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Original Article

Factors Affecting Survival in Patients with Stage I Rectal Cancer: A Single-institute Study

Yu-Che Tsai
Wen-Shih Huang
Chih-Chien Chin
Meng-Chiao Hsieh
Cheng-Yi Huang
Kuan-Chu Ho
Yi-Hung Kuo
Division of Colorectal Surgery, Department of Surgery, Chang Gung Memorial Hospital Chiayi Branch, Chiayi, Taiwan

Key Words
Stage I rectal cancer;
Survival rate;
Comorbidity

Purpose. For patients with rectal cancer, the chance of survival is higher when the disease is detected at stage I compared with at subsequent stages. This study investigated the factors affecting the survival of patients with stage I rectal cancer in a single hospital.
Materials and Methods. This retrospective study involved 75 patients who were diagnosed as having stage I rectal cancer at a single hospital between January 2014 and December 2017 and were followed up until December 2022. Through univariate analysis and multivariate Cox regression, the characteristics and comorbidities of the patients were analyzed and revealed to be correlated with survival outcome.
Results. The patients with 0-2 comorbidities exhibited more favorable 5-year overall survival and 3-year disease-free survival outcomes relative to those with > 2 comorbidities ($p < 0.001$). The patients with an American Society of Anesthesiologists (ASA) score of ≤ 2 exhibited more favorable 5-year overall survival and 3-year disease-free survival outcomes relative to those with an ASA score ≥ 3 ($p < 0.001$). A comparison of the 5-year survival group and 5-year death group revealed poor outcomes for patients with the following comorbidities: hypertension ($p = 0.008$), heart failure ($p < 0.001$), chronic obstructive pulmonary disease ($p = 0.002$), double cancer ($p < 0.001$), liver cirrhosis ($p < 0.001$), and cerebral vascular accident (CVA; $p < 0.001$).
Conclusion. The results suggest that, among patients with stage I rectal cancer, their comorbidities have a greater influence than their cancer on their survival outcomes. When patients with stage I rectal cancer are being treated, their characteristics and comorbidities should be considered. For patients with > 2 comorbidities or an ASA score of ≥ 3, the advantages and disadvantages of surgical intervention should be carefully considered.
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Rectal cancer is among the most common cancers of the gastrointestinal tract, and it accounts for at least 30% of all colorectal cancer cases.[1,2] Rectal cancer is increasingly being detected at an early stage because of early screening.[3,4] The 5-year overall survival of stage I rectal cancer (approximately 77%-96%) is more favorable relative to those of other stages of rectal cancer.[5-7] A recent study revealed an improvement in the survival of patients with stage I rectal cancer, which was attributed to early screening and improve-

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Correspondence to: Dr. Yi-Hung Kuo, Division of Colorectal Surgery, Department of Surgery, Chang Gung Memorial Hospital, No. 6, West Section, Chia-Pu Road, Putz, Chiayi 613, Taiwan. Tel: 886-5-362-1000 ext. 2862; Fax: 886-5-362-3001; E-mail: kuoyihung@gmail.com

ments in surgical techniques.[6-8] Radical surgery is the main treatment for patients with stage I rectal cancer, and those who had appropriate surgical management exhibited more favorable survival outcomes relative to those who did not.[7]

Patients with stage I rectal cancer exhibit a high 5-year survival rate. However, our hospital (ie, the hospital examined in the present study) reported a less favorable 5-year overall survival rate of 68%, which is nearly 10% lower than the average. Therefore, the objective of the present study is to understand the factors affecting the survival of the patients with stage I rectal cancer from our hospital. Therefore, we recruited patients with stage I rectal cancer and compared their data with international data and those collected from the Chang Gung Medical Foundation survival database (ie, data from other hospitals). The comparison results indicated that the 5-year survival rate of such patients at our hospital (ie, Chang Gung Memorial Hospital, Chia-Yi Branch) was lower than those reported by other hospitals and studies; thus, we examined the factors that affected the survival rate of our patients with stage I rectal cancer.

