Small-bowel neoplasms in patients undergoing video capsule endoscopy: a multicenter European study

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Institutions
Institutions are listed at the end of article.

Background and study aim: Small-bowel tumors account for 1%–3% of all gastrointestinal neoplasms. Recent studies with video capsule endoscopy (VCE) suggest that the frequency of these tumors may be substantially higher than previously reported. The aim of the study was to evaluate the frequency, clinical presentation, diagnostic/therapeutic work-up, and endoscopic appearance of small-bowel tumors in a large population of patients undergoing VCE.

Patients and methods: Identification by a questionnaire of patients with VCE findings suggesting small-bowel tumors and histological confirmation of the neoplasm seen in 29 centers of 10 European Countries.

Results: Of 5129 patients undergoing VCE, 124 (2.4%) had small-bowel tumors (112 primary, 12 metastatic). Among these patients, indications for VCE were: obscure gastrointestinal bleeding (108 patients), abdominal pain (9), search for primary neoplasm (6), diarrhea with malabsorption (1). The main primary small-bowel tumor type was gastrointestinal stromal tumor (GIST) (32%) followed by adenocarcinoma (20%) and carcinoid (15%). 66% of secondary small-bowel tumors were melanomas. Of the tumors, 80.6% were identified solely on the basis of VCE findings. 55 patients underwent VCE as the third procedure after negative bidirectional endoscopy. The lesions were single in 89.5% of cases, and multiple in 10.5%. Retention of the capsule occurred in 9.8% of patients with small-bowel tumors. After VCE, 54/124 patients underwent 57 other examinations before treatment; in these patients enteroscopy, when performed, showed a high diagnostic yield. Treatment was surgery in 95% of cases.

Conclusions: Our data suggest that VCE detects small-bowel tumors in a small proportion of patients undergoing this examination, but the early use of this tool can shorten the diagnostic work-up and influence the subsequent management of these patients.

Introduction

Although the small bowel represents 75% of the length and 90% of the overall mucosal surface of the alimentary tract, it is considered a rare location for the development of neoplasms, accounting for only 1%–3% of all primary gastrointestinal tumors [1,2]. A review of the Utah Cancer Registry from 1966 through 1990 showed that the overall age-adjusted yearly incidence of small-bowel cancers was 1.4 per 100,000. Over a 30-year period [3], Barclay [4] reported an incidence of 0.7/0.6 (male/female) malignant small-bowel tumors per 100,000, which accounted for 1.6% of all gastrointestinal tumors [5]. Approximately 40 different histological types of small-intestinal tumors have been identified [6]. Among malignant tumors, about 30%–50% are adenocarcinomas, 25%–30% are carcinoids, and 15%–20% are lymphomas. The majority of benign small-bowel tumors originate from the stromal layer [7] accounting for about 15%–20% of all small-bowel primary neoplasms [8,9]. Secondary neoplasia has been reported to be more frequent than primary small-intestinal neoplasms. Primary tumors of the colon, ovary, uterus, and stomach can metastasize to the small bowel by direct invasion or by intraperitoneal spread, whereas primaries from breast, lung, and melanoma metastasize by the hematogenous route [7]. In patients with skin melanoma, small-bowel metastases have been described in 1.5%–4.4% of cases in in-vivo studies [10,11] and in 58% of post-mortem specimens [10]. Small-bowel tumors grow slowly, extraluminally, remaining asymptomatic for years or presenting insidiously in patients with nonspecific complaints such as abdominal pain, diarrhea, iron de-
ficiency anemia, bleeding, extraintestinal symptoms (flushing, paraneoplastic syndromes), or acute obstruction [12]. In these patients, the results of routine diagnostic laboratory and other diagnostic tests, such as push enteroscopy, small-bowel series (SBS) or enteroclysis, computed tomography, and magnetic resonance imaging may frequently be inconclusive. For these reasons the diagnosis is often delayed [6,12], thus failing to prevent the development of locally advanced lesions or metastatic disease.

