Original Article

Prognostic Factors for Colorectal Carcinoids

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Key Words
Colorectal carcinoid;
Carcinoid tumor;
Rectal carcinoid

Purpose. To investigate the treatment outcome of colorectal carcinoids in an institution over an 18-year time period.
Materials and Methods. We performed a retrospective chart review of all the carcinoid tumors originating from the colon and rectum from January 1992 to December 2009. A total of 27 patients were included in the study. The patient's age, gender, tumor size, tumor location, disease stage, and management methods were recorded. All patients were treated using R0 tumor resection either by radical operation, wide local excision, or endoscopic excision. Disease-free and overall survival rates were compared on the basis of the tumor size, clinical stage, tumor location, and resection methods.
Results. The five-year overall and disease-free survival rates were 88.9% and 80.9%, respectively. For tumors larger than 10 mm or of colonic origin, there was a significant increase in the incidence of lymph node or distant metastasis ($p = 0.0006$ and $p = 0.03$, respectively). Patients with a tumor size ≤ 10 mm had better 5-year disease-free and overall survival rate ($p = 0.001$ and $p = 0.009$, respectively), as did patients with rectal carcinoids ($p = 0.006$ and $p < 0.001$, respectively). Patients at an early stage, according to American Joint Committee on Cancer (AJCC) staging system (stage I and II), had a better 5-year disease-free and overall survival rates compared with those at an advanced stage (stage III and IV) ($p < 0.0001$). For patients who underwent R0 resection with an adequate safety margin, neither surgery nor endoscopy could influence the 5-year disease-free or overall survival ($p > 0.05$).
Conclusions. The incidence of rectal carcinoids is much higher in this series than that of the colonic carcinoids. Compared with colonic carcinoids, rectal carcinoids tend to be smaller and rarely metastasize. Patients with a tumor size ≥ 10 mm have a significantly higher incidence of metastasis and poorer disease-free and overall survival rates. Endoscopic resection or wide local excision is adequate to treat small-sized carcinoids.
[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2013;24:65-71*]

Carcinoid tumors, originating from the enterochromaffin cells of the gastrointestinal tract, are relatively rare and slow growing. Their incidence is estimated from 0.65 to 4.48 per 100,000 population per year.[1] Most of the tumors occur at the appendix, rectum, ileum, bronchi and stomach.[2] In the 1980s, the appendix and the ileum were thought to be the most common sites of carcinoid tumor occurrence in

Received: Janurry 31, 2013. Accepted: July 23, 2013.
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the gastrointestinal system,[3] which was documented in a five decade analysis of all carcinoid tumors using the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute from 1973 to 1999.[4] However, with the increased incidence of screening colonoscopy for colorectal diseases, the incidence of the colorectal carcinoids seemed to be on the rise.[4,5] However, conclusions of the reported studies usually were confined in single institutions with diverse results.[6-9] Therefore, the current study was conducted to investigate the treatment outcomes of colorectal carcinoid patients in our hospital and to compare them with those reported in the literature.

Materials and Methods

A total of 30 consecutive patients, with carcinoid tumors located in either the colon or the rectum, were identified from the chart review from January 1992 to December 2009 at the National Cheng Kung University Hospital, Tainan, Taiwan. All patients were diagnosed and treated by physicians of our hospital. Appendiceal carcinoids were excluded due to their peculiar tumor behavior. The patient's age, gender, tumor size, tumor location, disease stage, and management methods were recorded. Surgical resection was defined as R0 resection with an adequate safety margin, including right hemicolectomy, anterior resection, low anterior resection, and wide local excision of the rectal tumor. Standard segmental hepatic resection was performed for one patient with liver metastasis. All patients achieved R0 resection, either surgically or endoscopically, and the specimens were all addressed by our on-duty pathologists. The follow-up was conducted for more than 3 years for every patient or until their death. A clinical stage evaluation was performed according to the American Joint Committee on Cancer (AJCC) cancer staging manual,[10] 7th edition. The clinical stages were then arbitrarily divided as early stage (stage I and II) and advanced stage (stage III and IV). The primary endpoint was the patient's death and the secondary endpoint was disease recurrence or distant metastasis. The survival duration was calculated from the time of surgical resection or endoscopic excision to the time of death or the last follow-up. Three rectal carcinoid patients were excluded from the analysis because these patients either died because of other diseases or were lost in follow-up. Therefore, a total of 27 patients were included in this study.