Materials and Methods

The present retrospective study involved 76 patients who were diagnosed as having stage I rectal cancer at a single hospital between January 2014 and December 2017 and were followed up until December 2022. Stage I rectal cancer was diagnosed using the pathologic reports of the surgical patients, and those who did not undergo treatment were diagnosed clinically through image studies and multidisciplinary team discussions. One patient was excluded because their medical records could not be accessed. Among the included patients, 53 and 22 were assigned to a 5-year survival group and a 5-year death group, respectively. The patients' characteristics (eg., age, gender, types of operative procedures that they underwent, and numbers of comorbidities) are listed in Table 1, which also lists their comorbidities, which include hypertension (HTN), diabetes mellitus, arrhythmia, coronary artery disease (CAD), congestive heart failure, chronic obstructive pulmonary disease (COPD) or asthma, double cancer, liver cirrhosis, hyperlipidemia, peripheral arterial occlusion disease, pulmonary embolism, ch-

Table 1. Characteristics between survival and death groups of stage I rectal cancer

Variables	5-year survival group N = 53 (%)	5-year death group N = 22 (%)	*p* value
Age, years			
Mean ± SD (range)	63.5 ± 12.1 (range: 38-86)	75.7 ± 10.7 (range: 54-92)	< 0.001
> 65 year-old	26 (49.1)	18 (81.8)	0.007
< 65 year-old	27 (50.9)	4 (18.2)	
Gender			0.126
Male	29 (54.7)	16 (72.7)	
Female	24 (45.3)	6 (27.3)	
Operation procedure			0.009
Standard-curative surgery	42 (77.8)	12 (54.5)	
Local excision (e.g. TRE)	11 (20.4)	7 (31.8)	
Without tumor excision (e.g. colostomy or no treatment)	0 (0)	3 (13.6)	
ASA			< 0.001
1	1 (1.9)	0 (0)	
2	50 (94.3)	2 (9.1)	
≥ 3	2 (3.8)	20 (90.9)	
Number of comorbidities			< 0.001
0-2	51(96.2)	3 (13.6)	
> 2	2 (3.8)	19 (86.4)	
Hypertension			0.008
Presence	16 (30.2)	14 (63.6)	
Absence	37 (69.8)	8 (36.4)	

Table 1. Continued

Variables	5-year survival group N = 53 (%)	5-year death group N = 22 (%)	p value
DM			0.054
Presence	12 (22.6)	10 (45.5)	
Absence	41 (77.4)	12 (54.5)	
Arrhythmia			0.125
Presence	2 (3.8)	3 (13.6)	
Absence	51 (96.2)	19 (86.4)	
CAD			0.153
Presence	1 (1.9)	2 (9.1)	
Absence	52 (98.1)	20 (90.9)	
Congestive heart failure			< 0.001
Presence	0 (0)	7 (31.8)	
Absence	53 (100)	15 (68.2)	
COPD/Asthma			0.002
Presence	0 (0)	4 (18.2)	
Absence	53 (100)	18 (81.8)	
Double cancer			< 0.001
Presence	1 (1.9)	10 (45.5)	
Absence	52 (98.1)	12 (54.5)	
HCC*	1 (1.9)	3 (13.6)	
Lung cancer*	0 (0)	3 (13.6)	
Buccal cancer*	0 (0)	2 (9.1)	
Prostate cancer	0 (0)	2 (9.1)	
Esophageal cancer	0 (0)	1 (4.5)	
Cervical cancer*	0 (0)	2 (9.1)	
Liver cirrhosis			< 0.001
Presence	0 (0)	5 (22.7)	
Absence	53 (100)	17 (77.3)	
Hyperlipidemia			0.039
Presence	2 (3.8)	4 (18.2)	
Absence	51 (96.2)	18 (81.8)	
PAOD			0.028
Presence	0 (0)	2 (9.1)	
Absence	53 (100)	20 (90.9)	
Pulmonary embolism			0.122
Presence	0 (0)	1 (4.5)	
Absence	53 (100)	21 (95.5)	
CKD			0.095
Presence	3 (5.6)	4 (18.2)	
Absence	50 (94.3)	18 (81.8)	
CVA			< 0.001
Presence	0 (0)	6 (27.3)	
Absence	53 (100)	16 (72.7)	
Rectal cancer relapse			0.360
Local	0 (0)	0 (0)	
Distant metastasis†	2 (3.8)	0 (0)	

* Double or triple cancer, with progression in another malignancy.

