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ORIGINAL PAPERS

Usefulness of endoscopic ultrasonography (EUS) for selecting carcinoid tumors as candidates to endoscopic resection

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ABSTRACT

Introduction: carcinoid tumors (CTs) represent the most common type of neuroendocrine tumors (NETs). Digestive CTs in the gastroduodenal and colorectal tracts may be assessed using endoscopy and echoendoscopy or endoscopic ultrasonography (EUS) with the goal of attempting local resection with curative intent without having recourse to surgery.

Objective: endpoints in this study included:

—Assessing the usefulness of EUS for selecting CTs as candidates to endoscopic excision.

—Assessing the effectiveness of local resection (complete carcinoid resection) and the safety (complications) of the technique involved.

Patients and methods: our series included 18 patients (12 males and 6 females) with 23 tumors. Sixteen patients (10 males and 6 females) were selected, with age ranging from 40 to 81 years (mean: 57 years), biopsied, endoscopically treated digestive carcinoid tumors, and a previous negative extension study. Twenty-one 2-to-20-mm (mean size 8 mm) tumors were resected in 23 procedures.

After endoscopy plus biopsy and echoendoscopy (EUS), excision was carried out with conventional polypectomy snare mucosectomy and submucosal injection with saline and/or adrenaline in most cases (15), and mucosectomy technique following lesion ligation with elastic bands for six cases. Two cases underwent transanal endoscopic surgery (TEM), one of them following non-curative polypectomy. A total of 23 local procedures were performed with the key goal of assessing efficacy (complete resection: CR) and safety (complications).

Results: there were no severe complications except for the last gastric mucosectomy for a 6-mm carcinoid, where a miniperforation occurred that was solved by using 3 clips (1/23: 4.3%).

EUS sensitivity was 94%. Complete resection was 90.5% (19/21).

RESUMEN

Introduccion: los tumores carcinoides (TC) son los tumores neuroendocrinos (TNEs) más frecuentes. Los TC digestivos localizados en el tracto gastroduodenal y rectocolónico pueden ser evaluados por endoscopia y por ecoendoscopia o ultrasonografía endoscópica (USE), con el objetivo de efectuar una resección local como tratamiento curativo sin recurrir a la cirugía.

Objetivo: los objetivos finales de este estudio fueron:

—Analizar si es útil la USE en la selección de TC como candidatos a una extirpación endoscópica.

—La evaluación de la eficacia de la resección local (resección completa del carcinoide) y la seguridad (complicaciones) de la técnica efectuada.

Pacientes y metodos: la serie consta de 18 pacientes (12 varones y 6 mujeres) con 23 tumores. Se han seleccionado 16 pacientes (10 varones y 6 mujeres) con un rango de 40 a 81 años (media: 57 años), con tumores carcinoides digestivos biopsiados y tratados endoscópicamente, con estudio previo de extensión negativo. Se resecaron 21 tumores de 2 a 20 mm (tamaño medio: 8 mm), en 23 procedimientos.

Después de endoscopia más biopsia y ecoendoscopia (USE), se llevó a cabo la extirpación mediante mucosectomía con asa de polipectomía convencional e inyección submucosa con suero salino y/o adrenalina en la mayoría de casos (15) y en seis con técnica de mucosectomía tras ligar la lesión con bandas elásticas. En dos casos con cirugía endoscópica transanal (TEM) (uno después de haber efectuado polipectomía no curativa). Se efectuaron en total 23 tratamientos localizados con el objetivo fundamental de evaluar la eficacia (resección completa: RC) y seguridad (complicaciones).

Resultados: no hubo complicaciones muy importantes, excepto en la última mucosectomía gástrica por un carcinoide de 6 mm, en la que se produjo una miniperforación (1/23: 4,3%) que se resolvió con la colocación de 3 clips.

La sensibilidad de la USE fue del 94%. La resección completa fue del 90,5% (19/21).

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Conclusions: the endoscopic mucosal resection of selected carcinoid tumors is a safe, effective technique. EUS is the technique of choice to select patients eligible for endoscopic resection (carcinoids smaller than 20 mm in superficial layers, with an unscathed muscularis propria and negative extension study).