The development and clinical implementation of video capsule endoscopy (VCE), an accurate, safe, and painless method of endoscopically evaluating all of the small bowel, has opened a new frontier in the field of small-bowel investigation. Since the introduction of this device into clinical practice, a few small series have been published showing an frequency of small-bowel neoplasms higher than previously expected, ranging between 2% and 9% [13 – 17], and some authors have speculated that routine use of wireless capsule endoscopy in the diagnostic algorithm for obscure gastrointestinal bleeding, iron deficiency anemia, and abdominal pain would lead to earlier diagnosis, and therefore improve the overall prognosis associated with malignant small-bowel tumors [18].

The aim of the present study was to describe the frequency, clinical presentation, endoscopic appearance, and diagnostic work-up related to small-bowel tumors in a large population of patients undergoing VCE.

Patients and methods

This study was carried out in 29 centers from 10 European countries. Each participating center reviewed its own series of consecutive patients undergoing VCE, from the beginning of the use of this device in clinical practice until October 2006. For each patient in whom VCE showed one or more lesions suggesting small-bowel neoplasia, and a subsequent diagnostic/therapeutic work-up led to histological confirmation, a specific structured questionnaire was completed. We decided to exclude from the study all patients with a known condition that increases the risk of small-bowel neoplasms (e.g. patients with refractory celiac disease or patients with familial adenomatous polyposis [FAP] or Peutz-Jeghers syndrome with alarm symptoms or under surveillance). The questionnaire collected data on:

- the center where VCE was performed (name of referring physician, number of VCE procedures performed at the time of data submission),
- the patient (age, sex, and length of clinical history),
- indication for VCE (for patients with obscure gastrointestinal bleeding [OGIB], their hemoglobin level at the time of VCE),
- diagnostic work-up before VCE,
- results of VCE (endoscopic appearance of the lesion, and location, estimated by the physician reviewing the video),
- complications related to VCE (e.g. capsule retention),
- diagnostic-therapeutic work-up after VCE (particularly a brief description of surgical intervention, if done, with appearance and location of the lesion),
- final histological diagnosis.

Statistical analysis

This was done using SPSS software (SPSS 14.0 for Windows, SPSS Inc. Chicago, Illinois, USA). To describe the population, we used mean and SD for data with a Gaussian distribution (e.g. age) and median and range for data with a non-Gaussian distribution (e.g. length of clinical history). To compare unpaired groups, we used the two-tailed t test for unpaired groups or the Mann-Whitney test, respectively, for data with Gaussian or non-Gaussian distributions.

The Spearman correlation test was used to quantify the association between variables. We calculated the value of r, which ranges between +1 and −1; a value of 0 means that the two variables do not vary together at all, while +1 or −1 indicate perfect correlation (respectively, direct or inverse).

To analyze contingency tables we used the X² test or Fisher’s exact test as appropriate. As usual, for all these tests, a P value of less than 0.05 was considered to be statistically significant.

Results

Frequency of small-bowel tumors

In 29 centers from 10 European countries, 5129 VCE examinations were performed, for any indication. Unfortunately we did not know when each center started to use VCE in clinical practice; thus we were not able to calculate the mean rate of examinations performed per center per year but only the total number of VCEs done at each center. From the 5129 examinations (Table 1), we collected data on 160 patients. A total of 36 questionnaires were excluded from further evaluation: 13 described small-bowel neoplasms in patients with refractory celiac disease (n = 8) or Peutz–Jeghers syndrome (n = 5), while 23 were incomplete. Thus, data from a total of 124 patients (mean age ± SD 60.3 ± 14.3 years) with histologically proven small-bowel neoplasms were evaluated.

The overall frequency of small-bowel tumors identified at VCE was 2.4%, ranging between 0.75% (3/400) and 9.3% (7/75) for the 29 centers. We found an inverse correlation (Spearman r = −0.56, 95% confidence interval [CI] −0.77 to −0.23; P < 0.002; Fig. 1) between the frequency of identification of small-bowel neoplasms and the number of VCE examinations performed at each center.

