The Role of Wireless Capsule Endoscopy (WCE) in the Detection of Occult Primary Neuroendocrine Tumors

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ABSTRACT

Background & Aims: Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms with unclear etiology that may show functioning or non-functioning features. Primary tumor localization often requires integrated imaging. The European Neuroendocrine Tumors Society (ENETS) guidelines proposed wireless-capsule endoscopy (WCE) as a possible diagnostic tool for NETs, if intestinal origin is suspected. However, its impact on therapeutic management is debated. We aimed to evaluate the yield of WCE in detecting intestinal primary tumors in patients showing liver NET metastases when first-line investigations are inconclusive.

Method: Twenty-four patients with a histological diagnosis of metastatic NET from liver biopsy and no evidence of primary lesions at first-line investigations were prospectively studied in an ENETS-certified tertiary care center. Wireless-capsule endoscopy was requested before explorative laparotomy and intra-operative ultrasound. The diagnostic yield of WCE was compared to the surgical exploration.

Results: Sixteen subjects underwent surgery; 11/16 had positive WCE identifying 16 bulging lesions. Minilaparotomy found 13 NETs in 11/16 patients (9 small bowel, 3 pancreas, 1 bile ducts). Agreement between WCE and laparotomy was recorded in 9 patients (Sensitivity=75%; Specificity=37.5%; PPV=55%; NPV=60%). Correspondence assessed per-lesions produced similar results (Sensitivity=70%; Specificity=25%; PPV=44%; NPV=50%). No capsule retentions were recorded.

Conclusions: Wireless-capsule endoscopy is not indicated as second-line investigation for patients with gastro-entero-pancreatic NETs. In the setting of a referral center, it might provide additional information when conventional investigations are inconclusive about the primary site.

Key words: wireless capsule endoscopy – non-functioning endocrine tumor – NET – diagnosis – diagnostic yield.

Abbreviations: DBE: double balloon enteroscopy; GEP-NET: gastro-entero-pancreatic neuroendocrine tumor; GI: gastrointestinal; ENETS: European Neuroendocrine Tumors Society; NET: neuroendocrine tumor; SSRS: somatostatin receptor scintigraphy; WCE: wireless capsule endoscopy.

INTRODUCTION

Gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs) are a heterogeneous group of neoplasms with unclear etiology that may present with or without symptoms. Epidemiological studies reported that the small bowel and the rectum are the most common site for primary GEP-NETs [1-3]. Unfortunately, a large number of patients (about 60% of small bowel NETs and 30% of rectal NETs) already have nodal or liver metastases and, consequently, poor prognosis at the time of diagnosis [1]. Also, approximately 11% to 14% of subjects with GEP-NETs have metastatic lesions with unknown primary tumor. Particularly, localization of mid-gut tumors might be challenging due to their usually small size. In these patients, resection of the primary lesion is a palliative treatment that could reduce local complications and might even increase survival [4, 5]. Therefore, a multimodality imaging approach including computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), somatostatin receptor scintigraphy (SSRS) and endoscopy is often necessary for detecting the primary tumor [6]. The recently updated European NET Society (ENETS) guidelines for the management of NETs consider wireless capsule endoscopy (WCE) in the workup of metastatic

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Received: 21.03.2017 Accepted: 29.05.2017 NET with unknown primary, but its impact on the clinical management of these patients is still debated and adequate data is lacking.

Our study aimed to evaluate the yield of WCE in detecting primary tumor in patients showing liver NET metastases when first-line investigations are negative or inconclusive.

Capsule excretion rate, level of bowel preparation, rate of adverse events were also assessed.