† s/p lobectomy and hepatectomy, no cancer relapse after metastasectomy.

SD, standard deviation; TRE, transrectal excision; ASA, American Society of Anesthesiologists; DM, diabetes mellitus; CAD, coronary artery disease; PAOD, peripheral arterial occlusion disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CVA, cerebrovascular accident.

ronic kidney disease, cerebrovascular accident (CVA), and rectal cancer relapse. Cirrhosis was defined and diagnosed through blood tests, abdominal echography, and computed tomography as well as consultation with the gastroenterology department of our hospital. Patients with cirrhosis who had a Child–Pugh score of at least grade A were included in the present study. Chronic kidney disease (CKD) was defined and diagnosed through blood tests, urine examinations, and image studies as well as consultation with the nephrology department of our hospital. Patients with CKD who had at least stage 3a (eGFR < 60 mL/min/ 1.73 m^2) were included in the present study. The data on the patients' characteristics and comorbidities were analyzed and correlated with survival outcomes through univariate analysis and multivariate Cox regression (Tables 1 and 2).

In the present study, categorical characteristics were compared by performing Pearson's chi-square test. Survival differences were estimated using the Kaplan-Meier method, and a comparison was performed using the log-rank test. Overall survival (OS) was defined as the interval between the date of cancer diagnosis and the time of death from any cause. Disease-free survival (DFS) was defined as the time from curative surgery to the date of disease recurrence or death.

Table 2. Multivariate Cox regression model for overall survival

Variables	HR	95% CI	*p* value
Gender			0.083
Male (n = 45)	1		
Female (n = 30)	0.088	0.006-1.372	
Age			0.461
> 65 year-old (n = 44)	1		
< 65 year-old (n = 31)	2.740	0.188-39.861	
Operation procedure			0.015
Local excision	1		
Curative resection	0.024	0.001-0.484	
Operation procedure			0.109
Local excision	1		
No tumor resection	50.613	0.416-6160.171	
ASA			0.075
1 or 2	1		
≥ 3	79.075	0.648-9654.637	
Number of comorbidities*	N/A	N/A	N/A
0-2 (n = 54)			
> 2 (n = 21)			
Hypertension			0.061
Absence	1		
Presence (n = 30)	52.830	0.827-3374.183	
DM			0.072
Absence	1		
Presence (n = 22)	0.063	0.003-1.285	
Arrhythmia			0.194
Absence	1		
Presence (n = 5)	17.190	0.234-1260.802	
CAD			0.336
Absence	1		
Presence (n = 3)	5.491	0.171-176.288	
Congestive heart failure			0.352
Absence	1		
Presence (n = 7)	5.253	0.160-172.146	
COPD/Asthma			0.173
Absence	1		
Presence (n = 4)	12.148	0.334-442.309	
Liver cirrhosis			0.007
Absence	1		
Presence (n = 5)	371.519	4.868-28352.079	
Hyperlipidemia			0.007
Absence	1		
Presence (n = 6)	0.025	0.002-0.368	
PAOD			0.636
Absence	1		
Presence (n = 2)	4.117	0.012-1455.149	
Pulmonary embolism			0.301
Absence	1		
Presence (n = 1)	0.486	0.000-73.043	
CKD			0.729
Absence	1		
Presence (n = 7)	0.594	0.031-11.286	
CVA			0.004
Absence	1		
Presence (n = 6)	514.164	7.227-36581.267	
Double cancer			0.476
Absence	1		
Presence (n = 11)	5.728	0.047-698.912	
Rectal cancer relapse†	N/A	N/A	N/A
Presence (n = 2)			

* Degree of freedom was diminished due to correlation between comorbidity and ASA.
† Coefficient misconvergence due to no mortality event in analysis.
HR, hazard ratio; 95% CI, 95% confidence interval; ASA, American Society of Anesthesiologists; DM, diabetes mellitus, CAD, coronary artery disease; PAOD, peripheral arterial occlusion disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CVA, cerebrovascular accident.