Indication for VCE

The indication for VCE was obscure gastrointestinal bleeding (OGIB) in 108 patients (108/124, 87.1%), which was obscure-occult in 52 (52/108, 48.2%), ongoing overt in 36 (36/108, 33.3%) and previous overt in 20 (20/108, 18.5%). In the remaining 16 patients (16/124, 12.9%), the indication for VCE was abdominal pain in 9, investigation for primary neoplasms in patients with liver metastases or carcinoid syndrome in 6, and diarrhea with severe malabsorption in 1.

Diagnostic work-up before VCE

Of the 124 patients, 55 (44.4%) underwent VCE as the third examination after negative bidirectional endoscopy, while the remaining 69 (55.6%) had undergone at least one further examination aimed to evaluate the small-bowel before VCE. These 69 patients underwent 102 examinations specifically addressed to evaluate the small bowel (not including repeated gastroscopies and colonoscopies) before capsule endoscopy (mean number of diagnostic procedures per patient 1.47); in 45 out of these 69 pa-
patients the diagnostic work-up was completely negative while 24 patients had at least one examination with positive results. The examinations performed before VCE and their diagnostic yield are shown in Table 2. Taking together the patients who underwent VCE immediately after negative bidirectional endoscopy (n = 55) and the patients with a negative diagnostic work-up despite further examinations (n = 45), capsule endoscopy had a direct impact on diagnosis, identifying an unexpected small-bowel tumor, in 80.6 % of patients (100/124).

Endoscopic appearance and histological classification

The endoscopic appearance of lesions identified by VCE was: polyp or mass in 94 patients (75.8 %); ulcers in 10 (8.1 %); fresh blood in 8 (6.5 %); stenoses in 8 (6.5 %); and cobblestone in 4 (3.2 %). Fig. 2 shows a polypoid, ulcerated lesion that was confirmed at surgical intervention (Fig. 3). These lesions were single in 111 cases (89.5 %) and multiple in 13 (10.5 %). Of 124 lesions identified, 112 were primary neoplasms (112/5129 or 2.2 %) while the other 12 cases were small-bowel metastases (12/5129 or 0.2 %). The most frequent histological type of primary tumors was gastrointestinal stromal tumor (GIST) (32.1 %) followed by adenocarcinoma (20.5 %) and carcinoid (15.6 %). In 8 out of 12 cases with metastatic small-bowel tumors, the metastases were from a previously removed skin melanoma. The histological classification of the 124 lesions is shown in Table 3.
tological classification of the small-bowel primary neoplasms is shown in Table 3.

**Location of tumors**

On the basis of further diagnostic and/or therapeutic work up carried out after VCE, the definitive location of single lesions was established as the jejunum in 70.3% of cases, the ileum in 22.5%, and the duodenum in 7.2%. There was 92.8% agreement (103/111 cases) between the location of single lesions as assessed by VCE and that established on the basis of further diagnostic and/or therapeutic work-up.

**Complications of capsule endoscopy**

All patients enrolled in this study (except one in whom the capsule was placed in the stomach using the endoscope), swallowed the capsule easily. Among the 38 patients (30.9%) in whom the

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**Table 2** Diagnostic yield of examinations performed before video capsule endoscopy (VCE) in 69 patients, and after VCE in 112 patients without capsule retention

<table>
<thead>
<tr>
<th>Examinations performed before VCE</th>
<th>Examinations performed after VCE</th>
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<tbody>
<tr>
<td>Total patients, n = 69</td>
<td>Total patients, n = 112</td>
</tr>
<tr>
<td>Number of examinations, n</td>
<td>Number of examinations, n</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Small-bowel series/small-bowel enteroclysis</td>
<td>49</td>
</tr>
<tr>
<td>Abdominal CT scan</td>
<td>19</td>
</tr>
<tr>
<td>Bleeding nuclear scan</td>
<td>13</td>
</tr>
<tr>
<td>Push enteroscopy</td>
<td>10</td>
</tr>
<tr>
<td>Octreoscan</td>
<td>4</td>
</tr>
<tr>
<td>Angiography</td>
<td>2</td>
</tr>
<tr>
<td>SPECT</td>
<td>2</td>
</tr>
<tr>
<td>Meckel’s scan</td>
<td>1</td>
</tr>
<tr>
<td>Double-balloon enteroscopy</td>
<td>1</td>
</tr>
<tr>
<td>Surgical intervention</td>
<td>1</td>
</tr>
<tr>
<td>Gastroscopy</td>
<td>None</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>None</td>
</tr>
<tr>
<td>MRI enteroclysis</td>
<td>None</td>
</tr>
<tr>
<td>CT enteroclysis</td>
<td>None</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>102</strong></td>
</tr>
</tbody>
</table>