Key words: Digestive carcinoid tumors. Gastroduodenal and colorectal carcinoid tumors. Endoscopic ultrasonography. Endoscopic mucosal resection. Polypectomy. Mucosectomy. With bands. Transanal endoscopic microsurgery. Complications.

Conclusiones: la resección mucosa endoscópica de tumores carcinoides seleccionados es una técnica segura y eficaz. La USE es la técnica de elección para seleccionar los pacientes candidatos a resección endoscópica (carcinoides menores de 20 mm situados en las primeras capas, con muscular propia indemne y con estudio de extensión negativo).

Palabras clave: Tumores carcinoides digestivos. Tumores carcinoides gastroduodenales y rectocolónicos. Ultrasonografía endoscópica. Resección mucosa endoscópica. Polipectomía, mucosectomía. Con bandas. Microcirugía endoscópica transanal.

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INTRODUCCIÓN

Carcinoid tumors (CTs) are the most common neuroendocrine tumors (NETs) with an incidence of 1 case/100,000 people/year (1), and are on the rise in the last few years.

Pulmonary CTs represent around 2% of all primary lung tumors and fewer than 25% of all CTs; the rest are digestive lesions (74%) (2,3).

Gastric CTs (GCTs) may be associated with type-A chronic atrophic gastritis or pernicious anemia (GCT type 1, up to 75%, 50% multifocal), Zollinger-Ellison syndrome (ZES), and multiple endocrine neoplasm (MEN-1) (GCT type 2, 5-10% of cases), or may be sporadic (GCT type 3, 15-25%), many of them single and metastatic lesions (3).

Digestive CTs in the gastroduodenal (5%) and colorectal (10 and 11%) tract may be assessed with endoscopy (2) and with echoendoscopy or endoscopic ultrasonography (EUS) with the goal of performing an endoscopic mucosal resection as curative therapy instead of surgery for local disease.

Gastroduodenal and rectal carcinoids smaller than 1 cm develop metastatic disease in fewer than 2% of cases (4,5); thus, when EUS reveals an unscathed muscularis propria local treatment can be effectively and safely performed.

When CT size is 1-2 cm therapy selection may be controversial since 10-15% (5) are estimated to develop metastasis, hence the treatment of choice will depend on patient age and surgical risk.

Tumors greater than 2 cm will develop metastatic disease in 60-80% of cases (4,5), with rectal lesions infiltrating the muscularis propria in 88% of cases, which demands radical surgery.

OBJECTIVE

Study endpoints included:

—Analyzing whether EUS is useful for screening CTs eligible for endoscopic excision.

—An assessment of local resection effectiveness (complete resection) and technique safety (complications).

PATIENTS AND METHODS

Our series includes 18 patients (12 males, 6 females) with 23 tumors identified from January 1st, 1997 to January 1st, 2009. Two patients with tiny tumors smaller than 5 mm in the rectum were excised, and biopsy samples were obtained.

Sixteen patients were selected (10 males and 6 females) with age ranging from 40 to 81 years (mean: 57 years) with digestive CTs biopsied and endoscopically treated from 1997 to 2009, and with a previous negative extension study; they were seen at Centro Médico Teknon, Barcelona, Hospital Universitario de Bellvitge, Hospitalet de Llobregat, and Centro Médico Delfos, Barcelona. This was a retrospective study.

Six physicians (2 per site) cooperated in therapies performed.

Twenty-one 2-20-mm tumors were resected (mean size: 8 mm).

Inclusion criteria for local therapy included patients with submucosal tumors smaller than 1 cm where EUS showed an unscathed muscularis propria, absence of perilesional adenopathies, and an extension study ruling out distant metastases.

Patients with tumors 1-2 cm in size and high surgical risk were also included.

Exclusion criteria included: size greater than 2 cm, muscularis propria infiltration, presence of perilesional adenopathies, and/or presence of distant metastases.

All patients with an identified digestive submucosal lesion and/or biopsy consistent with CT underwent EUS with a conventional radial or sectorial 7.5-to-20-MHz echoendoscope or 12-15-20-MHz miniprobe.

Parameters primarily assessed included size, EUS pattern and lesion depth, involved layers, and the presence of perilesional adenopathies.

All explorations were performed with an informed consent and under sedation (propofol) by an anesthetist.

Resection was performed using a conventional polypectomy loop, mucosectomy assisted by saline and/or diluted adrenaline submucosal injection, or mucosectomy aided by elastic band placement (6 cases).