In the context of cancer, DFS refers to the length of time after the completion of primary cancer treatment during which the patient does not exhibit any signs or symptoms of that cancer. OS was treated as the primary end point, and DFS was treated as a second end point in the present study. The confounders were controlled for by applying a Cox regression model in multivariate analysis. All statistical analyses were performed using SPSS (version 19.0; SPSS, Chicago, IL, USA). All p values were two tailed and regarded as statistically significant if they were < 0.05.

Results

We discovered that patients with > 2 comorbidities or an ASA score of ≥ 3 exhibited poorer 5-year OS and 3-year DFS outcomes relative to those with ≤ 2 comorbidities or an ASA score of < 3; comorbidities such as CVA, cirrhosis, hypertension, heart failure, and COPD could be independent risk factors for poor OS.

The clinical data and characteristics of the 75 studied patients are presented in Table 1. The average age of the patients was 63.5 years (38-86 years) in the 5-year survival group and 75.7 years (54-92 years) in the 5-year death group ($p < 0.001$). No statistical differences were noted between the sexes ($p = 0.126$). The outcomes of operative procedures (eg., standard curative surgery) were more favorable in the 5-year survival group than in the 5-year death group ($p = 0.009$). The patients with 0-2 comorbidities had more favorable 5-year survival outcomes relative to those with > 2 comorbidities ($p < 0.001$). In the 5-year survival group and 5-year death group, patients with the following comorbidities had poorer outcomes relative to those without these comorbidities: HTN ($p = 0.008$), heart failure ($p < 0.001$), COPD ($p = 0.002$), double cancer ($p < 0.001$), liver cirrhosis ($p < 0.001$), and CVA ($p < 0.001$). The patients with an ASA score of ≥ 3 had poor survival outcomes ($p < 0.001$). Two patients in the 5-year survival group experience a cancer relapse with distant metastasis. One experienced liver metastasis, for which a hepatectomy was performed and no cancer relapse was reported following metastasectomy. The full data of one patient could not be accessed because of restrictions to the access of their medical records. Three patients in the 5-year death group did not undergo surgical excision for their primary tumors. One only underwent biopsy without treatment because of pulmonary embolism; one was incidentally diagnosed with adenocarcinoma in specimen after fistulectomy and underwent chemoradiation therapy (5000 cGy/25 fx with UFUR/LV for 10 months); one underwent T-colostomy for diversion only. The patients who had curative resection or local excision did not undergo further chemoradiation therapy, and tumor-free margins were noted in their pathologic reports. None of the patients who underwent surgical treatment died within 30 days postoperation. One patient died 30 days after being diagnosed as having stage I rectal cancer, and the patient did not undergo treatment because of a sudden collapse. This patient had a history of congestive heart failure with a poor ejection fraction of approximately 25%; the patient had also undergone permanent pacemaker implantation. Table 2 presents the overall survival analysis results as obtained through a multivariate cox regression model. The degree of freedom for the difference between patients with 0-2 comorbidities and those with > 2 comorbidities was reduced because of the correlation between the number of comorbidities and ASA scores. The patients with liver cirrhosis exhibited poorer outcomes relative to those without cirrhosis ($p = 0.007$). The patients with CVA exhibited poorer outcomes relative to those without CVA ($p = 0.004$).

