

Factors associated with complete local excision of small rectal carcinoid tumor

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Abstract

Purpose Although small rectal carcinoid tumors can be treated using local excision, complete resection can be difficult because tumors are located in the submucosal layer. We evaluate the factors associated with pathologically complete local resection of rectal carcinoid tumors.

Methods Data were analyzed of 161 patients with 166 rectal carcinoid tumors who underwent local excision with curative intent from January 2001 to December 2010. A pathologically complete resection (P-CR) was defined as an en bloc resection with tumor-free lateral and deep margins. The study classified treatments into three categories for analysis: conventional polypectomy (including strip biopsy, snare polypectomy, and hot biopsy), advanced endoscopic techniques (including endoscopic mucosal resection with cap and endoscopic submucosal dissection), and surgical local excision (including transanal excision and transanal endoscopic microsurgery). We evaluated the P-CR rate according to treatment method, tumor size, initial endoscopic impression and the use of endoscopic ultrasound (EUS) or transrectal ultrasound (TRUS).

Results The mean tumor size was 5.51 ± 2.43 mm (range 2–18 mm) and all lesions were confined to the submucosal layer. The P-CR rates were 30.9, 72.0, and 81.8 % for conventional polypectomy, advanced endoscopic techniques, and surgical local excision, respectively. Univariate analysis showed that P-CR was associated with treatment

method, use of EUS or TRUS, and initial endoscopic impression. Multivariate analysis showed that only treatment method was associated with P-CR.

Conclusion Pathologically complete resection of small rectal carcinoid tumors was more likely to be achieved when using advanced endoscopic techniques or surgical local excision rather than conventional polypectomy.

Keywords Rectal carcinoid tumor · Pathologically complete resection

Introduction

The number of cases of neuroendocrine tumors has increased over time, most likely due to increased awareness among physicians and greater use of endoscopy [1, 2]. Endoscopic screening has not only increased the number of rectal carcinoid tumor cases, but has also led to earlier detection [2].

A standardized treatment for small rectal carcinoid remains to be established. Small rectal carcinoid tumors without muscularis propria invasion can be treated using local excision since they rarely metastasize [3–6]. Following local excision, patients may need to undergo further treatment according to margin status, the size of the primary tumor, the depth of invasion, the presence of angiolymphatic invasion, and the mitotic rate. Achieving complete excision has a major bearing on the type of post-excision treatment. However, carcinoid tumors arise from the deep portion of the epithelial glands and then penetrate the muscularis mucosa into the submucosal layer where they form a nodular lesion. Those characteristics have made it difficult to achieve a tumor-free resection margin using conventional polypectomy and have led to the development of new

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endoscopic resection methods, including endoscopic mucosal resection with cap (EMR-C) and endoscopic submucosal dissection (ESD) [7–12].

The present study analyzed the treatment and outcomes of rectal carcinoid tumor patients who underwent local excision in our hospital. The study identified factors that were associated with a pathologically complete resection (P-CR).

Patients and methods

Patients

From January 2001 to December 2010, a total of 299 patients with colorectal carcinoid tumors were treated at the National Cancer Center in South Korea. We reviewed patient medical records and analyzed the endoscopic findings, procedures, and pathology reports. The study was approved by our institutional review board (NCCNCS-11-530). The study excluded patients with metastatic disease ($n=10$), who underwent radical surgery for primary therapy ($n=33$) and concurrent chemoradiotherapy for synchronous anal cancer ($n=1$), who were diagnosed pathologically in other hospitals ($n=91$), and who had colon carcinoid tumors located more than 15 cm above the anal verge ($n=3$). Following exclusions, there were 161 patients who had 166 rectal carcinoid tumors which were diagnosed as well-differentiated neuroendocrine tumors (Grade I) according to the WHO classification.