Statistical Analysis

The survival curves were assessed using the Kaplan–Meier analysis, and survival rates in different groups were compared using the log-rank test. The categorical variable comparison was performed using the Fisher's exact test. A p value of < 0.05 (two-tailed) was regarded as statistically significant.

Results

The patient demographics are summarized in Table 1. The median age was 51 years (range, 25-75 years), with a slight male predominance (16/27, 59.3%). Tumors were located mainly in the rectum (22/27, 81.5%) and tended to be smaller than those in the colon. Most colonic carcinoids (4/5, 80%) presented as a huge intra-abdominal mass, with either lymph nodes or distant metastases (stage III or IV) and required radical surgical resection. The liver was the most common site for distant metastasis on initial presentation (2/5, 40%). Whereas, most rectal carcinoids (19/22, 86.4%) presented as small submucosal tumors ($\leq$ 10 mm), which could be completely removed by endoscopic forceps or wide local excision, and showed low incidence of relapse in the long term. In patients with tumor diameter $\geq$ 10 mm, there was a significant increase in overall incidence of lymph node or distant metastasis (Table 1, $p = 0.0006$). Compared to patients with rectal carcinoids, those with colonic carcinoids had a significantly higher chance of initial lymph node metastasis and higher trend of initial distant metastasis (Table 1, $p = 0.03$ and $p = 0.079$, respectively).

Recurrence and Survival

The median overall survival of our patients was 106 months (2-248 months), and all the patients were followed up for more than 3 years. The 5-year overall survival and disease-free survival rates were 88.9% and 80.9%, respectively (Fig. 1). Patients with rectal carcinoid tumors presented with significantly better disease-free and overall survival rates, compared with those suffering from colonic carcinoid tumors (Fig. 2, $p = 0.006$). Four patients (14.8%) showed distant disease recurrences in the liver, one of whom also

Table 1. Patient demographics

Variables		*p*-value
Age (years) (median, range)	51 (25-75)	
Gender (male/female)	16/11 (59.3%/40.7%)	
Carcinoid tumor location		
Colonic	5/27 (18.5%)	
Sigmoid	3	
Transverse	1	
Cecum	1	
Rectal	22/27 (81.5%)	
Tumor size (mm)		
Colonic	46.2 (4-80)	
Rectal	10.2 (4-40)	
Management		
Surgical resection	16/27 (59.3%)	
LAR	5	
Right hemicolectomy	2	
Wide local excision	9	
Endoscopic resection	11/27 (40.7%)	
Disease stage[#]		
I	19/27 (70.4%)	
II	2/27 (7.4%)	
III	1/27 (3.7%)	
IV	5/27 (18.5%)	
Overall lymph node or distant		0.0006
Metastasis		
Tumor ≦ 10 mm	1/19(5.3%)	
Tumor > 10 mm	6/8(75%)	
Initial lymph node metastasis*		0.03
Colonic carcinoid	3/5 (60%)	
Rectal carcinoid	2/22 (9.1%)	
Initial distant metastasis[$]		0.079
Colonic carcinoid	2/5 (40%)	
Rectal carcinoid	1/22 (4.5%)	

[#] AJCC (American Joint Committee on Cancer) cancer staging.
* Confirmed by pathologic examination.
[$] Confirmed by computed tomography or pathologic examination.

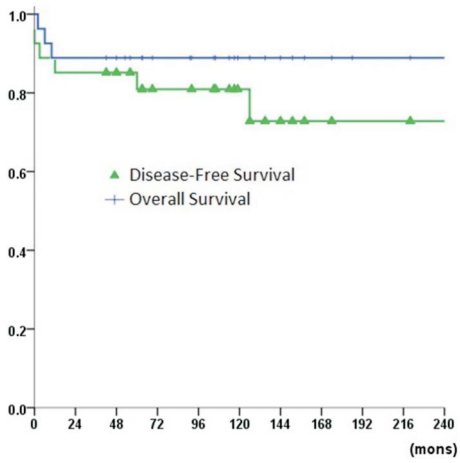

Fig. 1. The 5-year overall and disease-free Kaplan-Meier survival rates were 88.9% and 80.9%.