The patients with > 2 comorbidities exhibited poorer OS and DFS relative to those with 0-2 comorbidities ($p < 0.001$; Fig. 1A, 1B). The 5-year OS of the patients with > 2 comorbidities and those with 0-2 comorbidities was 14.3 and 94.0%, respectively. The 3-year DFS of the patients with > 2 comorbidities and those with 0-2 comorbidities was 31.8% and 100%, respectively. The patients with an ASA score of ≥ 3 also exhibited poorer OS and disease-free outcomes relative to those with an ASA score of ≤ 2 ($p < 0.001$; Fig. 2A, 2B). The 5-year OS of the patients with ASA scores of ≥ 3 and ≤ 2 was 13.6% and 95.8%, respectively. The 3-year DFS of the patients with ASA scores of ≥ 3 and ≤ 2 was 31.8% and 100%, respectively. The

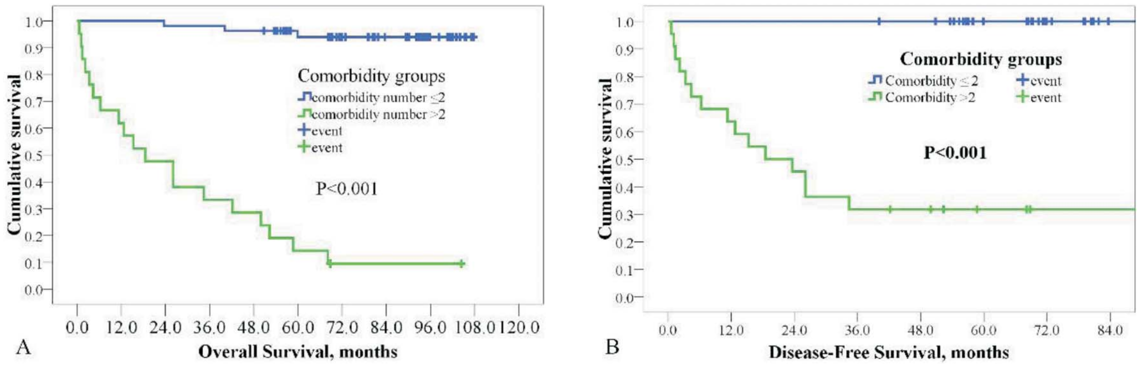

Fig. 1. Comparing with survival of patients with 0-2 comorbidities, patients who had > 2 comorbidities had significant lower 5-year overall survival (A) and 3-year disease-free survival (B) in Kaplan-Meier method for survival analysis.

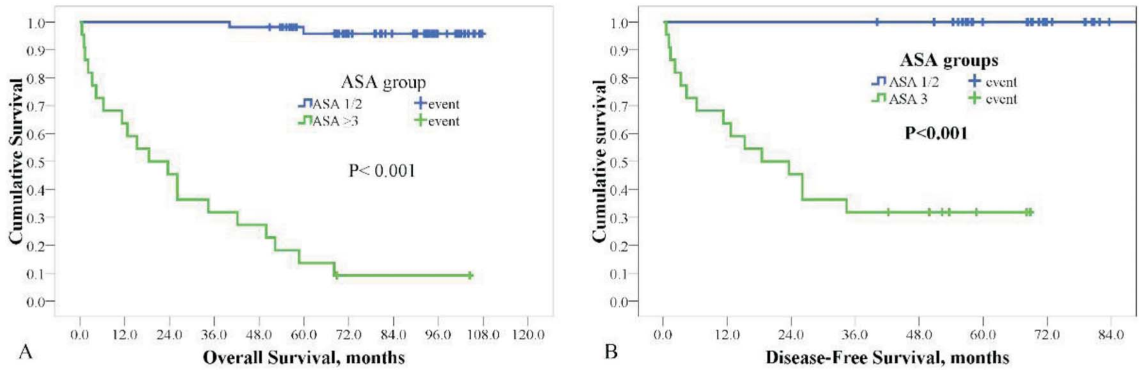

Fig. 2. Comparing with survival of patients with ASA score ≤ 2, patients who had ASA score ≥ 3 had significant lower 5-year overall survival (A) and 3-year disease-free survival (B) in Kaplan-Meier method for survival analysis.