Patients underwent local excision using endoscopic or surgical resection. Resection was performed based on a colonoscopy diagnosis of a rectal polyp or a submucosal tumor regardless of histological confirmation. All resected lesions were ultimately diagnosed as being rectal carcinoid tumors upon histological examination. All patients were evaluated for metastasis to a distant organ or a regional lymph node using abdominopelvic computed tomography (CT). All specimens were referred to pathologists and examined microscopically for tumor size, depth of invasion, angiolymphatic invasion, and resection margin status. P-CR was defined as an en bloc resection with tumor-free lateral and deep margins.

Endoscopic procedures

Before October 2003, local excision of small rectal carcinoid tumors was achieved using conventional polypectomy (including strip biopsy, snare polypectomy, and hot biopsy), or surgical local excision (including TAE and TEM). The advanced endoscopic procedures of EMR-C and ESD were used from October 2003 and March 2007, respectively. Endoscopists have preferred ESD to EMR-C for resecting

the carcinoid tumor since March 2007. EMR-C and ESD were performed by five and four expert endoscopists, respectively. Endoscopic ultrasound (EUS) was used to assess rectal carcinoid tumor depth of invasion from 2007. The choice of resection method for rectal carcinoid tumors and the use of EUS were left to the respective operators. The details of all procedures have been presented in previous reports [13, 14].

Data analysis

We evaluated the P-CR rate according to treatment method, tumor size, initial impression at colonoscopy and the use of EUS or transanal ultrasound (TRUS). Tumor size (i.e., the longest diameter) was determined using colonoscopic findings. For analysis, tumors were categorized into three sizes: (a) <5 mm, (b) ≥ 5 mm but <10 mm, and (c) ≥ 10 mm.

Categorical data were compared using chi-squared or Fisher's exact tests. Multivariate logistic regression analysis was performed to identify factors associated with P-CR. $P < 0.05$ was considered to indicate significance. Statistical analyses were performed using the SPSS 14.0 statistical software package for Windows (SPSS Inc, Chicago, IL, USA).

Follow-up

Follow-up treatment differed according to whether P-CR was achieved. Patients with a tumor-free resection margin were recommended for repeat sigmoidoscopy every 6 months for the first 2 years. Patients with tumor removal that was pathologically incomplete but clinically complete were recommended to undergo a sigmoidoscopy every 3 months with a biopsy on scar tissue for the first 1 year. Rectal carcinoid tumors that were ≥ 10 mm in size, were positive for angiolymphatic invasion, or had invaded deeper than the submucosal layer were recommended to be treated with radical resection. Endoscopic resection or surgical local excision was again attempted in cases of clinically incomplete removal but in the absence of the aforementioned features (i.e., ≥ 10 mm in size, positive for angiolymphatic invasion, and had invaded deeper than the submucosal layer). All patients underwent an annual follow-up involving chest radiography and abdominopelvic CT, in addition to endoscopy.

Results

The mean age of the 161 patients was 52.65 ± 10.15 years (range 32–77 years, median 52.0 years), and the mean tumor diameter for the 166 lesions was 5.51 ± 2.43 mm (range 2–18 mm, median 5.0 mm) (Table 1). All lesions were confined to the submucosal layer without invading the proper muscle layer.

Table 1 Characteristics of patients and lesions

Characteristic	Value
Age, year	
Mean (range)	52.65 (32–77)
Median	52.0
Sex (male:female)	96:65
Mean distance from anal verge (range), cm	6.84 (2–15)
Tumor size	
Mean (range), mm	5.51 (2–18)
Median, mm	5.0
<5 mm, <i>n</i>	62
5 mm ≤ lesion < 10 mm, <i>n</i>	93
≥ 10 mm, <i>n</i>	11

The overall P-CR rate was 59.0 % (98 of 166 lesions). The P-CR rate was 66.2 % (90 of 136 lesions) when the initial endoscopic impression was a submucosal tumor. The P-CR rates were 30.9, 72.0, and 81.8 % for conventional polypectomy, advanced endoscopic techniques, and surgical local excision, respectively. Univariate analysis showed that P-CR was associated with treatment method, use of EUS or TRUS, and initial endoscopic impression (Table 2). We performed a multivariate analysis to determine whether treatment method, use of EUS, or initial endoscopic impression had an effect on P-CR. We found that P-CR was only associated with treatment method (Table 3).