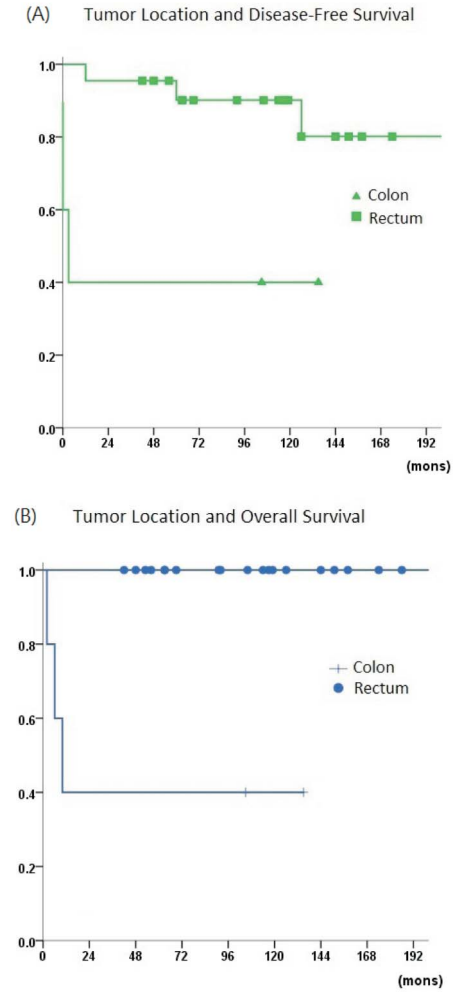

Fig. 2. (A) The 5-year disease-free survival rates of colonic carcinoid and rectal carcinoid were 40% and 90.2%. The *p* value was 0.006. (B) The 5-year overall survival rates of colonic carcinoid and rectal carcinoid were 55.6% and 93.3%. The *p* value was < 0.001.

showed bone and peritoneal involvement. The median disease-free survival was 36 months (range, 3-126 months). Two patients (2/22, 9%) with small rectal carcinoids, measuring 10 mm and 15 mm each, underwent low anterior resection and endoscopic excision, respectively; but showed disease recurrence in the liver after 60 and 126 months, respectively.

Patients with a tumor size ≤ 10 mm had better 5-year disease-free and overall survival rates (Fig. 3, $p = 0.001$ and $p = 0.009$, respectively). Advanced tumor stage was another poor prognostic factor for both disease-free and overall survival rates (Table 2, $p < 0.0001$ and $p < 0.0001$, respectively). Patients who are disease-free for ≥ 1 year tended to have a chance of survival for ≥ 3 years ($p = 0.0014$, data not shown). For patients who underwent R0 resection with an adequate safety margin, neither surgery nor endoscopy could affect the 5-year disease-free or overall survival (Table 2, $p > 0.05$).

