

Endoscopic mucosal resection of duodenal carcinoid tumors: a single tertiary care center experience

Abstract

Background and Aims: There is no consensus on the optimal treatment of duodenal carcinoid tumors. Endoscopic mucosal resection (EMR) is considered appropriate for tumors <1cm in size confined to the mucosa/submucosa. In this retrospective study we examine the safety and efficacy of duodenal carcinoid EMR at a single tertiary care center.

Methods: All patients with duodenal carcinoids resected via EMR at Duke University Medical Center from 1999 to 2012 were identified. All had pathologic diagnoses and endoscopic ultrasound (EUS), followed by EMR using cap-ligation or standard snare polypectomy.

Results: 43 duodenal carcinoids were resected in 40 patients. 91% of tumors were located in the bulb. All tumors were limited to the mucosa or submucosa. Mean tumor size was 7.0mm. 28 tumors were removed using cap-ligation and 15 using snare polypectomy. Two post-procedure GI bleeds and two perforations occurred (one managed endoscopically, one managed surgically). 17 (40%) resected tumors had positive margins. 13 cases were lost to follow-up. Of the other 27 patients, 3 went on to surgical resection (all had positive margins at EMR). Mean follow-up time was 28.3 months. Three patients had local recurrence (2/3 had positive margins on initial resection), and three had lymph node metastases (all had positive margins on initial resection).

Conclusion: This is the largest single center study of its kind. Endoscopic resection of duodenal carcinoids should be considered prior to surgical resection after EUS evaluation to exclude muscularis propria involvement and lymph node spread. The significance of positive margins requires further study. Careful follow-up is necessary.

Keywords: carcinoid, duodenum, endoscopic mucosal resection

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Introduction

Carcinoid tumors are relatively uncommon neoplasms. They arise from neuroendocrine cells, and are most commonly found in the gastrointestinal tract, with 61% of all neuroendocrine tumors (NETs) gastroenteropancreatic in origin.¹⁻⁵ The term “carcinoid” is synonymous with “well-differentiated neuroendocrine tumor” when gastroenteric in origin.⁶ Carcinoid tumor cells contain neurosecretory granules composed of a variety of hormones and biogenic amines. One of the best known of these is serotonin. These substances are responsible for the symptoms of carcinoid tumors, including the “carcinoid syndrome”.^{7,8}

In most instances they are discovered incidentally at the time of surgery, endoscopy or on radiology studies. The average age at diagnosis is 65. Patients can become symptomatic due to mass effect or to secreted hormones and biogenic amines. The classic “carcinoid syndrome”, characterized by flushing and diarrhea, occurs in less than 10% of patients.⁹ Because they are commonly asymptomatic when confined to the GI tract, carcinoids are often diagnosed after metastasis. When the carcinoid syndrome is absent, peritumoral fibrosis often leads to symptoms due to resultant intestinal obstruction by adhesions and other complications such as mesenteric and retroperitoneal fibrosis.¹⁰⁻¹³ Other serious complications of GI carcinoid fibrosis include pulmonary fibrosis and serotonin related cardiac fibrosis, which is responsible for one third of the deaths in patients with carcinoid syndrome.^{14,15} The incidence of carcinoid tumors is unknown as many are indolent in nature. The incidence appears to be rising over time, at least in part due to increased detection through endoscopy and imaging.¹⁻⁵

Carcinoid tumors can be classified based on their location within an embryologic division in the gut. The histology, immunochemistry and clinical behavior of carcinoid tumors vary based on location in the foregut (stomach, duodenum, biliary system and pancreas), midgut (small intestine, appendix, cecum and proximal colon) or hindgut (distal colon and rectum).¹⁶ Tumors originating in the duodenum typically elaborate one or more polypeptide hormones, including somatostatin, gastrin, serotonin, calcitonin and insulin.¹⁴

