TRANSANAL ENDOSCOPIC MICROSURGERY IN THE MANAGEMENT OF RECTAL CARCINOID

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ABSTRACT

AIMS: Carcinoid tumors, a type of neuro-endocrine tumors (NETs), comprise a heterogeneous group of neoplasms arising from cells of the neuro-endocrine system. Rectal carcinoid tumors are relatively uncommon, representing 1,1% to 1,3% of all rectal neoplasms. Their incidence is dramatically increasing. The aim of this study was to review our department's experience and assess the efficacy of transanal endoscopic microsurgery (TEM) in the management of rectal carcinoid tumor.

METHODS: Between 2013 and 2015, four patients with rectal carcinoid underwent TEM, and their clinical data were reviewed retrospectively.

RESULTS: Two patients (50%) were identified as high-risk patients and underwent TEM, full-thickness excision and two ones (50%) were identified as low-risk patients and underwent TEM, submucosal resection. One patient from the high-risk group was referred to us by gastroenterologist from another hospital for complete surgery after endoscopic polypectomy with microscopically tumor positive resection margin. Tumor size was bigger in high-risk patients than in low-risk ones (14 and 20 mm versus 7 and 9 mm). There was no lymphovascular invasion in both groups. The operation time was longer in the full-thickness excision than in the submucosal resection group (45 and 55 min versus 27 and 33 min). One patient with full-thickness excision was complicated with acute urinary retention. There was neither local recurrence, nor distant metastasis in our patients during the follow-up period.

CONCLUSIONS: Our data suggest that TEM is a safe, minimally invasive approach for local excision of rectal carcinoid tumors and, generally, leads to good oncological and surgical outcomes. Furthermore, for patients with microscopically positive margins after endoscopic polypectomy, TEM can be an effective surgical option for complete residual tumor removal. *Scr Sci Med.* 2017;49(4):64-72

Keywords: rectal carcinoid, transanal endoscopic microsurgery, full-thickness excision, submucosal resection

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INTRODUCTION

Carcinoid tumors, a type of neuro-endocrine tumors (NETs), comprise a heterogeneous group of neoplasms arising from cells of the neuro-endocrine system. Rectal carcinoid tumors are relatively uncommon, representing 1,1% to 1,3% of all rectal neoplasms. Their incidence is dramatically increasing (1,2). These tumors can show a broad range of clinical behavior, from benign and asymptomatic to disseminated and metastatic (3). Because rectal car-

cinoid tumors often present as small and localized tumors that rarely recur after resection. Rectal carcinoid tumors have the best prognosis among all carcinoid tumors with a five-year survival rate at 88.3% and radical resection of these tumors on the basis of conventional risk stratification may be unnecessary (4-6).

A high risk of metastasis is associated with colorectal carcinoids exhibiting lymphovascular invasion or having a size >10 mm (7). One study reported metastases (including lymph node and distant metastasis) in 2% of the patients with rectal carcinoids measuring <10 mm, 10-15% of the patients with tumors measuring 10-20 mm, and 60-80% of the patients with tumors measuring >20 mm (8). Tumor size >11 mm and lymphatic invasion are independent predictors of lymph node metastasis, while tumor size >21 mm and venous invasion are predictive of distant metastasis (7). These findings support a strong correlation between tumor size and tumor metastasis in patients with colorectal carcinoids.

Previously reported risk factors for distant or lymph node metastasis include tumor size, histopathological differentiation, muscular invasion, and lymphovascular invasion (7,9-12). Patients with these risk factors are consequently referred to as high-risk patients who are recommended to undergo radical excision in order to decrease the possibility of distant metastasis. In fact, Onozato *et al.* observed no local or distant recurrence in 40 cases of rectal carcinoids with no associated risk factors (tumor size >1 cm in diameter or muscular invasion) among the rectal carcinoid cases treated by endoscopy (13). They recommended the following criteria for endoscopic treatment of rectal carcinoid tumors: diameter ≤10 mm, no muscular layer invasion, and no metastases to the pararectal lymph nodes (13,14). Park *et al.* reported similar clinical outcomes of endoscopic treatment and surgical treatment in patients with rectal carcinoids measuring 10-15 mm in diameter and with no associated metastasis (15).