Salvage treatment and follow-up

A total of 153 lesions were followed-up, and the median follow-up period was 31.0 months (mean 33.26 ± 24.02, range 1–105 months). After histopathologic assessment, additional treatment was undertaken for 25 lesions; those treatments comprised 15 endoscopic excisions, five surgical local excisions, and five radical operations with regional lymph node dissection.

Although 14 lesions met the criteria for additional radical surgery, only five lesions underwent radical operations due to patient refusal, old age, or another coexisting malignancy. Four cases showed metastasis to a regional lymph node according to the final pathology report after radical surgery. Of those, two cases had tumors less than 10 mm in size with positive angiolymphatic invasion. Neither local recurrence nor metastasis to regional lymph node or distal organs was found in any of the 153 lesions during the follow-up period.

Discussion

Small rectal carcinoid tumors located within the submucosal layer are considered candidates for local treatment even though a consensus has yet to be reached regarding a

Table 2 Pathologically complete resection rates according to various factors

	Complete resection, <i>n</i> (rate, %)	<i>p</i> value
Gender		0.426
Male	61/99 (61.6)	
Female	37/67 (55.2)	
Distance from anal verge		0.261
<7 cm	49/75 (65.3)	
≥7 cm	49/88 (55.7)	
Procedure		<0.001
Polypectomy	5/27 (18.5)	
Strip biopsy	12/28 (42.9)	
EMR-C	38/53 (71.7)	
ESD	34/47 (72.3)	
TEM/TAE	9/11 (81.8)	
EUS or TRUS		0.026
Yes	24/31 (77.4)	
No	74/135 (54.8)	
Size (on colonoscopic report)		0.132
<5 mm	34/62 (54.8)	
5 mm ≤ lesion < 10 mm	60/93 (64.5)	
≥ 10 mm	4/11 (36.4)	
Initial endoscopic impression		<0.001
SMT	90/136 (66.2)	
Polyp	8/30 (26.7)	

EMR-C endoscopic submucosal resection with cap, ESD endoscopic submucosal dissection, TEM Transanal endoscopic microsurgery, TAE Transanal excision, SMT submucosal tumor

threshold size for local excision. Achieving complete tumor removal has a major impact on the type of further treatment, and various treatment modalities have been reported to achieve clear margins using deeper resection [7–12].

The present study found that treatment method was the only factor that independently affected the P-CR rate. Advanced endoscopic resection techniques including EMR-C and ESD or surgical local excision were found to be superior to conventional polypectomy to achieve the P-CR. However, the P-CR rates for advanced endoscopic technique and surgical local excision were found to be similar. The present ESD P-CR rate was lower than rates reported elsewhere

Table 3 Multivariate analysis to determine factors associated with pathologically complete resection

	OR (95 % CI)	<i>p</i> value
Procedure ^a	4.0 (1.65–9.70)	0.002
EUS	1.765 (0.652–4.783)	0.264
Initial endoscopic impression	1.959 (0.658–5.834)	0.227

^a Advanced endoscopic methods and surgical local excision were compared with conventional polypectomy

[15–17]. This may have been because our study included our early experience with ESD, which may have lowered the P-CR rate for that technique.