Within the gastrointestinal tract, the most common locations are the rectum (17.7% of all NETs), small intestine (17.1% of NETs, most in the ileum) and colon (10.1% of NETs). Primary duodenal carcinoids account for only 3.4% of carcinoid tumors, but are increasingly recognized with more widespread use of endoscopy. Primary duodenal carcinoids are usually discovered at endoscopy performed for another indication.¹⁻³

Carcinoid tumors often exhibit a malignant clinical course. They may penetrate the lamina propria and invade the submucosa in the early stages. In general, 45.3% of all carcinoids present with metastases.² Several studies have shown that the chance of finding metastases increases with tumor size in the duodenum, small intestine and rectum. Invasion into the muscularis propria and the presence of mitotic figures also predicts metastatic disease. Studies have suggested that duodenal carcinoid tumors smaller than 2cm in size and limited to the submucosa have limited metastatic potential and can, therefore, be managed by local excision alone.¹⁷⁻²⁰ A Japanese registry study, however, found that 13% of duodenal carcinoids smaller than 1 cm had associated regional lymph node metastases.²¹ The natural history of carcinoid tumors and the risks for metastatic disease have not yet

been clearly delineated. For this reason there are no clear guidelines to indicate which carcinoid tumors are best managed endoscopically versus surgically.²²

Endoscopic resection of duodenal carcinoids can be difficult because they frequently invade the submucosa or deeper layers, and the duodenal wall is thin. Care must be taken when resecting these tumors, and it is therefore a concern that deep tumor margins may not be cleared. In theory the band ligation technique, versus standard snare technique, may produce a more reliable deep tissue resection and reduce the risk of positive resection margins, but this remains unclear.

In this retrospective study we examine the safety and efficacy of duodenal carcinoid EMR by standard wire snare polypectomy and cap-ligation techniques at Duke University Medical Center (DUMC), a single tertiary care center.

Patients and methods

The endoscopy and pathology databases at DUMC were reviewed to identify all patients with duodenal carcinoids resected via EMR between January 1999 and January 2012. Clinical and pathologic data was collected, including patient age and gender; lesion location, size and endosonographic depth of invasion; resection technique and adverse events; specimen histological analysis, including tumor-free margins; and, patient follow-up, including need for surgery and evidence of local recurrence or distant metastasis. This study was

approved by the Duke University School of Medicine Institutional Review Board.

All patients had histologic confirmation of carcinoid tumor, obtained by endoscopic biopsy. All underwent endoscopic ultrasound prior to resection to determine tumor depth, exclude muscularis propria involvement and exclude lymph node metastasis. EMR was performed using submucosal injection with saline with/without methylene blue and/or diluted epinephrine. This was followed with resection by cap-ligation technique with the Duette Multi-band Mucosectomy device (Cook Medical), or by standard wire snare polypectomy technique. The choice of standard snare versus cap-ligation was at the discretion of the endoscopist. All tumors were resected en bloc with electrocautery assistance.

Results

We retrospectively identified 40 patients with duodenal carcinoids. A total of 43 tumors underwent EMR (3 patients had 2 tumors each at diagnosis). The characteristics and outcomes are summarized in Table 1. 17 patients were female (42.5%) and 23 were male (57.5%). The mean age at time of resection was 64 (range 43 to 83). 39 tumors (91%) were located in the duodenal bulb, one (2%) at the junction of the first and second portions of the duodenum, and three (7%) in the second portion of the duodenum. One tumor was limited to the mucosa, while all others extended to the submucosa on EUS. The mean maximum tumor dimension via EUS was 7.0mm (range 3.1-11.3mm). There was no endosonographic evidence of lymphadenopathy or metastasis.

Table 1 Patient, tumor and treatment characteristics.