There are several methods that can be used in the resection of rectal carcinoid tumors. Recently, the endoscopic submucosal dissection (ESD) method has been widely adopted by many centers, and its use in the resection of rectal carcinoid tumors is increasing (16). ESD is a very attractive method in terms of its

high rates of *en bloc* and complete resection (5,17-22). On the other hand, ESD is associated with a high risk of complications, especially when the endoscopist is not well-trained.

Transanal endoscopic microsurgery (TEM) was developed by Buess *et al.* (23) in Germany and introduced into clinical practice in 1983. TEM procedure offers several advantages over conventional transanal excision by providing much improved visualization, exposure, and access to higher lesions in the rectum. It enables accurate determination of margins and the execution of wide, full-thickness excisions under high magnification. TEM clinical efficacy for benign adenomas and T1 low-risk cancer with subsequent low complication and acceptable recurrence rates has already been widely reported (24-27). However, there is little literature regarding TEM for rectal carcinoid tumors, and the role of TEM in the treatment of rectal carcinoid tumor has not been fully detailed.

We report our clinical experiences involving four patients with rectal carcinoid tumors treated by TEM and assess the efficacy of this technique in rectal carcinoid management.

MATERIALS AND METHODS

Between 2013 and 2015, four patients with rectal carcinoid underwent TEM in our institution. Three patients were males (75%) and the median age was 66.3 years among all of them (range: 54 to 76 years). Fourth patient was a 62 year-old female (25%). The most common presenting symptoms were rectal bleeding, anal pain and discomfort. Data about patients' demographics, clinical presentations, treatment modalities, recurrence, and survival were retrospectively reviewed and analyzed (Table 1).

All tumors were located within 15 cm from anal verge and diagnosed by colonoscopy, biopsies and histopathologic evaluation. The tumor size was defined by the largest diameter of the tumor. Preoperative patients' examinations did not show any regional lymph node enlargement on computed tomography (CT) scanning or endorectal ultrasonography (EUS). All specimens were referred to pathologists and examined microscopically for tumor size, invasion depth, and resection margin status.

TEM, submucosal resection in adequately clear margins was considered as curative treatment for

Table 1. Patients' demographics, clinical characteristics and operative technique

	Overall	Tumor size <10 mm low-risk	Tumor size >10 mm high-risk
Age (median)	65.2	58	72.1
Male/Female	3/1	1/1	2/0
Bleeding	4	2	2
Tenesmus	3	1	2
Rectal mass	1	0	1
Anal pain	1	0	1
Anal discomfort	2	1	1
TEM, full-thickness excision	2	0	2
TEM, submucosal resection	2	2	0

low-risk patients with small rectal carcinoids (<10 mm). For high-risk patients with larger rectal carcinoids (>10 mm) or those with positive margin after polypectomy, TEM, full-thickness excision would be performed. All TEM procedures were performed with the patient under general anesthesia, lithotomy position, prone or left or right lateral position, so that the lesion was situated at the bottom of the operation field. Anal dilatation was first accomplished to facilitate insertion of the operating rectal tube in anal canal. TEM, submucosal resection was performed using mixture of glycerin and fructose, normal saline, adrenaline, and methylene blue for injection into the submucosal plane to create a visible submucosal cushion for elevation of the lesion (Fig. 1 and Fig. 2). Submucosal resection was completed using the ultra-

Fig. 2. Case 3. Injection into the submucosal plane *Fig. 1. Case 3. Carcinoid recti, sessile type (0-Is)* *Fig. 3. Case 3. TEM, submucosal resection is completed*

Fig. 4. Case 2. Carcinoid recti

Fig. 6. Case 2. TEM, full-thickness excision

Fig. 5. Case 2. TEM, full-thickness excision

Fig. 7. Case 2. TEM, full-thickness excision is completed

Table 2. Clinicopathological and surgical characteristics of patients with rectal carcinoid treated by TEM

Case	1	2	3	4
Age	54	69	62	76
Sex	M	M	F	M
High/Low-risk	High-risk	High-risk	Low-risk	Low-risk
Location	Rb	Ra	Ra	Rs
Distance from the dentate line (cm)	5	8	10	13
Size of primary tumor (mm)	14	20	9	7
Depth of invasion	Submucosa	Muscularis propria	Submucosa	Mucosa
Lymphatic invasion	Absent	Absent	Absent	Absent
Vascular invasion	Absent	Absent	Absent	Absent
Operation time (min)	45	55	27	33
Resection	R0	R0	R0	R0
Follow-up (months)	34	22	29	46

sonic scissors, then the wound was closed with absorbable sutures (Fig. 3).