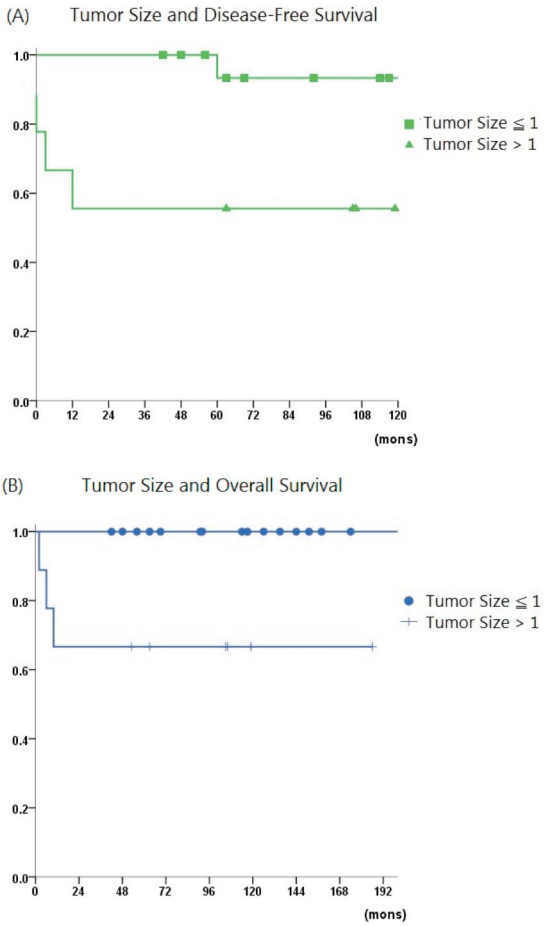

Fig. 3. (A) The 5-year disease-free survival rates of colorectal carcinoids according to tumor size > 1 or ≦ 1 were 55.6% and 93.3%. The *p* value was 0.001. (B) The 5-year overall survival rates of colorectal carcinoids according to tumor size > 1 or ≦ 1 were 66.7% and 100%. The *p* value was 0.009.

Discussion

This study investigated the treatment outcome of the colorectal carcinoid tumors in a medical center of southern Taiwan over a period of 18 years. Our studies revealed that colorectal carcinoids had a slight male predominance. Additionally, rectal carcinoids were much more common and presented with smaller tumors than the colonic carcinoids. Our results were very similar to a 35-year retrospective, pathologic review conducted in a medical center in northern Taiwan, which stated that rectal carcinoids showed a male predominance and were the most common carcinoid tumors in the whole gastrointestinal tract, representing over 80% of the entire gastrointestinal cohort.[1] Contrary to the studies conducted in the western countries, all the studies conducted in Asia affirmed that carcinoid tumors had a strong tendency to manifest at the rectum,[1] which could probably be re-

Table 2. Univariate analysis for disease-free and overall survival predictors

Variables	Number (Total = 27)	*p*-value (Disease-free survival*)	*p*-value (Overall survival*)
Tumor size		0.001	0.009
≦ 10 mm	19		
> 10 mm	8		
AJCC staging		< 0.0001	< 0.0001
I + II	21		
III + IV	6		
Tumor location		0.006	< 0.001
Colon	5		
Rectum	22		
Resection method		0.168	0.138
Surgery	16		
Endoscopy	11		

Note. * Disease-free survival and overall survivalduration are defined as 60 months after surgical resection or endoscopic excision.

lated to differences in race, although the environmental influence could also be a contributing factor. This result was supported by an epidemiological study, which showed that the incidence of rectal carcinoids was three times higher among the black and Asian populations than the white population within the United States, suggesting that genetics might play an important role in disease development.[4]

Several other studies have already identified the tumor size and location at the initial presentation as important prognostic factors.[1,2,5,6,8,9,11,12] Most of these studies concluded that the rectal carcinoids were usually small in size and rarely metastasized, compared with the colonic carcinoids. In addition, most of the studies defined 10 mm as a cut-off size for a substantial metastasis risk in colorectal carcinoids. In contrast, colonic carcinoids clinically presented when the disease was already at an advanced stage. One study conducted in a Brazilian medical institution revealed the picture of this rare but aggressive tumoral behavior, in which colonic carcinoids were generally large in size and often had already metastasized at the initial presentation.[7] According to our study, patients with a tumor ≥ 10 mm in size had a significantly higher incidence of either lymph node or distant metastasis at the initial presentation, and a significantly poorer disease-free and overall survival. The colonic carcinoid patients in this study showed an especially poor prognosis; 4 patients (4/5, 80%) presented with large tumor ranging from 27 to 80 mm and 3 patients (3/5, 60%) died from the disease within a year of detection. Similarly, among 4 rectal carcinoid patients (4/22, 18.2%) who had a tumor ≥ 10 mm (14-40 mm), 2 (2/4, 50%) had lymph node metastasis at the initial presentation. Despite receiving standard surgical resection, these two patients still presented with multiple disease recurrences 1 and 10 years after surgery, respectively. Therefore, according to the study tumors ≥ 10 mm have metastatic potential and, due to its slow-growing nature, disease-free status cannot be ascertained until several years of follow-up. However, previous studies have already documented that colorectal carcinoid tumors ≤ 10 mm still have metastatic potential.[5,12] Identifying the optimal cut-off tumor size for possible metastasis requires larger population-based studies.