**Table 3** Histological classification of small-bowel neoplasms

<table>
<thead>
<tr>
<th>n</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td><strong>Primary small-bowel neoplasms</strong></td>
<td></td>
</tr>
<tr>
<td>GIST</td>
<td>36</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>23</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>17</td>
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<tr>
<td>Lymphoma</td>
<td>12</td>
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<tr>
<td>Lipoma</td>
<td>10</td>
</tr>
<tr>
<td>Angioma</td>
<td>4</td>
</tr>
<tr>
<td>Neuroendocrine tumor</td>
<td>4</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Juvenile hamartoma</td>
<td>2</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>112</strong></td>
</tr>
<tr>
<td><strong>Small-bowel metastases</strong></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>8</td>
</tr>
<tr>
<td>Colonic carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Seminoma</td>
<td>1</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>12</strong></td>
</tr>
</tbody>
</table>

GIST, gastrointestinal stromal tumor.
capsule did not reach the ileocecal valve during the examination period, in 12 (12/124, 9.7%) the capsule was stuck at the site of the tumor. Five of these 12 patients (41.6%) had undergone an SBS or small-bowel enteroclysis before VCE, with negative results. In 2/12 patients (16%) the capsule was retrieved with the push enteroscope and in 10 (84%) by surgical intervention. The relevant data for these 12 patients is presented in Table 4. Capsule retention occurred only in patients with stenoses (n = 6) or polyps/masses (n = 6). As expected, stenoses led to capsule retention more frequently than polyps/masses (6 cases of retention in 8 patients with stenoses vs. 6 in 94 with polyps/masses; Fisher test, P = 0.002).

There was no difference in the occurrence of retention according to type of OGIB, location, or histological type of tumor. None of these 12 patients had acute obstruction due to capsule retention. In the remaining 26 patients, in whom the capsule did not reach the ileocecal valve during the examination period but was not retained, the capsule was egested naturally in the stool within 7–15 days.

Diagnostic and therapeutic work up after capsule endoscopy

A total of 110 patients were treated by surgery alone, 8 received a combination of surgery and chemotherapy, 1 underwent endoscopic polypectomy, while 1 was left untreated because of poor general condition and 4 were lost to follow-up. Among 112 patients without capsule retention, treatment was given directly after VCE in 58 patients, while 54 underwent further examinations (Table 2), which were negative in 9. Thus, in 67 patients therapy was done solely on the basis of the diagnosis made by VCE, in 35 it was based also on the results of further tests, while 12 underwent operation following capsule retention.

Discussion

Since the introduction of VCE in clinical practice, several studies have shown that the performance of this technique is superior to that of other diagnostic modalities in detecting small-bowel abnormalities including vascular lesions, inflammation and tumors [19–22]. Nowadays, it is well accepted that VCE plays a key role in the diagnostic work-up of obscure gastrointestinal bleeding, in the diagnosis of suspected Crohn’s disease and in the evaluation of the small bowel in patients with refractory celiac disease, but the role of capsule endoscopy in the diagnosis and management of small-bowel tumors is still debated, despite a growing body of evidence in this field [13–18]. The aim of the present study was to describe the frequency, clinical presentation, endoscopic appearance, and diagnostic work-up of small-bowel tumors in a population that was as large as possible of patients undergoing VCE. For this purpose, the study protocol was sent to all members of the European Capsule Endoscopy Group (ECEG) and a specific notice was placed in the home page of the website www.capsuleendoscopy.org. On the one hand, this method of data collection allowed us to create the largest database published so far of small-bowel tumors detected by capsule endoscopy (124 tumors with 5129 capsule procedures performed); on the other hand, this led to the inclusion of a group of centers that were heterogeneous (in terms of number of patients referred for VCE, number of tumors identified, number of capsule examinations performed, and the diagnostic and therapeutic work-up done before and after VCE). The fact that the majority of cases came from Italy and Spain is probably due to the existence in both countries of a capsule endoscopy study group that facilitated case collection.