Two anorectal carcinoids underwent transanal endoscopic microsurgery (TEM).

The pathology study included immunohistochemistry for chromogranin and synaptophysin in most cases, and Ki 67 in 4 cases.

Follow-up consisted of endoscopic crust biopsies at months 1, 6 and 12 following resection.

RESULTS

EUS failed to detect a tiny lesion, a false negative (F-) result, and there was a false positive (F+) finding; hence sensitivity was 94%.

Twenty-one carcinoid tumors in 16 patients with a mean age of 57 years (range 40-81 years) were treated. Ten were found in males (62.5%) and six in women (37.5%).

Demographic characteristics are listed in table I.

Bleeding rate was 0% whereas perforation rate was 4.3% (gastric miniperforation solved by 3 clips and observational follow-up for 72 hours).

Complete resection (CR) was 90.5% (19/21) with a minimum follow-up of 12 months.

In cases undergoing conventional polypectomy CR was 86.7% (13/15) *versus* 100% (8/8) with band-aided mucosectomy or TEM.

Table I

Variables	*Number of patients (%)*
Patients	16
Gender:	
Males	10 (62.5%)
Females	6 (37.5%)
Resected CTs	21
Procedures	23
Patients with multifocal CTs	7 (43%)
Associated conditions	
Atrophic gastritis. type A	2
MEN-1	2
Location:	
Stomach	13 (62%)
Duodenum	4 (19%)
Rectum	4 (19%)
Size	
Smaller than 10 mm	17 (80.9%)
10-20 mm	3 (14%)
More than 20 mm	1 (4.7%)
Resection technique	
Conventional snare-assisted polypectomy with subm. inj	15 (65%)
Band-assisted mucosectomy	6 (26%)
Transanal endoscopic microsurgery (TEM)	2 (8.7%)
Complete resection	19/21 (90.5%)
Complications	
Mini-perforation	1 (4.3%)
Bleeding	0 (0%)

DISCUSSION

Endoscopic resection for carcinoid tumors has been performed for ten years now, particularly by Japanese authors (6). Imada-Shirakata (7) and Higaki et al (8) demonstrated that rectal carcinoid tumors smaller than 10 mm and with extension within the submucosal layer (intact muscularis propria) have a minimal risk for metastatic disease.

Yohikane (9) treated 7 cases of duodenal (bulbar) carcinoid tumors 1.5 to 7 mm (X: 4.3 mm) in size with a complete resection rate of 100%. See Table 2. There was a good correlation between size as estimated by EUS and resected piece (9) (13).

Kobayashi (15) studied 66 rectal carcinoids -- 57 were smaller than 10 mm, and 9 (14%) were greater than 11 mm; the latter subgroup showed muscularis propria infiltration in 5 cases and metastatic disease in 4 cases. In our series we found no muscularis propria infiltration or distant metastases for tumors measuring 1-2 cm (14%); in one case where EUS showed submucosal involvement and muscularis propria compression (Figs. 1 and 2), TEM was performed following polypectomy because of uncertainty regarding the resected piece (deep infiltration), and no persistent carcinoid was found following TEM.

Various techniques have been described: a) conventional technique with polypectomy loop, b) technique aided by submucosal injection with various substances, c) lesion aspiration within a cap, d) lesion rising using elastic band ligation, double-band ligation, mixed techniques, etc.

Kajiyama et al (6) state that using an aspiration method, whether a cap or band ligation, is more effective