Before TEM, full-thickness excision the scheduled resection area, including the tumor and a clearance margin of 1 cm, was circled with coagulation dots by a needle electrode, and resection was completed using the ultrasonic scissors (Fig. 4, Fig. 5, and Fig. 6). Excision included tumor and surrounding tissue in adequately clear margins, down to perirectal fat (Fig. 7). The defect in the rectal wall then was irrigated with 100 mL of diluted povidone-iodine and closed by a continuous running suture with 3/0 ab-

Fig. 8. Case 2. TEM, endoscopic suture of the rectal wall defect

Fig. 9. Case 2. Final view after TEM full-thickness excision

sorbable monofilament (Fig. 8 and Fig. 9). Postoperatively, an antibiotic was administered for three days.

The patients were followed-up by digital examinations performed at four weeks after operation, and then at every 2-3-month intervals in the first and second year, as well as by colonoscopy at 3, 6 and 12 months and then annually thereafter. CT scan was used annually in patients with high-risk to look for regional and distant metastasis.

Fig. 10. EUS in Case 3. Arrows show submucosal layer, it is narrowed but not completely disrupted

RESULTS

In total, four patients with rectal carcinoid tumors were identified. Of them, two (50%) were considered high-risk patients, who underwent TEM, full-thickness excision and other two (50%) were considered low-risk ones, and they underwent TEM, submucosal resection.

The clinicopathologic and surgical characteristics of rectal carcinoid patients enrolled in this study were summarized in Table 2. High-risk patient's age was 54 and 69 years while low-risk patient's age was 62 and 76 years. Tumor location on rectal wall based on the Japanese Classification of Colorectal Carcinoma (28) in terms of borders of 1 cm, 6 cm, and 12 cm above dentate line (DL) was the following: Rb (1.1-6.0 cm above DL), Ra (6.1-12 cm above DL), and Rs (12.1-15 cm above DL). In our study, tumor locations were all in rectum with majority of rectal tumors located in the middle rectum (n=2, 50% - Ra), one in the low-

er rectum (25% - Rb), and one in the upper rectum (25% - Rs).

Tumor size was bigger in high-risk patients (14 and 20 mm) than in low-risk ones (7 and 9 mm), two tumors invaded the submucosal layer (Case 1 and 3), one - the mucosa (Case 4), and another one - the muscularis propria (Case 2) on EUS and CT examinations, none showed metastatic disease to lymph nodes, vessels and/or distal organs. Based on the preoperative endoscopic findings, all the rectal carcinoid tumors were classified as sessile type (0-Is).

The operation time was longer in the full-thickness excision group than in the submucosal resection one (45 and 55 min versus 27 and 33 min) (Table 2). The overall rate of *en bloc* resection with lateral and vertical tumor-free margins was 100% (4/4) regardless of tumor size.

Histopathologic evaluation confirmed that all the tumors were classified as well-differentiated endocrine tumors (classical-type carcinoid) with architecture of trabecular or insular cell clusters with minimal cellular pleomorphism and sparse mitosis. Chromogranin A, a glycoprotein stored in secretory granules of neuroendocrine cells, was positive in 75% of the patients (Cases 1, 2, and 3). Synaptophysin, a neuron-specific enolase test, was found positive in 100% of the patients.

One patient from the high-risk group was referred to us by gastroenterologist from another hospital for complete surgery after endoscopic polypectomy with microscopically tumor positive resection margin (Case 1).

During the earlier postoperative period, one patient with full-thickness excision was complicated with acute urinary retention. He was successfully managed by consultation with urologist and conservative treatment, and no major morbidities occurred. All the patients in the study started walking on postoperative day (POD) one and peroral intake and hospital discharge was initiated on POD two.

No additional radical surgery was performed after TEM. Neither local recurrence, nor metastases to lymph nodes or distal organs was found in any of our patients during the follow-up period of mean duration of 32.7 months (range, 22-46 months). No patients died during the study period.

DISCUSSION

Rectal carcinoid tumor is a rare condition accounting for only 1.3 % of the overall rectal tumor cases (29,30). Tumor size is a known prognostic factor for rectal carcinoid tumors. Metastasis occurs in 5-15% of the tumors measuring 10 to 19 mm, but this incidence increases up to 80% for tumors 20 mm in size or larger (31). However, tumor size, invasion depth (muscularis propria or beyond), central depression or ulceration, mitotic index, vascular invasion, and Ki-67 labeling index may predict the risk of recurrence.