	Age	Sex	Tumor Location	No.	Size (mm)	Depth	Management	Adverse Events	Margins	Surgery	Follow-Up (months)	Local Recurrence	Metastases
1	77	F	Bulb	1	5.6	SM	Snare	None	Free	No	2	No	No
2	57	M	Bulb	1	NR	SM	Snare	None	Free	No	9	No	No
3	67	M	Bulb	1	5	SM	Snare	None	Free	Lost	Lost	-	-
4	56	F	D2	1	NR	SM	Snare	None	Free	No	32	No	No
5	60	F	D2	1	5.6	SM	Snare	None	Free	No	5	No	No
6	54	M	Bulb	1	11.3	SM	Snare	None	Free	No	79	No	No
7	51	F	Bulb	1	NR	SM	Snare	None	Free	No	86	No	No
8	80	M	Bulb	1	9	SM	Snare	None	Free	No	Lost	-	-
9	73	F	Bulb	1	5.1	SM	Snare	UGIB	Free	No	Lost	-	-
10	55	F	Bulb	1	6.3	SM	Cap	None	Free	No	65	No	No
11	75	M	Bulb	1	NR	SM	Cap	None	Free	Lost	Lost	-	-
12	79	M	Bulb	1	10	SM	Cap	None	Free	No	24	No	No
13	49	M	Bulb	1	8	SM	Cap	None	Free	No	35	No	No
14	61	M	Bulb	1	9	SM	Cap	None	Free	Lost	Lost	-	-
15	66	F	Bulb	1	3.3	SM	Cap	Perforation	Free	No	75	Yes	No
16	50	F	Bulb	1	5.4	SM	Cap	None	Free	No	6	No	No
17	66	M	Bulb	2	7	SM	Cap	None	Free	Lost	Lost	-	-
					5	SM	Cap	None	Free				
18	63	M	Bulb	1	8.4	Mucosa	Cap	None	Free	No	11	No	No
19	51	F	Bulb	1	9	SM	Cap	None	Free	No	6	No	No
20	61	M	Bulb	1	5.4	SM	Cap	None	Free	No	4	No	No
21	55	M	Bulb	1	3.1	SM	Cap	None	Free	No	Lost	-	-
22	76	M	Bulb	1	8	SM	Cap	Perforation	Free	No	Lost	-	-
23	72	M	D2	1	NR	SM	Cap	UGIB	Free	No	37	No	No
24	83	F	Bulb	1	6.7	SM	Snare	None	Positive	Lost	Lost	-	-
25	74	F	Bulb	1	8.8	SM	Snare	None	Positive	No	59	No	No
26	78	M	Bulb	1	5	SM	Snare	None	Positive	No	28	No	No
27	51	F	Bulb	1	5	SM	Snare	None	Positive	No	Lost	-	-

Table continued...

Age	Sex	Tumor Location	No.	Size (mm)	Depth	Management	Adverse Events	Margins	Surgery	Follow-Up (months)	Local Recurrence	Metastases
28 79	F	Bulb	1	small	SM	Snare	None	Positive	No	27	No	None
29 69	M	Bulb	1	medium	SM	Snare	None	Positive	No	7	Yes	None
30 43	M	Bulb	1	NR	SM	Cap	None	Positive	No	54	No	Yes
31 61	M	Bulb	2	7.3	SM	Cap	None	Positive	Yes	1	No	Yes
				8.9	SM	Cap	None	Free				
32 73	M	Bulb	1	9.7	SM	Cap	None	Positive	Lost	Lost	-	-
33 82	F	Bulb	2	5.4	SM	Cap	None	Positive	No	16	No	No
				5	SM	Cap	None	Free				
34 61	M	Bulb	1	7.3	SM	Cap	None	Positive	Yes	63	No	No
35 51	F	Bulb	1	8	SM	Cap	None	Positive	No	10	No	No
36 57	F	Bulb	1	9.2	SM	Cap	None	Positive	Yes	23	No	Yes
37 58	M	D1/D2 junction	1	5	SM	Cap	None	Positive	No	9	Yes	Unknown
38 73	M	Bulb	1	9	SM	Cap	None	Positive	No	5	No	No
39 64	F	Bulb	2	diminutive	SM	Cap	None	Positive	No	Lost	-	-
40 49	M	Bulb	1	7.4	SM	Cap	None	Positive	No	Lost	-	-