METHODS

Study population and design

The study was performed at the Fondazione IRCCS Istituto Nazionale dei Tumori, National Cancer Institute, ENETS centre of excellence (Milan, Italy). In this setting, about 70% of the patients with GEP-NET already present liver metastases at the time of diagnosis, of whom 10% have unknown primary tumor location after initial investigations. In a small percentage of these cases, the primary neoplasia remains undetected even after second-line examinations have been performed. From January 2007 through October 2012, 24 patients (mean age, 53 years range 33-75; M/F:13/11; BMI 23 kg/m², range 16.5-29.4; 23 Caucasian/1 Hispanic; 3 heavy smokers; 1 celiac disease) with histologic diagnosis of NET obtained on liver biopsies and no evidence of primary lesions after full investigations were referred to our Centre. No family history of NETs was reported. All patients had negative or inconclusive total body CT, MRI, PET, SSRS, double-contrast barium enema, upper- and lower GI endoscopy. Part of them (21%) underwent also PET/ CT without clear findings. Wireless capsule endoscopy was therefore requested before surgical exploration. Endoscopic ultrasound was not performed and patients underwent directly intra-operative ultrasound. Sixteen out of 24 (69.5%) were symptomatic for carcinoid syndrome.

Informed consent describing the clinical issue and evaluating risks and benefits of the suggested procedures was signed by patients before performing any diagnostic or therapeutic investigations. As this study is a secondary data analysis of consolidated clinical practice at our institution, patients were not required to sign a specific consent form for research.

Wireless capsule endoscopy

Patients were asked to fast at least 8 hours before the exam. Bowel preparation was performed by using a standard preparation for colonoscopy (4 liter of polyethylene glycol electrolyte lavage solution the day before plus 1 liter of water the day of the examination, associated with a 3 days fiber-free diet).

Wireless capsule endoscopy was performed using the PillCam SB 1 and PillCam SB 2 capsules (Given Imaging Limited, Yoqneam, Israel). Entire WCE recordings were analyzed by means of Rapid Software (Given Imaging Ltd). Images were evaluated on QuadView automatic modality at 15 frames first, and switched to manual modality, double or single photogram, in case of suspected lesions. Red marks were reviewed at the end of the analyses. The WCE images were analyzed by an expert physician (> 250 procedures performed in subjects with suspected small intestine tumor). The SPICE index was calculated for each suspicious bulges. Wireless capsule endoscopy were considered positive in the presence of bulges with an index of 2 or higher [7].

Surgical exploration

Surgical exploration was performed by means of a minilaparotomy approach through a midline incision across the umbilicus. The whole duodenum, jejunum, ileum and colon were inspected and palpated looking for any nodules within the intestinal wall. Also the mesentery was accurately checked for the presence of lymph node metastases that, when present, can drive the surgical exploration towards a better defined region. Intraoperative pancreatic ultrasound was also performed.

Once the intestinal and lymph node extension were evaluated, the primary tumor(s) was/were resected with an adequate margin (approximately 10 cm) together with the relative portion of the mesentery and the tributary vessels and lymph nodes. Enlarged lymph nodes close to the root of the mesenteric vessels were removed, preserving when possible the vascular supply to the intestinal tract. The intestinal continuity was restored avoiding in all cases any temporary bowel deviation. Surgeons were not blinded to the WCE findings.

Statistical analysis

Data are expressed as mean values, ratio and frequency. Sensitivity and specificity of WCE were elaborated together with the relative Confidence Interval. Statistical analysis was performed with MedCalc Software, (MedCalc Software, Mariakerke, Belgium) and with GNU Software (PSPP, Boston, MA, USA).

RESULTS

Wireless capsule endoscopy provided good visualization of the small bowel in 21/24 subjects. Three patients were excluded due to poor small bowel cleansing. Intestinal preparation was judged as optimal in 74% of cases. No cases of capsule retention were recorded. Mean gastric transit time was 40 ± 21 minutes; mean small intestinal transit time was 274 ± 115 minutes. Despite the physicians' advice, five patients refused to undergo surgical exploration. Sixteen subjects agreed to undergo surgery and were enrolled into the study. Among these latter, 11 (68.7%) had a positive WCE examination identifying a total of 16 bulging lesions (2 jejunum, 10 ileum, 1 ileocecal valve, 3 undetermined jejunum or ileum). Mini-laparotomy was able to find the primary tumor in 11/16 patients: 7 subjects had NET of the small bowel, whereas 3 had pancreatic NET (1 associated with appendix lymphangitic neoplasm) and 1 biliary well-differentiated NET. One of the 7 patients with primary intestinal NETs had three multifocal jejunal tumors. Totally, 9 intestinal NETs were diagnosed by surgery (3 jejunum, 1 jejunum-ileum passage, 4 ileum and 1 ileocecal valve). Wireless capsule endoscopy finding of small ileal polyps was considered as a negative case since diagnosis of NET was histologically ruled out from samples obtained during previous ileum-pancolonscopy. Moreover, one patient had mesenteric infiltration by extra-lymph node tumoral growth at surgery and sign of ileal compression at WCE. Although the anomaly of the intestinal wall was not due to a primary tumor, the two investigations were considered from a diagnostic point of view as concordant.