The current study was mainly focused on P-CR rather than clinically complete resection. Some endoscopists regard successful en bloc resection as clinically complete resection and put more weight on it than P-CR based on endoscopic cauterization eradicating tumor cells close to the resection margin. However, only lesions considered completely clinically removed but pathologically incompletely removed are considered to need more frequent surveillance, albeit that a consensus protocol has yet to be established. An incompletely removed conventional polypectomy resection specimen can sometimes be difficult to histopathologically evaluate in order to determine the size of the primary tumor and angiolymphatic invasion. In our study, four of the five cases that underwent radical operations were found to involve lymph node metastasis. All of those cases involved tumors ≥ 10 mm with a tumor-involved resection margin or a positive angiolymphatic invasion. Those factors (i.e., tumor size and angiolymphatic invasion) have been shown to be risk factors for lymph node metastasis [5, 6, 18]. Tumor size and angiolymphatic invasion are important factors in terms of treatment following local excision, and a completely removed specimen would be helpful to determine the precise size and the occurrence of angiolymphatic invasion.

We usually applied local treatment for rectal carcinoid tumors lesser than 10 mm in diameter and confined to the submucosal layer without definite evidence of lymph node metastasis in imaging test including abdominal and pelvic CT scan. Patients with carcinoid tumors more than 10 mm in size or positive angiolymphatic invasion were recommended with

radical operation. In our study, 14 patients were recommended with radical operation after local treatment but only five patients underwent the additional operation (Table 4). Although recurrences or metastases were not occurred yet during follow-up period in our patients, further longer follow-up should be needed because carcinoid tumors are known to be slow-growing tumors.

We anticipated that using EUS to determine the degree of submucosal invasion would result in better treatment selection and hence a better P-CR rate. For example, surgical local excision or deeper endoscopic submucosal dissection could be chosen for carcinoid tumors located deep in the submucosal layer. However, we found that use of EUS did not improve the P-CR rate (data not shown).

This study found the increase of P-CR rate when the submucosal tumor was suspected on colonoscopy. This increase was thought to be because advanced endoscopic techniques or surgical local excision was usually performed in those cases. Rectal carcinoid tumors typically appear as sessile, submucosal tumors covered with yellow-discolored mucosa on colonoscopy [19], and endoscopically, it is not very difficult to distinguish them from polyps. Therefore, when the gross endoscopic impression is a submucosal tumor including a rectal carcinoid, it would be expected that complete resection would be achieved using one of the advanced endoscopic resection methods or surgical local excision rather than conventional polypectomy.

In conclusion, advanced endoscopic techniques and surgical local excision were found to more likely result in pathologically complete resection compared to conventional polypectomy in local treatment of small rectal carcinoid tumors.

Table 4 Patients with high-risk tumors for metastases or recurrences

Case	Sex	Age	Local treatment	Risk factors (size, margin, ALI)	Results of radical operation (LN: metastatic LN/harvest LN)
1	F	66	ESD	10 mm, Pos, Neg	no residual tumor, LN 1/17
2	F	44	EMR-C	10 mm, Pos, Neg	reject operation
3	F	56	EMR-C	10 mm, Neg, Neg	reject operation
4	F	55	ESD	11 mm, Pos, Neg	no residual tumor, LN 0/21
5	M	71	TEM	11 mm, Neg, Neg	reject operation
6	F	58	EMR-C	12 mm, Pos, Pos	no residual tumor, LN 3/16
7	M	38	EMR-C	12 mm, Pos, Neg	reject operation
8	M	59	EMR	13 mm, Neg, Neg	reject operation
9	M	42	snaring	13 mm, Neg, Neg	reject operation
10	M	47	TEM	16 mm, Pos, Neg	reject operation
11	F	63	EMR	18 mm, Neg, Neg	reject operation
12	M	37	EMR-C	6 mm, Neg, Pos	no residual tumor, LN 3/19
13	M	56	TEM	8 mm, Neg, Pos	reject operation
14	M	53	ESD	6 mm, Pos, Pos	no residual tumor, LN 0/11

EMR-C endoscopic submucosal resection with cap, *ESD* endoscopic submucosal dissection, *TEM* Transanal endoscopic microsurgery, *ALI* angiolymphatic invasion, *LN* lymph node, *Pos* positive, *Neg* negative

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