patients who underwent curative resection exhibited more favorable survival outcomes relative to those who only underwent local excision (eg., endoscopic mucosal resection [EMR] or transrectal excision [TRE]) ($p = 0.015$; Table 2). The patients who underwent local excision exhibited nonsignificant favorable survival outcomes relative to those who did not undergo tumor treatment ($p = 0.109$; Table 2). In the no-resection group, 3 patients (66.7% of the group) had a mean age of 85 years (83-89), and > 2 comorbidities. In the local excision group, 18 patients (44.4% of the group) had a mean age 69 years (42-85 years) and > 2 comorbidities. In the curative surgery group, 54 patients (20.4% of the group) had a mean age 65.4 years (38-92 years) and > 2 comorbidities.

Discussion

Comorbidities are a key concern with respect to the survival outcomes of surgical patients and patients with cancer.[9-11] However, no researcher has conducted a data analysis to examine survival and comorbidities in the context of stage I rectal cancer.

The present study revealed that among the patients with stage I rectal cancer, those with > 2 comorbidities or an ASA score of ≥ 3 exhibited poorer OS and DFS relative to those with 0-2 comorbidities or an ASA score of ≤ 2 (Fig. 1A, 1B, 2A, 2B). Being an older patient (ie, > 70 years) with cancer may be related to poorer survival and the presence of more comorbidities.[1,12,13] For older patients with cancer, the literature reported that those who were widowed or not married exhibited the worst overall prognosis.[14] In the present study, the patients with the following comorbidities had poorer outcomes relative to those without these comorbidities: HTN ($p = 0.008$), heart failure ($p < 0.001$), COPD ($p = 0.002$), double cancer ($p < 0.001$), liver cirrhosis ($p < 0.001$), and CVA ($p < 0.001$). Several studies have indicated that cardiovascular disease is the most common cause of noncancer death among patients with cancer.[9,15,16] Although CAD was not an independent factor for survival in the present study, cardiovascular disease remained as a key factor that should be examined in further studies with a larger sample size. We also discovered that the patients with liver cirrhosis had poorer outcomes relative to those without liver cirrhosis. Liver cirrhosis related to surgical and cancer mortality and morbidity has been discussed in several studies.[17-19] In the present study, CVA was an independent factor that affected the survival outcomes of patients. Among older patients with colorectal cancer, having a neurologic comorbidity increased their likelihood of experiencing postoperative complications.[9] In our study, hyperlipidemia was associated with a more favorable OS ($p = 0.007$). However, a recent study indicated that dyslipidemia is associated with poor outcomes in patients with cancer because it promotes tumor invasion and metastasis and contributes to cancer drug resistance.[20] This result may be related to retrospective data bias and the use of a small sample size in the present study. Specifically, some patients could have been misidentified as not having hyperlipidemia because they had no lipid profiles or were not diagnosed as having hyperlipidemia in clinical settings.

For older patients, comorbidities appeared to influence their survival and intent to undergo curative surgical treatment. After the comorbidities in older patients were adjusted for, they still exhibited poorer survival relative to patients from other age groups.[21] Although age of < 65 years was associated with a higher hazard ratio in the present study, this association was nonsignificant ($p = 0.461$, Table 2); this finding may be related to the small sample size of the present study. Despite discussion of comorbidities affecting survival in stage I rectal cancer patients, researchers should also consider patients who have many comorbidities and cannot receive curative surgical treatment. Comorbidities may lead to altered treatment and poorer survival among older patients with colorectal cancer.[11,15,21] In the present study, the patients who underwent curative resection exhibited more favorable survival outcomes relative to those who only underwent local resection (eg., EMR or TRE) ($p = 0.015$; Table 2). The patients who underwent local excision exhibited more favorable survival outcomes relative to those who did not undergo tumor treatment; however, this difference was nonsignificant ($p = 0.109$; Table 2). Among the patients with stage I rectal cancer, a poorer outcome was observed among those who did not undergo curative resection than among those who did.[15] Although the patients who underwent curative resection exhibited more favorable outcomes in the present study, selection bias shoud be considered because the present study adopted a retrospective design. The findings pertaining to the patients who underwent local excision or did not undergo any treatment may be related to the effects of comorbidities and their unsuitability for curative resection. The absence of significant differences in survival outcomes between the patients who underwent local excision and those who did not undergo treatment may be related to the small sample size of the present study.