Fig. 1. Flow-chart illustrating the study design.

All primary lesions were histologically classified as well differentiated, except for one with a poorly differentiated pancreatic NET. A scheme of the study design is illustrated in Fig. 1. Wireless capsule endoscopy and laparotomy were in agreement in 9 cases (both positive in 6 subjects, both negative in 3 subjects). Two had negative WCE and positive laparoscopy, 5 had positive WCE and negative laparotomy (Sensitivity 75%, 95%CI 0.44-1.00; Specificity 37.5%, 0.39-0.71; PPV 55%, 0.2-0.54; NPV 60%, 0.17-0.3). When correspondence between the two investigations was referred to each bulging lesion (correct diagnosis and same intestinal site), results were as follows: 7 tumors were identified by both WCE and laparotomy, 9 suspected bulging lesions found by WCE were not confirmed by laparoscopy (in 6 cases no tumor was found and in the remaining 3 a lesion was found in a different location), 3 NETs found by laparotomy in the small bowel were not visualized by WCE and 3 negative WCE were confirmed by the negative surgical exploration of the intestine (Sensitivity 70%, 95%CI 0.42-0.98; Specificity 25%, 0.05-0.49; PPV 44%, 0.19-0.68; NPV 50%, 0.1-0.9).

Overall, the diagnostic yield of WCE on a per-patient and per-lesion analysis was 56% and 45%, respectively. Findings of capsule endoscopy and surgical exploration are detailed in Table I. An example of correctly diagnosed NET and false positive findings at WCE are illustrated in Fig. 2.

DISCUSSION

In all our 24 subjects having histologically diagnosed NET with liver metastases, traditional upper plus lower GI endoscopy and integrated imaging (such as multidetector CT scan, MR, and SSRS) were performed without identifying the primary site of the neoplasms. Therefore, investigation of the mid-gut was conducted by means of WCE, which was preferred to double balloon enteroscopy (DBE) because of its low invasiveness, lower risks and costs, considering that DBE would not have spared the patients the surgical exploration. Moreover, DBE strictly depends on the operator' skills and bares further risks related to anesthesia. Furthermore, at the time of the study, DBE was not an available technique at our Institution. Finally, data from previous studies regarding the diagnostic yield of DBE in case of suspect GEP-NETs are contrasting. Bellutti and coworkers reported a diagnostic yield of DBE for primary tumor search in patients with metastatic or suspected NET of 33%, that is, inferior to the one achieved in our study by means of WCE [8]. Moreover, other studies evaluated the diagnostic yield of WCE and DBE at detecting small bowel mass lesions responsible for OGIB, reporting divergent findings [9, 10]. In our Institution, PillCam SB1 system was used on 5 cases, whereas the remaining 19 subjects underwent videocapsule endoscopy by means of the PillCam SB2 system. Despite the PillCam SB2 providing superior image

underwent videocapsule endoscopy by means of the PillCam SB2 system. Despite the PillCam SB2 providing superior image quality to the PillCam SB1, several studies demonstrated that the PillCam SB2 did not produce a statistically greater diagnostic yield [11, 12]. For this reason both groups were included in the design of the study. Poor small bowel cleansing occurred in 3 patients, which were excluded from the study, thus accounting as a limitation of wireless endoscopy. The cases with failed preparation could have been repeated, but resources for such an expensive procedure have to be considered as another potential limiting factor. These limitations are eventually counterbalanced by the limited tools available in order to directly explore the small intestine.

