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MISE AU POINT

Current role of small-bowel capsule endoscopy in neoplastic diseases

Rôle actuel de la capsule endoscopique dans la détection des tumeurs néoplasiques de l'intestin grêle

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Abstract

Although small-bowel tumors are a small proportion of gastrointestinal neoplasms recent studies suggest that the incidence of these diseases is increasing. In fact, using new diagnostic modalities, their frequency has been shown to be slightly superior than previously thought. Until recently, diagnosis and management of these tumors were delayed by the difficult of access to the small bowel and the poor diagnostic capabilities of the available diagnostic techniques. An array of new methods has recently been developed, increasing the possibility of detecting these tumors at an earlier stage. In this particular subset of patients capsule endoscopy, despite its possible limitations, may provide crucial information changing the subsequent patient management and possibly influencing the long-term clinical outcome.

Keywords
Capsule endoscopy, Enteroscopy, Obscure Gastrointestinal Bleeding, Small-bowel tumors, Polyposis syndromes

Résumé

Bien que les tumeurs de l'intestin grêle ne représentent qu'une faible proportion des lésions néoplasiques du tractus digestif, de récentes études ont mis en évidence une légère augmentation de leur incidence. En fait, grâce aux nouvelles modalités diagnostiques, leur fréquence s'est avérée légèrement supérieure à ce qui était précédemment rapporté. Jusqu'à très récemment, le diagnostic et la prise en charge de ces tumeurs étaient retardés en raison d'un accès difficile à l'intestin grêle et aux faibles capacités diagnostiques des moyens techniques disponibles. Tout un éventail de nouvelles méthodes ont récemment été mises au point, améliorant la possibilité de détecter ces lésions à un stade plus précoce. Pour cette catégorie spécifique de patients avec lésions de l'intestin grêle, la capsule endoscopique, en dépit de ses limites, peut fournir une information cruciale influant par conséquent sur la prise en charge du patient et sur les résultats cliniques au long cours.

Mots-clés
Capsule endoscopique, Entéroscopie, Hémorragie gastro-intestinale occulte, Tumeurs de l'intestin grêle, Syndrome de polypose

Introduction

Tumors of the small intestine present a unique challenge to the clinicians across medical specialties. Although the small bowel represents 75% of the length and 90% of the overall mucosal surface of the alimentary tract and despite its anatomic location between two regions of high cancer risk, the small bowel is generally considered as a rare location for the development of neoplasms, accounting for only 1-3% of all primary gastrointestinal (GI) tumors [1-3].

The overall age-adjusted incidence of small-bowel cancers estimated in population based studies in Western countries

ranges between 0.9 and 1.4 (Table 1) [1,4-9]; malignant tumors account for about one half of all new cases of small-bowel tumors reported [10]. The incidence rate of small-bowel cancer varies among populations: cancer rates are high among the Maori of New Zealand (about 4 cases per 100.000 per year) and among ethnic Hawaiians, and low in India, Romania, and other parts of Eastern Europe [1]. Some recently published studies reported an increasing incidence of these neoplasms over the last 20 years. Bilimoria *et al.* [11] reported that, in the United States, the incidence of small bowel tumors increased from 11.8 cases per million in 1973 to 22.7 cases per million in 2004.

Because small-bowel tumors are relatively rare compared with other neoplasms of the gastrointestinal tract, several factors have been proposed to explain or understand this disparity: 1) a quick transit allowing only short contact of possible carcinogens from food with the intestinal mucosa; 2) the intestinal content is mixed together with a great volume of intestinal juices decreasing the concentration of irritating agents; 3) a decrease in mechanical and/or chemical inflammation of the mucosa because of the liquidity and alkaline pH of the small-bowel contents; 4) the high concentration of lymphatic tissue and of immunoglobulin exerts an effective immune surveillance; 5) the low bacteria concentration in the small intestine processing the intestinal content produces a low amount of carcinogens; 6) the rapid turnover of epithelial cells should decrease the potential growth and development of neoplastic cells [1,10-12].

Genetics could also play a role in some particular subgroups of patients; subjects affected by familiar adenomatous polyposis, Lynch syndrome, Crohn's disease, celiac disease, Peutz-Jeghers syndrome, and several other diseases must be surveyed for the risk of small intestine tumor [9,13,14].