Thus, rectal carcinoids that are 10 to 19 mm in size do not have predictable behavior, and there is no consensus in the literature concerning the appropriate therapy for tumors of this size. However, it is currently difficult to decide between treatments such as conventional polypectomy, TEM technique, and radical surgery. It appears that small rectal carcinoids <1 cm in size can be safely managed by various types of endoscopic resection techniques such as strip biopsy, endoscopic mucosa resection (EMR) with cap aspiration, and ESD. For tumors >1 to ≤2 cm, TEM - local excision is usually recommended (32). In the current study, these two tumors ranging from 10 to 19 mm in size were completely resected by TEM, full-thickness excision. Radical surgery should be considered if there is evidence of invasion to the muscularis propria or lymph node metastasis. The preoperative pelvic radiological evaluations, such as CT or EUS are critical, and no enlarged lymph nodes were found in patients before surgery.

In our study, EUS was useful for measuring the size or depth of rectal carcinoid tumors, and the accuracy of the preoperative determination was 100% (Fig. 10). For rectal carcinoid tumors, EUS was not considered difficult because the endoscope is easily maneuvered in the rectum and the tumor was visualized as a low echoic mass with clear margins. Therefore, preoperative EUS assessment can be recommended to general surgeons, colorectal surgeons, and gastrointestinal endoscopists as an excellent diagnostic tool for rectal carcinoid tumors.

Most rectal carcinoids extend into the submucosa, as shown in the current study, and conventional polypectomy can't remove the tumors completely. There is a relatively high incidence rate of tumor-

positive resection margins or subsequent recurrences. The incidence rate of a positive margin after endoscopic polypectomy for rectal carcinoid tumors is 17%, even in an institution with much experience (33). Therefore, patient's selection for endoscopic polypectomy should be carefully done, and, probably, limited to small carcinoids growing like a polyp, because endoscopic polypectomy using a two channel colonoscope often results in crush injury of resected specimens (34). Otherwise, it is advisable to perform TEM as the intervention to achieve complete removal of rectal carcinoid in selected high-risk patients.

If the resected margin is identified as tumor positive after endoscopic rectal polypectomy, TEM can be an effective option for completion surgery, as described in this paper. Indeed, our case with positive margins after endoscopic rectal polypectomy has microscopic evidence of residual tumors shown in specimens obtained by TEM.

There was neither local recurrence, nor metastasis after careful follow-up assessment of our patients following TEM as completion surgery for rectal carcinoid tumor. For such patients, a major surgical procedure such as anterior resection seems too invasive because of the high incidence rate of complications as compared with TEM.

In a follow-up period, colonoscopy would be considered every 3-5 years with an aim to rule out local recurrence and metachronous colorectal malignancy (35,36). Although most local recurrences could be detected by digital examination and colonoscopy in our patients, some smaller submucosal recurrence could still be missed. In this case, EUS can play a role in identifying the small submucosal recurrence, and it is recommended as a surveillance tool for monitoring the local disease recurrence (35,36). For stage II/III diseases, CT surveillance would be essential to look for any distant metastases, particularly liver metastases, as we have been offering to our patients. As distant metastases may occur years after the initial treatment, long-term surveillance beyond five years was suggested in patients with high-risk factors (36).

CONCLUSIONS

Our data suggest that in appropriate patients, TEM is a safe, minimally invasive approach for local excision of rectal carcinoid tumors and, generally, leads to good oncological and surgical outcomes.

Furthermore, for patients with microscopic positive margins after endoscopic polypectomy, TEM can be an effective surgical option for complete residual tumor removal and allows precise histologic assessment of the resected specimen.

With the TEM technique, not only horizontal but also vertical margins of rectal carcinoid tumors can be visualized directly during the procedures. This procedure can provide adequate thickness of submucosa and other parts of rectal wall, and undamaged resected specimens can be obtained.

The present study has several notable limitations. First, the number of patients is too small to offer conclusive results. In addition, the follow-up period is limited. There may be a case with late relapse, however, the biological behavior of this tumor remains unclear. However, given the lack of evidence concerning TEM-local resection in high-risk rectal carcinoid patients, the results of this study may be useful to motivate future research and prompt selection of less invasive treatments.

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