15 tumors (35%) were removed using standard snare technique and 28 (65%) were removed using cap-ligation technique. In one case cap-ligation was attempted first, but snare was used instead as band-ligation was not possible due to tumor location close to the pylorus. All tumors were resected en-bloc. There were two perforations, both in patients undergoing cap-ligation EMR (4.7% of total EMR, 7.1% of cap-ligation EMR, $p=0.5349$). Both perforations occurred in the duodenal bulb. One was managed endoscopically with clips and the other was managed surgically after endoscopic clipping was unsuccessful. Two patients (4.7%) had post-procedure GI bleeding requiring transfusion (one after snare polypectomy in the setting of anticoagulation and one after cap-ligation, $p = 1.0000$). The overall adverse event rate was 9.3% (6.7% in the snare group, 10.7% in the cap-ligation group, $p = 1.0000$). There were no adverse events in those with positive margins on histologic analysis of the resected tumors.

17 (40%) resected tumors had positive margins, including 6 of 15 tumors resected via snare (40% of the snare group) and 11 of 28 tumors resected via cap-ligation (39% of the cap-ligation group). There was no significant difference in positive tumor margins between the techniques used ($p = 1.0000$). The mean age of patients was 63 in the group with negative margins and 65 in the group with positive margins ($p = 0.6082$). Likewise, there was no significant difference in gender ($p = 0.7492$) or mean tumor size (6.8mm in negative margin group, 7.2mm in positive margin group, $p = 0.6116$).

13 cases were lost to follow-up after the initial procedure, 5 with positive margins and 8 with negative margins. Mean follow-up in the other 27 patients was 28.3 months (range 1 to 86 months). Of the 12 patients with positive resection margins not lost to follow-up, 3 underwent surgical resection. One had focal residual carcinoid tumor removed with negative surgical resection margins and negative surveillance upper endoscopy at 5 years after surgery; one had carcinoid tumor resected with negative surgical margins and 1/4 regional lymph nodes positive for metastatic carcinoid tumor, with surveillance CT showing likely hepatic metastasis 20 months after surgical resection; and one had carcinoid tumor resected with positive surgical margins and 1/18 regional lymph nodes positive for metastatic disease and no surveillance studies to date. None of the patients with negative resection margins underwent surgical resection.

On follow-up EUS examinations, three patients had local recurrence. One of these had negative margins and 2 had positive

margins on initial resection. Three patients had lymph node metastases on follow-up EUS (all of these had positive margins on initial resection). There were no metastases in patients with tumor free margins on initial resection.

Discussion

The understanding of duodenal carcinoid tumor biology and clinical behavior is limited. Five types of duodenal carcinoids are currently recognized and include (1) gastrinomas, (2) somatostatinomas, (3) nonfunctioning, (4) poorly differentiated and (5) duodenal gangliocytic paragangliomas.²³ Duodenal gangliocytic paragangliomas and nonfunctioning carcinoids carry a relatively favorable prognosis, whereas gastrinomas and poorly differentiated duodenal carcinoids often present with early metastasis.¹⁶

Carcinoid tumors arising in the small intestine have a greater propensity to metastasize, even at small sizes, compared to those in the appendix, colon and rectum. Invasion beyond the submucosa and the presence of mitotic figures are associated with metastatic disease.¹⁸ The frequency of metastases has been reported between 11-25% for tumors <10mm in size, 72-74% for tumors 11-19mm, and 73-95% for tumors >19mm in size.²⁴⁻²⁶ These data, however, are from analysis of carcinoids arising from any location in the small bowel, and therefore represent a bias for the more common location of carcinoids in the ileum. Duodenal lesions represent a unique dilemma. Unlike wide segmental excision of the distal small bowel, duodenal resection is a more complex undertaking. There is currently no consensus on the best approach to management. Proposed treatment of duodenal carcinoids has spanned a broad spectrum, including aggressive resection by pancreaticoduodenectomy, transduodenal local excision, full thickness laparoscopic excision and more conservative endoscopic resection.²⁰