Table II. Literature review

Author and year	*No. cases*	*Perforation*	*Bleeding*	*CR*	*Follow-up*
Kajiyama 1996	Cap or band aspiration Polypectomy (P)			87% 74%	
Yohikane 1998	7 c. Bulb X: 4.3 mm (1.5-7 mm) (P)	1/7 (14%)	0 (0%)	100%	6-46 m
Ichikawa 2003	5 gastric c. (P)			100%	6-66 (32 m)
Ono 2003	14 bands 14 polyp.			100% 58%	 10.5 m
Varas 2003	9 P and 1 band	(0%)	0 (0%)	100%	
Martínez 2004	22 P and 2 band 21 c. with 24 tumors X: 8.95 *vs.* 9 mm	(0%)	1 (4%)	100%	12 m.
Kobayashi 2005	66 c. rectal (P):	57 smaller than 10 mm 9 greater than11 mm 5 MP infiltration and 4 metastases		83%	
Sakata 2006	8 bands 7 polyp.	(0%)		100% 57%	 36 m
Moon 2006	11 double band	(0%)	0 (0%)	100%	
Zhou 2007	25 R(3-15 mm) (B) (0%)	0 (0%)		100%	18 m
Kim 2008	30 c. R (X: 6.29 mm) (Cap.)			70%	19 m
Sohn 2008	41 c. with 42 R Cap (0%)	0 (0%)		85.7%	
Mashimo 2008	63 R with bands	(0%)	5 (7.9%)	95%	0% 24 m
Abe 2008	20 R with bands 3D-EUS	(0%)	0 (0%)	100%	
Yamaguchi 2010	20 rectal ESD. X: 7.6 mm (3-16 mm)	1/20 (5%)	0 (0%)	90%	4-34 m
Onozato 2010	40 R < 1 cm	(0%)	0	85% EMR *vs.* 78% ESD	76.8 m
Varas 2010	21(4 R)(6 B) 1/23 (4.3%) Various techniques:16 c. with 21 X tumors: 8 mm (2-20 mm) Polypectomy Bands and TEM	0 (0%)		90.5% 86.7% 100%	12.0 m
Summary	> 400 cases	0-14% (2%)	0-7.9% (1%)	57-100%(88%)	4-76 m

CR: complete resection. ESD: endoscopic submucosal dissection.

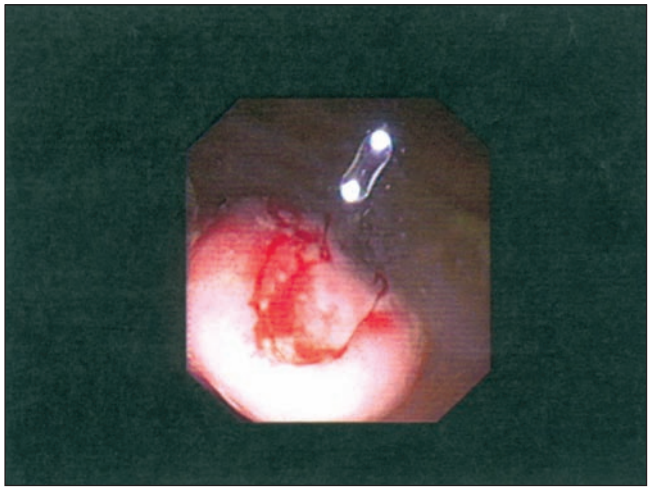

Fig. 1. Polypectomy for rectal carcinoid.

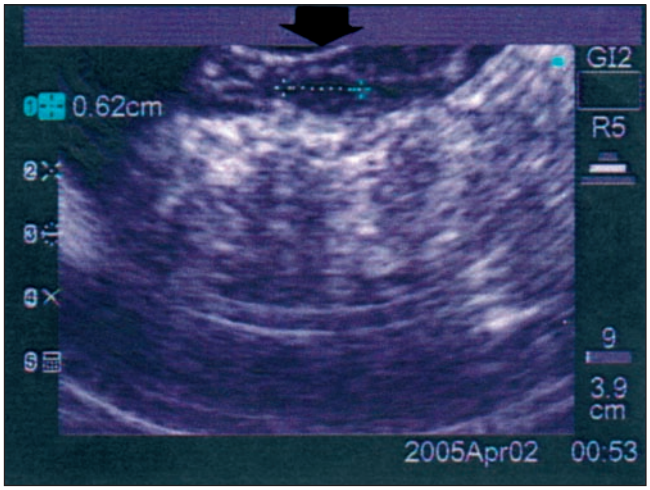

Fig. 2. Sectorial 7.5-MHz EUS for a 6.2-mm rectal carcinoid.

than assisted polypectomy (87% vs. 74%).

Ono (11) and Sakamata (16) compared the conventional technique with elastic bands, showing vastly superior results with the latter (58-57 vs. 100%). However, some author has suggested that double-band should be the technique of choice (17) for preventing perforation and bleeding (0%), with a CR rate of 100%.

These results differ from our experience in our country in that polypectomy led to good results in 100% of subjects (12) (13). On separating CTs into two groups according to treatment we obtained 86.7% versus 100%, even with a limited sample size.

