-regression hazard model carefully, retrospective design possibly made causal fallacy. The patient records were not perfectly complete, for example, there were some few laboratory data losses, and we had no data of microsatellite instability or other biomarkers including KRAS, or BRAF. However, KRAS mutation may be linked with higher chance of distant metastasis.[43]

Conclusions

In this analysis for early stage rectal cancer, "Preoperative CEA ≥ 5 (ng/mL)" and "Early post-operative morbidity" were significant risk factors for distant metastasis; "Resection margin ≤ 0.1 (cm)" was a significant risk factor for local recurrence. "Lympho-vascular invasion" and "Tumor diameter ≥ 3 (cm)" had borderline significance. Overall, there were 18 (5.1%) distant metastases and 8 (2.3%) local recurrences in our study. We suggest carefully follow-up plan for those who has early stage rectal cancer and high-risk factors. Further study on follow-up strategy and adjuvant treatment are needed to achieve better survival.

Abbreviations

LAR: low anterior resection, LVI: lympho-vascular invasion, PNI: perineural invasion BMI: body mass index, CEA: carcinoembryonic antigen, DAV:

distance from anal verge, CCRT: concurrent chemoradiation, DFS: disease-free survival, HR: hazard ratio, TEM: trans-anal endoscopic microsurgery, CT: computed tomography, MRI: magnetic resonance imaging.

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Supplement

Supplementary Table 1. Resection margin, operation methods, and local recurrence

Resection margin (cm)	≤ 0.1	0.2-0.5	0.6-2.0	> 2.0
Local excision	32	23	3	0
LAR	11	37	154	64
APR	0	0	7	14
Subtotal colectomy	1	1	0	0
Hartmann's operation	1	1	0	1
Total number	45	62	164	79
Local recurrence	4	1	2	1

LAR: low anterior resection; APR: abdomino-perineal resection.

In this supplementary table, there were 4 patients (2 received LE, 2 received LAR) had local recurrences. Despite very close resection margin, none of them received adjuvant therapy (including CCRT or chemotherapy). Local excision was thought to have higher chance of local recurrence due to close resection margin, however, 58 patients who received local excision had similar local recurrence rate with those received other surgical methods. Nearly half of these 58 patients received adjuvant therapy, which might bring survival benefits in this study.

原　著

早期中低位直腸癌術後局部復發及遠端轉移之危險因子分析

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目的　對於接受根治性手術的早期直腸癌病人來說，疾病的復發並不常見，也對給予治療的醫師帶來挫折感。本研究討論遠端轉移及局部復發，企圖分別找出兩種不同復發方式的危險因子。

方法　篩選於 2005 年至 2016 年間，林口長庚醫院接受局部切除或廣泛切除的根治性手術的病人，且其病理腫瘤分期為 T1 或 T2。危險因子藉由 Kaplan-Meier 存活分析辨識，經 Log-rank test 檢定 p 值 < 0.1 者進入多因子迴歸分析，結果以風險比例 (Hazard Ratio) 呈現。

結果　本研究共有 350 個病例，術後追蹤期中位數為 73.8 月。「術前癌胚抗原 (CEA) 大於等於 5 (ng/mL)」或「術後 30 天內有併發症」為遠端轉移的顯著危險因子；「腫瘤切除邊界小於等於 0.1 公分」為局部復發的顯著危險因子。其餘「淋巴血管侵犯」或「腫瘤直徑大於等於 3 公分」也有較高風險比例，但未達顯著統計差異。

結論　對早期直腸癌來說，復發並不常見。就本研究發現的危險因子，或能提供有此類危險因子的病人，審慎的調整追蹤策略。對於輔助性治療的研究，也能提供有價值的啟發作用。

關鍵詞　早期直腸癌、遠端復發、局部復發、危險因子分析。