Optimal management requires excision of the tumor beyond its deep margin. This can be challenging in the endoscopic resection of carcinoids in the duodenum due to the thin duodenal wall, which represents a higher risk for perforation. Endoscopic submucosal dissection (ESD) of rectal carcinoids appears to be a safe and effective technique to obtain complete resection;²⁷ however, the thin wall of the duodenum differs greatly. A Japanese case series reported 2 perforations in 3 cases of ESD for duodenal carcinoids, and the authors concluded that ESD is less desirable for duodenal lesions than

for gastric and rectal lesions.²⁸ Evidence for ESD in the duodenum is limited to case series and thus far requires further research and development. Resection beyond the deep margin in EMR can be aided by lifting the submucosal plane with submucosal injection. Aspiration with a cap may result in a more reliable deeper resection, as has been concluded in studies examining rectal carcinoid tumor resection.^{29–33} In a meta-analysis of several small series, Dalenback, et al concluded that endoscopic removal of duodenal carcinoids <10 mm, outside the periampullary region, with no EUS signs of invasion, is safe and effective.³⁴

The cohort presented here represents the largest single-center study of its kind, with 40 patients undergoing endoscopic mucosal resection of 43 carcinoid tumors. In our study, we report positive margins in 40% of the resected tumors, with no significant difference between the snare and cap-ligation techniques. A 40% rate of positive margins can be considered high, but interpretation of positive margins is not always straightforward. Cautery artifact likely plays a role, as the outer margins of cauterized tissue are fulgurated. These margins may contain normal tissue, but cautery can cause increased eosinophilia and elongate cells and nuclei, causing normal tissue to appear more dysplastic. Cautery can also simply destroy normal tissue.³⁵ This may especially be the case with longer cautery time with larger lesions. Tumor margin may be contained in the cautery margins of carcinoids resected in the duodenum, where wide resection may not be possible due to the relatively thin wall. In this case the pathologist reports that the tumor extends to the cautery margin, and we must assume that margins are positive. A better clinical mark may be that 10 of the 12 patients with positive margins not lost to follow-up had no local recurrence on the most recent follow-up.

Of the 28 EMRs using cap-ligation, 2 resulted in perforations. Although both perforations occurred in the cap-ligation group, the perforation rate was not statistically significant, and one perforation was managed conservatively without surgery with endoscopic clipping. Two patients had post-procedure GI bleeding requiring transfusion, one from the snare group and one from the cap-ligation group. The two GI bleeding events were resolved with transfusions. While the adverse event rate was 9.3% (4 patients) overall, only one patient required surgery, and the rest were managed conservatively. Interestingly, there were no adverse events in the patients with positive resection margins, which may indicate that a shallower resection may have led to fewer adverse events, but more positive margins.

This study has several weaknesses. It is a retrospective study with all the limitations of this type of analysis. There were also a large number of patients lost to follow-up. Though this did not affect our evaluation of the adverse event rate, it likely affected the evaluation of EMR efficacy in resecting duodenal NETs and avoiding surgery. As a large referral center, many patients are referred for the procedure and initial follow-up, and return back to their original physicians for further follow-up. Even in patients not entirely lost to follow-up, several had few follow-up visits, reducing the mean follow-up time. Pathology analysis of resection specimens did not include subtyping of NETs, and therefore no distinction can be made in this study between different types of carcinoids and their clinical outcomes.

Management of duodenal carcinoids remains a problematic issue. Although there were positive margins in 40% of resected tumors in our study, only 3 patients had to undergo surgical resection. Thus, it appears that endoscopic mucosal resection is a safe means of tumor removal in selected patients. EMR of loco-regional duodenal NETs 1cm or less should be the first line of treatment after EUS evaluation to

determine tumor size and exclude muscularis propria involvement and the presence of lymph node metastases. The significance of positive margins requires further study. Careful follow-up is necessary for patients with these tumors. Patients with positive resection margins who do not undergo surgical resection should undergo annual follow-up EUS evaluation. The appropriate duration of follow-up is unclear, and future investigation should include longer follow-up times.

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Conflicts of interest

Author declares there are no conflicts of interest.

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