Subsequently, WCE study was followed within one month by surgical exploration, which provided accurate evaluation of liver, pancreas, lymph nodes and suspicious masses thanks to intra-operative ultrasound in addition to palpation. Therefore, it was used as standard of reference for the diagnosis. Indeed, a recent study demonstrated both laparotomy and laparoscopic exploration can effectively identify the unknown primary lesion in patients presenting only with liver or node NETs metastases in 86.7% of the cases [13]. Moreover, the authors found multifocal intestinal lesions in 52.4% of the cases. In these patients, it could be important to localize and remove the primary lesion for different reasons. First, curative treatment can be achieved in case of feasible resection of the distant metastasis, which is often the case for liver metastases it has

Lesions per patient	WCE	Laparotomy	mts	Pathology
1	Jejunum-ileum	Jejunum-ileum	Liver, LN	well diff carcinoid tumor
2	Ileum	Pancreas	Liver	moderate diff carcinoid tumor
3	Bulging close to the valve	Ileum	Liver	well diff carcinoid tumor
4 a	Jejunum	Jejunum		well diff carcinoid tumor
b	Jejunum	Jejunum	Liver, LN, peritoneum	well diff carcinoid tumor
с	Ileum	-		
d	_	Jejunum		well diff carcinoid tumor
5	_	Ileum	Liver, LN	well diff carcinoid tumor
6	Multiple small polyps jejunum/ileum (-)	Biliary trees adenoma	Liver	well diff carcinoid tumor
7	Ileum	Pancreas and Appendix	Liver	well diff carcinoid tumor
8	Ileum	_	Liver	
9 a	Ileum	Intestinal wall infiltration by lymph knot	Liver, LN	well diff carcinoid tumor
b	Ileum	_		
10	Ileum	Ileum	Liver	well diff carcinoid tumor
11	_	Pancreas	Liver, LN	well diff carcinoid tumor
12 a	Jejunum-ileum	_		
b	Jejunum-ileum	_	Liver	
13 a	Ileum	Ileum	Liver, LN	well diff carcinoid tumor
Ь	Ileum	_		
14	_	Ileum	Liver, LN	well diff carcinoid tumor
15	IIleum	_	Liver	
16	_	_	Liver	

 Table I. Results of diagnostic procedures. Comparison between wireless capsule endoscopy (WCE) and surgery.

Multifocal lesions are indicated with letters (N°a,b,c,d...); (-): lack of a corresponding lesion at capsule endoscopy and/or surgical exploration; LN: lymph nodes; mts: metastases.



Fig. 2. Wireless capsule endoscopy images showing 2 bulges falsely interpreted as submucosal mass (a,b) and 2 intraluminal masses confirmed as ileum NETs after surgical exploration and resection (c,d).

the palliative aim of avoiding local complications, such as obstruction and bleeding. Finally, even when curative resection of liver metastases is no longer a possibility, the resection of primary tumors (mesenteric lymph node metastases included) may still provide substantial survival benefit [4,5,14-16]. However, strong evidences supporting this approach are lacking and the ENETS Consensus Guidelines suggest caution: an interdisciplinary team should evaluate patients that fit for surgery with unresectable liver metastases [17].

In our series, 8 cases out of the 24 originally screened, were not eligible to complete the study. Therefore, comparative analysis between endoscopy and laparoscopy was performed on 16 subjects. However, the relatively small number of patients enrolled reflects the rarity of the very selected disease described.

Previous studies investigating the yield of WCE in the detection of small intestinal lesions in comparison with various imaging techniques have shown that WCE is superior to CT enteroclysis and small-bowel follow-through [18-21]. Indeed, the introduction of WCE has significantly improved the diagnostic yield of small bowel tumors whose detection has been notoriously challenging due to the limitations of other imaging modalities. Nearly one third of the NETs affect the small bowel and studies addressing the detection of these tumors by WCE after failure of other techniques have produced mixed results [22-25]. Van Tuyl et al. in 20 consecutive NET patients with unknown primary showed that WCE was able to reveal small bowel abnormalities in 12 (60%) patients and the diagnosis of NET was histologically confirmed in half of them [23]. However, since in this study not all patients underwent surgery, the number of false positive and negative WCE findings remains unclear. During the conduction of this study, Frilling et al. evaluated 10 patients with metastasized NET with an undetected primary site on standard imaging and showed that WCE identified lesions suggestive of small bowel tumors in 8 (80%) patients [25]. Again, surgical exploration and histological confirmation of small bowel NET was possible in only 6 patients; this represents an important limitation since without histology as a gold standard, WCE diagnostic accuracy cannot be reliably measured.