For Korean authors (18), bands lead to CR in 100% of cases, whereas conventional polypectomy has a CR rate of around 75%. EUS had an accuracy and sensitivity of 100%, similar to that obtained by us (95%).

The latest results regarding band-managed rectal carcinoids provide a complete resection rate of 95% with no perforations and with hemoclip-controlled bleeding (21), and of 90% when endoscopic submucosal dissection (ESD) was used (23). This same figure was obtained in this study for gastroduodenales and rectal carcinoids where several treatment techniques were used.

Two of our cases underwent transanal endoscopic microsurgery (TEM) with good results, as already indicated by the literature on rectal carcinoid management (25).

Our approach to small (smaller than 2 cm) rectal carcinoids relies on EUS or previous endoanorectal ultrasounds; in the absence of muscularis propria infiltration an endoscopic resection rather than local surgical resection will be performed (26). TEM will be used for positive resection margins, and radical surgery is restricted to lesions greater than 2 cm, as metastatic disease rates approach 83% and muscularis propria infiltration rates are 88% in such cases (27). Surgical rectal resection may also be recommended for tumors 1-1.9-cm in size with high-risk changes such as muscularis propria infiltration, and lymphovascular or perineural involvement (28), albeit endoscopic treatment suffices for most cases (lesions smaller than 1 cm limited to the mucosa) (28) (29) (30).

Our way of approaching gastric carcinoid, types 1 and 2, when smaller than 5 mm is endoscopic control (31) (32); when equal to or greater than 10 mm with no muscularis propria infiltration, endoscopic resection (33). For type-3 gastric carcinoids smaller than 20 mm we also perform endoscopic resection, and keep surgery for lesions greater than 20 mm with muscularis propria infiltration or perilesional adenopathies.

Complication (bleeding, perforation) rates are usually small; bleeding is more common (0 to 7.7%) (mean: 1%) -- it may be self-limited at times or can be endoscopically managed, particularly for gastric carcinoids (13) (Tables 2 and 3).

EUS may be useful for detecting blood vessels neighboring the carcinoid (13), and for diagnosis, with an accuracy and sensitivity of 100% (18), 94% for us, and 71% precision is a recent study of 20 gastroduodenal carcinoids (34), most of them homogeneous, hypoechogenic lesions smaller than 1 cm with well-defined margins and extension within the submucosa.

Perforation rates are around 1-2%. A minimal technique-related gastric perforation occurred in our series (4.3%), which was treated with 3 clips and resolved after 72 hours of clinical surveillance.

In series with smaller numbers of gastric carcinoids (10) (14) (31) (32) complications amounted to 0%, but greater series showed 10% bleeding (13), as well as a miniperforation in ours (Table 3).

Our overall perforation rate (4.3%) was the lowest described in the literature, and other authors report rates at 14% (9) and 5% (23).

In summary, endoscopic treatment for digestive CTs is a valid, safe, effective alternative wherever patients are screened with EUS, as this is the most accurate technique

Table III. A literature review of gastric carcinoid tumors (GCTs) managed with polypectomy (except for the last authors, who used multiband mucosectomy (31) or bands and a cap (32))

Author and year	*No.*	*Perforation*	*Bleeding*	*CR*	*Follow-up*
Ichikawa 2003	5 c./ 4 c. < 10 mm, with hypergastrinemia			100%	32 m
Higashino 2004	6 c. with 8 G (P)	0 (0%)	0 (0%)	75%	30 m
Martínez 2004	10 c. (P)	0 (0%)	1 (10%)	100%	12 m
Varas 2009	13 c. (P and B)	1/13 (7.7%)	0 (0%)	100%	12 m
Hopper 2009 (31)	8 c. with 34 G. 7/8 type I, 1/8 c. type III	0 (0%)	0 (0%)	100%	
Muro 2009 (32)	1 c. with 4 G	0	0	100%	18 m
Massironi 2009 (33)	Review				
Varas (2010) (35) 14 G from a series with 40 CTs and literature review					
Summary	74 GCT	0-7.7% (1.3%)	0-10%	(1.7%) 96%	21 m

for assessing tumor size and muscularis propria integrity, factors that seem to condition the potential for distant metastasis.

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