Although carcinoid tumors had initially been termed as friendly tumors, they have now been known to develop in the mucosal gland, gradually infiltrate the submucosa, and subsequently metastasize. The oncologic society has already stipulated the clinical stages in the AJCC cancer staging manual, which is proof alone that the metastatic potential of this disease has been recognized. In our study, we arbitrarily divided these clinical stages into two groups due to limited sample size. The advanced stage, showing lymph node or distant metastasis, had a significantly poorer disease-free and overall survival rates, than the early stage. In other words, our data confirmed the metastatic potential of colorectal carcinoid tumors. However, one interesting fact emerged during our review; some patients without a disease-free status were able to survive for several months or even years due to its slow-growing nature.[13] A review of previous literature showed that disease-free survival had not been identified as a prognostic factor. In this study, we found that patients who later on presented with disease recurrences, showed a binominal distribution of disease-free survival. A survival of ≥ 60 months could be seen in patients with disease-free survival ≥ 12 months. In contrast, those patients with a disease recurrence in ≤ 12 months died several months later. Therefore, according to our data, we deduce that two different patterns of aggressiveness may exist in colorectal carcinoid presentation. Patients who remain disease-free for ≥ 1 year have a higher probability of survival for ≥ 3 years. However, a limited sample size of this study necessitates a further scrutiny of this conclusion, including a proper pathologic review to define the histopathological features of the tumors.[9]

Due to the rare incidence of carcinoid tumors, it is difficult to achieve statistically significant results to determine the optimal resection method for these types of tumor. Two reports in 1990s questioned the necessity of aggressive surgery for every anorectal carcinoid.[9,15] Recently, a Korean study with 500 cases of rectal carcinoids had concluded that, for tumor ≤ 10 mm, regional resection, including endoscopic excision, was adequate.[5] Another Korean study also demonstrated that endoscopic resection of small rectal carcinoids could be safe and efficacious.[14] Our study

also demonstrated that, as long as a R0 resection with adequate safety margin was performed, endoscopic resection could obtain comparable disease-free and overall survival with radical resection.

Conclusion

The incidence of rectal carcinoids is much higher than colonic carcinoids. Rectal carcinoids tend to be small in size and rarely metastasize. Patients with a tumor ≥ 10 mm have a significantly higher incidence of metastasis and have poorer disease-free and overall survival rates. For small-sized carcinoids, endoscopic or local excision is adequate to obtain a good treatment outcome. If patients could achieve disease-free status for ≥ 1 year, they may have a greater chance of survival for ≥ 3 years.

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原　著

大腸直腸類癌的預後分析

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目的　我們進行院內的病歷回顧，並分析治療結果。

方法　我們總共分析了 18 年內 27 個接受腫瘤切除的病人。比較分析包括病人的腫瘤大小、腫瘤位置、疾病分期、腫瘤切除方式、無病存活和總存活期。

結果　病人的總存活及無病存活月數各別為 88.9% 及 80.9%。腫瘤大於一公分或源自於大腸，較容易出現淋巴或遠處轉移 (p = 0.0006 和 0.03)。直腸類癌、較早疾病期別 (第一、二期)、或腫瘤小於 (等於) 一公分都有較好的 5 年無病及總存活期。對於可完整切除的類癌，內視鏡切除或手術切除兩者對存活期的影響並無差異。

結論　直腸類癌的發生率比大腸類癌高得多，且多半體積較小，也不容易出現轉移病灶。腫瘤若大於一公分，病人較容易出現轉移病灶，且無病存活及總存活期會顯著惡化。對於腫瘤較小的類癌，內視鏡切除或手術局部切除是合適的。

關鍵詞　大腸直腸類癌、類癌、直腸類癌。