In our study the frequency of small-bowel tumors (2.4%) was surprisingly and substantially lower than that reported in other studies in which, as in the present one, the authors collected both benign and malignant neoplasms [13–16,18,19]. The strict patient selection (particularly the requirement for histological confirmation of lesions identified by capsule endoscopy, and
the exclusion of patients with a high pre-test probability of having a tumor) could be a possible explanation for this difference. On the other hand, while our series is comparable to the other published series [13–19] in terms of age and gender of the patients and of clinical indication for VCE, an important difference is the number of VCE examinations performed, which in our study is almost ten times larger than that of the largest previously published series. To ascertain whether the number of examinations is in any way related to the frequency of tumor detection, we examined the relationship between frequency of tumors found and number of VCE examinations performed in the centers participating in the study. Indeed, this analysis revealed a significant inverse correlation (Spearman \( r = -0.56, P < 0.002; \) Fig. 1), suggesting that the high number of VCEs carried out might in some way be related to the low frequency of tumor detection that we found. Interestingly, our figures are in keeping with those of the second largest existing study, by Pasha et al. [23], that was recently presented at an international meeting; this included 1000 VCE examinations, with a 1.6% frequency of small-bowel tumors. There is no obvious explanation for this. It is possible that centers where fewer examinations were carried out adopted stricter criteria for patient selection than larger centers; however, the characteristics of the patients enrolled in the different participating centers in our study were homogeneous. In our series, as in other studies, OGIB was the leading indication for capsule endoscopy. This was expected, since OGIB is the indication for VCE in 65%–100% of cases in all published series [13,18].

The design of the study does not allow estimation of the sensitivity and specificity of capsule endoscopy for small-bowel tumors. Recently published studies with double-balloon enteroscopy (DBE) [24] clearly demonstrated that capsule endoscopy can miss even large malignant masses (a pooled analysis of previously published studies [21] showed a miss rate of up to 18.9%). On the other hand, the difficulties in distinguishing bulges from masses underline the main limitation of capsule endoscopy, i.e. the inability to take biopsies. Furthermore, we could not evaluate the role of DBE in confirming or disproving the diagnoses made by capsule endoscopy, since during the collection of our cases DBE was not widely available at the participating centers. Despite these limitations, our study confirms that nowadays capsule endoscopy is often used as the third examination (in about 50% of patients) after a negative bidirectional endoscopy, especially in patients with obscure gastrointestinal bleeding [19,25,26].

As far as the diagnostic work-up before VCE is concerned, all our patients underwent at least one gastroscopy and one colonoscopy, especially in patients with obscure gastrointestinal bleeding, as reported also by Bailey et al. [15]. Concerning the impact of VCE on diagnosis, we were conservative and counted only the patients in whom VCE showed a tumor undetected by other techniques. Nevertheless, 80% of tumors were identified solely by VCE, and this figure is much higher than that reported by others [17]. Enteroscopy (both push and balloon enteroscopy) was seldom performed before VCE, and had a low diagnostic yield (Table 2; 1/11, 9%). On the other hand, when conventional enteroscopy (push or DBE) was performed after a positive VCE examination, the diagnostic yield rose sharply (Table 2; 27/35, 77%; \( P < 0.0001 \)), suggesting that VCE can be useful in indicating the utility of conventional enteroscopy for obtaining tissue samples.