Approximately 40 different histological types of small intestinal tumors have been identified [15]. Among malignant tumors, about 30-50% are adenocarcinomas, 25-30% are carcinoids, and 15-20% are lymphomas. A recently published study, including 1260 cases of small-bowel tumor, showed that they seem to be frequently located in the ileum (about 30% of cases) or in the duodenum (about 25% of cases) [9]; the sites at highest risk for malignant neoplasms have been reported to be the duodenum for adenocarcinomas and the ileum for carcinoids and lymphomas [1,11]. One reason why adenocarcinomas tend to arise in the duodenum may implicate bile or its metabolites in the etiology of the neoplasm at this site [16]. However, among patients with Crohn's disease, which generally affects the ileum rather than the more proximal small bowel, adenocarcinomas tend to occur in the terminal ileum [1].

Secondary neoplastic involvement of the small intestine has been reported to be more frequent than primary small intestinal neoplasms. Primary tumors of the colon, ovary, uterus, and stomach can involve the small bowel (by direct invasion or by intraperitoneal spread) whereas primaries from breast, lung, and melanoma metastasize to the small bowel by the haematogenous route [17]. Small bowel metastases from melanoma have been described in 1.5-4.4% of patients [18,19] with previously removed skin melanoma and in 58% of post-mortem specimens [18].

In the majority of cases, the diagnosis of small-bowel tumors is delayed. This could be due to several factors:

- small-bowel tumors grow slowly, extraluminally, remaining asymptomatic for years or presenting insidiously with non-specific complaints such as abdominal pain, diarrhea, iron deficiency anemia, bleeding, extra intestinal symptoms (flushing, para-neoplastic syndromes) [20]. Obstruction is also a common presentation; indeed, small-bowel tumors are the third most common cause of small-bowel obstruction in the United States [21];
- the rare incidence of small-bowel tumors may contribute to the relatively low index of clinical suspicion for their presence;
- routine laboratory tests and other diagnostic tests may frequently be inconclusive; as a consequence, diagnostic laparoscopy or exploratory laparotomy may be indicated not only to deliver an effective treatment but also to reach a definitive diagnosis.

Since the introduction in clinical practice of capsule endoscopy (CE), several case reports describing primary and secondary tumors affecting the small bowel have been published. More recently, a few retrospective studies collecting series of patients in which this technology was able to show the presence of a small-bowel tumor have also been published. On the other hand, recent studies also suggest that some new techniques, other than

Table 1. Incidence of small-bowel tumors (modified from Neugut AI et al. [1])

Population/area	Ref.	Time interval	Cases of SB tumour	Incidence per million
Los Angeles County	4	1972-1985	264	-
Nine SEER Registers	5	1973-1982	366	9,6
Cancer register of British Columbia, Alberta, Saskatchewan, Manitoba	6	1975-1989	263	11
Utah Cancer registry	7	1966-1999	442	14
Nine SEER registers	8	1973-1991	892	13
Connecticut Tumor registry	9	1980-2000	1 260	8,8
National Cancer Database and Surveillance Epidemiology and End Results	11	1973-2004	67 843	11,8-22,7

SEER: Surveillance Epidemiology and End Result

capsule endoscopy, specifically designed for the study of the small bowel, have been introduced in clinical practice [22-27].

Capsule endoscopy in the diagnosis of small-bowel tumors

In a recently published paper, the hypothesis of an increased incidence of small-bowel tumors in recent years was put forward, based on the increasing number of cases diagnosed by means a non-invasive methods such as CE and small-bowel ultrasound [28]. In fact, compared with previously mentioned diagnostic techniques for the study of the small bowel, CE seems to be an ideal tool to recognize the presence of neoplastic lesions along the small bowel. The potential of CE for the diagnosis of small-bowel tumors, as well as for the surveillance of subjects at increased risk of developing them, depends largely on the technical characteristics of this diagnostic device. CE is a non-invasive tool, well accepted by patients, which can allow for the visualization of the entire small bowel; high-quality images of the small-bowel mucosa may be captured and small and flat lesions recognized, without exposure to radiation.