At present, for the management of stage I rectal cancer, surgical interventions such as radical surgery or total mesorectal excision without neoadjuvant therapy have led to excellent oncologic outcomes.[7] Despite improvements in rectal cancer surgery, medical treatments, and new technologies, the mortality of older patients aged ≥ 80 years has not improved.[1]

In Chia-Yi, the county in Taiwan with the oldest population, older patients with more comorbidities are commonly admitted to our hospital because it is a regional center in Chia-Yi.[22] A higher ASA score was associated with older age and having more comorbidities. In another study, a higher ASA score was reported to be related to worse oncological outcomes after rectal cancer resection.[23] Improved medical treatments and control for comorbidities and surgical techniques should be implemented for the treatment of stage I rectal cancer.

The present study has several notable limitations. We recruited 76 patients over a period of 7 years and excluded 1 patient because of restrictions to the access of their medical records. Therefore, potential bias may exist because of the quality of the collected data and the size of the examined sample. Furthermore, for the comorbidities for which nonsignificant results were obtained with respect to their correlation with poor survival outcomes, different results may be obtained if a larger sample size is used. Because the present study was a retrospective study that examined the data collected from a single hospital, our finding can serve as a reference for clinicians who treat patients with stage I rectal cancer.

Conclusions

Among patients with stage I rectal cancer, their comorbidities have a greater influence than their cancer on their survival outcome. When patients with stage I rectal cancer are being treated, their characteristics and comorbidities should be considered. Curative surgical interventions appear to lead to favorable survival outcomes; however, they may not be suitable for patients with multiple comorbidities. For patients with > 2 comorbidities or an ASA score of ≥ 3, the advantages and disadvantages of surgical intervention should be carefully considered.

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原　著

影響第一期直腸癌病患存活率的危險因子

蔡育哲　黃文詩　靳志堅　謝孟樵　黃政義　何寬助　郭益宏

嘉義長庚紀念醫院　大腸直腸外科

目的　在所有直腸癌的病患中，第一期直腸癌的病患有較好的存活率。我們的研究是想探討可能會影響第一期直腸癌病患存活率的危險因子。

方法　這是一篇回顧性研究，收集從 2014 年 1 月到 2017 年 12 月在單一醫院診斷為第一期直腸癌的 75 位病患，且追蹤至 2022 年 12 月。通過單變量分析及多變量存活分析，評估了病患的特徵及共病與存活率的關聯性。

結果　在第一期直腸癌的病患中，有 0 至 2 種共病的病患會比有大於 2 種以上共病的病患有較好的五年整體存活率及三年無病存活率 ($p < 0.001$)。美國麻醉醫學會分級小於等於 2 分相較於大於等於 3 分的病患，亦有較好的五年整體存活率及三年無病存活率 ($p < 0.001$)。在五年存活組和五年死亡組的比較中，有以下共病的病人有較差的存活率，例如：高血壓 ($p = 0.008$)，心衰竭 ($p < 0.001$)，慢性阻塞性肺疾 ($p = 0.002$)，兩種癌症 ($p < 0.001$)，肝硬化 ($p < 0.001$)，腦血管病變 ($p < 0.001$)。

結論　對於第一期直腸癌的病患來說，共病對於病患存活率的影響更勝於癌症所致。在治療第一期直腸癌的病患時，需評估病患的特徵和共病。在有大於 2 種以上共病或美國麻醉醫學會分級大於等於 3 分的病患，手術介入的好處與壞處須審慎評估。

關鍵詞　第一期直腸癌存活率共病。