In the present study, WCE identified the small bowel as the site of the primary tumor in 11 subjects. However, diagnosis of small bowel NET was confirmed only in 5 (41%) cases after surgical and ultrasound exploration were performed. Our results are more in line with what was found in a smaller series by Johanssen and coworkers, in which surgery was performed in all patients with positive WCE but not in those with normal endoscopic findings [24]. Indeed, our per-patient diagnostic yield was higher than the one reported in that study (56% vs 45%). However, due to the limited dimensions of the populations enrolled in both studies, such difference has to be considered cautiously.

In our series, WCE examinations showed more than one lesion in 4 (25%) patients. If correspondence between the two investigations was referred to each bulging lesion. Only 6 of the 15 bulging lesions on WCE corresponded to surgical findings. Thus 9 of 15 cases were false-positive results. False positive results are usually caused by small bowel contractions, extrinsic compression, lymph stasis or submucosal lesion of other type. The nature of a mass lesion at WCE cannot be reliably determined by the endoscopic appearance. The presence of alarm signs (bleeding, mucosal disruption, irregular surface) has been shown to improve diagnosis of small bowel tumors and reduce false positive findings [25-27]. However, as is the case in our series, when these signs are lacking the distinction between an innocent bulge and a malignant mass is even more difficult. Recently, a scoring system based on morphological semi-objective criteria has been proposed to increase a diagnostic yield in the definition of small bowel bulges detected by WCE without alarm signs [7]. We applied this index in our selected population with confirmed liver NET metastases and unknown primary tumor in order to better discriminate suspicious bulges and to provide further data in literature about its clinical application. The characteristics of our study population and the fact the physician analyzing the WCE recordings was not blinded to the patient's medical file could at least in part explain the higher rate of false positive cases found compared to other studies [25-27]. On the other hand, 2 out of 5 patients with negative WCE were found to have small bowel NET. False-negative results for small bowel tumors on WCE have been previously reported [28] but data from NET patients are only from one recent study; when findings from surgical specimens were compared to endoscopic results, small NETs (< 1 cm) with sub-mucosa extension were not detected by WCE [25]. Indeed, in our population, in one of the two patients with negative WCE the size of the escaped nodule was 0.8 cm. Other possible factors for false negative findings might be rapid small bowel transit, orientation of the camera away from the lesions, partial bowel preparation, delayed small bowel transit or perceptual error.

Finally, intraoperative ultrasound allowed to identify three cases of pancreatic NETs, two of which were patients originally identified by WCE as suspected ileal carcinoid (false positive) and one had a negative capsule endoscopy. It must be acknowledged that performing EUS would have likely detected these lesions and samples could have been obtained for histologic examination. This should be considered as a limitation of our study. Indeed, EUS is a very sensitive technique for the detection of early pancreatic lesions but, unlike capsule endoscopy, it does not allow the exploration of the entire length of the small intestine [29, 30]. Nevertheless, WCE has been performed in highly selected and complex patients, without baring risks or discomfort to them as compared to other methods. No case of capsule retention or peri-procedure adverse events have been recorded, confirming the safety of WCE in this type of patients.

CONCLUSION

In our experience, WCE is not indicated as a second line investigation for patients with suspicious GEP-NET due to a limited diagnostic yield. However, in the setting of a referral center where a multi-disciplinary team is available, this methodology might provide helpful additional information and guide surgery when conventional investigations and integrated imaging do not clarify the primary tumor site. The proposed surgical exploration was proved to be very successful during the study, confirming data reported by previous works. **Conflicts of interest**: No conflict to declare. **Financial support**: No financial support has been received to perform this study.

Authors' contribution: M.F., A.B., E.S., V.M., E.M., G.B.: design of the study, writing of the manuscript; M.F., G.D., G.B., F.C., and E.M.: data collection and analysis; T.V.: data analysis, writing of the manuscript; D.C.: data collection. All authors approved the final version of the manuscript.

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