As reported in other recently published series [13–18], adenocarcinomas, GISTs, carcinoids and lymphomas account for about 90% of small-bowel neoplasms. The most frequent tumor type in our series was GIST. When it is located in the small bowel, it is generally considered to be malignant in about 50% of cases; however, from an oncological standpoint, GISTs form a continuum. In general, size and mitotic activity [27,29] are used to judge the oncologic potential of these tumors. Unfortunately, we do not have mitotic activity data for the GISTs in our series, and therefore we decided not to classify them as malignant or benign. Our study also confirms the high tropism of skin melanoma for the small-bowel mucosa [10,11,13–16,18,30,31].

As expected, the majority of small-bowel tumors in our study were lesions that protruded into the lumen located in the jejunum, an area that is difficult to evaluate with other diagnostic techniques. Since confirmation of the diagnosis was obtained in all cases by conventional endoscopic or surgical means, we were able to compare the location of the lesion as assessed by the VCE reviewer with that found at endoscopy or surgery: in patients with a single lesion we found an impressive agreement (92.8%), which is comparable with that reported by Pasha et al. [23]. Among the eight cases in which the location of the lesion was misjudged at capsule endoscopy, in four cases the lesion was more proximal than expected on the basis of the capsule examination and in four cases it was more distal.

We did not use the standard definition of capsule retention [32], i.e. retention of the capsule in the small intestine for more than 15 days, because in some cases the procedure planned to solve the clinical problem was performed earlier than 15 days from ingestion. Therefore, we defined capsule retention as having occurred when the videos showed repetitive images, suggesting stenosis, and the capsule was retrieved at the site of the lesion by surgery or push enteroscopy. According to these criteria, capsule retention occurred in about 10% of cases. This rate is similar to the 11.5% reported by Bailey et al. [15] and substantially higher than those reported by Urbain et al. [17] and Cobrin et al. [0%] [14], while Pasha et al. [23] reported a very high occurrence (about 25%) of capsule retention in patients with small-bowel tumors.

We do not have a obvious explanation for these differences among studies. As reported in several studies [32,34] a negative SBS or enterolysis performed before VCE does not guarantee the passage of the capsule: in our series five patients with capsule retention had undergone an SBS or enterolysis with negative findings before the VCE.

Acute obstruction due to capsule retention is a rare complication [35] of capsule endoscopy and capsule retention can be considered, particularly in this subset of patients who often require surgical intervention, as a “positive complication” leading to diagnosis. None of our patients with capsule retention experienced acute obstruction, as reported also by Bailey et al. [15]. We can hypothesize that in patients with small-bowel tumors, the slow growth and the development of pre-stenotic dilatation, often described at the time of surgical intervention, can prevent acute obstruction. The development of a dissolvable capsule to
test bowel patency, by Given Imaging (Yoqneam, Israel) [37 – 41], and the recently achieved possibility of retrieving retained cap-
sules with DBE [36], will probably decrease the occurrence and
clinical consequences of this complication.

Capsule endoscopy appears thus to be appropriate as the first
step in the diagnostic process of small-bowel tumors, since it
may direct further diagnostic procedures (push enteroscopy,
DBE) aimed at obtaining tissue: in our series this led to a defini-
tive histologic diagnosis in 77% – 80% of cases. In addition, cap-
sule endoscopy has a direct impact on therapy, since 60% of our
patients in whom the capsule was not retained underwent surgical
or endoscopic therapy immediately following capsule endos-
copy. At present, surgery is by far the most frequently used treat-
ment in these patients [14 – 18, 23].

Whether the timely and widespread use of capsule endoscopy in
patients with obscure gastrointestinal bleeding or other unex-
plained abdominal complaints will lead to the earlier identifica-
tion of patients with small-bowel tumors, resulting ultimately in
a survival benefit for the patients, will have to be clarified in
specifically designed studies. Such studies will help define the best
diagnostic/therapeutic algorithm for these patients, and the
place of capsule endoscopy in such an algorithm.

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Competing interests: Roberto de Franchis has a consultancy
agreement with Given Imaging.

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Appendix

The following also contributed to the study:

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