In fact, since the introduction of CE in clinical practice, some studies have been published [29,30-34,39,40,44-45] reporting a frequency of small-bowel tumors higher than previously expected, ranging between 2.4% and 11%. One study [32] reported a prevalence of small bowel tumors in patients undergoing CE higher than 30%; however in this paper the Authors described lesions as "tumour" without histological confirmation. Two recent studies, coming from the USA and Europe, one of them published only in abstract form [38,39], examined large populations of patients undergoing CE (respectively 2000 [38] and more than 5000 cases [39]) in whom the definitive diagnosis was confirmed by means of tissue sampling (Table 2). They both reported a small-bowel tumor frequency of 2.4%, only slightly above that reported in previous surgical series. In both these papers the Authors also confirmed that the main clinical indication for CE in patients with small-bowel tumors is obscure GI bleeding (in about 90% of cases). Other indication for CE in both these studies were: chronic diarrhea, abdominal pain, para-neoplastic syndromes or, in a small group of patients, presence of conditions increasing the risk to develop a small-bowel tumor (such as refractory celiac disease, familial adenomatous polyposis or Peutz-Jeghers syndrome). In some rare cases CE was also used to confirm the presence of a tumor previously suspected by other imaging modalities. Although Cobrin *et al.* [30] underlined that in their study the percentage of patients with tumor was greater among patients younger than 50 years, the median age of patients enrolled the above mentioned large studies ranged between 59 years [39] and 63 years [30], (Table 3).

Confirming data previously reported in surgical series [9,10] the majority of tumors identified by CE (from 63% [31] to 86% [38]) are malignant neoplasms and the most frequent histological types are adenocarcinomas, carcinoids (in about 20% of cases each [30,31,34]), and GISTs. Of note, this tumor accounted for more than one third of all collected cases in the large multi-center European study [39]. As far as small-bowel metastases are concerned, these lesions mainly (about 1/3 of cases [39]) derived from previously removed skin melanomas [44], but there are also some papers reporting lesions derived from colorectal cancers [31], from hepatocellular carcinoma or from rare tumors such as seminomas [39].

Small-bowel tumors appear at CE as masses (Fig. 1) or polyps in about 70-80% of cases [31-39] and as ulcers (Fig. 2) (sometimes actively bleeding) or stenoses in 20-30% of cases. Unfortunately, it is not possible to determine pathology and tumor type based on the capsule endoscopic appearance of lesions. These tumors are located, based on the capsule transit time, in about 50% of cases in the mid- or distal small bowel [31-39]. This could be a partial explanation of the extensive (and mainly negative) diagnostic work-up performed in patients enrolled in all these studies. Each patient underwent a mean of 2-4.6% [31,34] examinations before

Table 2. Summary of CE studies for small-bowel tumors

Study [ref.]	Population N	Tumor Cases N, (%)	Mean age of patients with tumors yrs	Malignant Tumors %	Tumors leading to capsule retention %
Cobrin *et al.* [30]	562	50 (8.9)	63	48	0
Bailey *et al.* [31]	416	27 (6.3)	61	63	11.5
Estevez *et al.* [32]	320	23 (7.8)	63	NA	NA
Urbain *et al.* [33]	443	11 (2.5)	63	100	0
Schwartz *et al.* [34]	NA	87 (NA)	60	60	NA
Spada *et al.* [35]	280	13 (3.4)	58	77	23
Trifan *et al.* [36]	102	5 (4.9)	55	NA	0
Pasha *et al.* [38]	2000	45 (2.4)	62	66	17
Rondonotti *et al.* [39]	5129	124 (2.4)	59	NA	9.7

NA: not applicable (these data are not reported in the paper)

Table 3. Frequency of capsule retention in patients undergoing capsule endoscopy (modified from Pennazio M. [60])

Clinical Indication	Frequency of capsule retention %
Healthy volunteers	0
Obscure GI bleeding	1.5
Suspected Crohn's disease	1.4
Known Crohn's disease	4-13
Small-bowel tumor	10-17
Suspected small-bowel obstruction	21

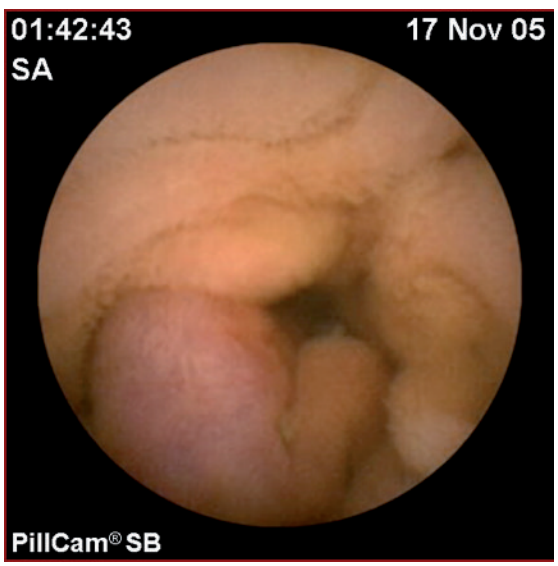

Figure 1
Submucosal jejunal mass with central ulcer. Histology revealed a GIST

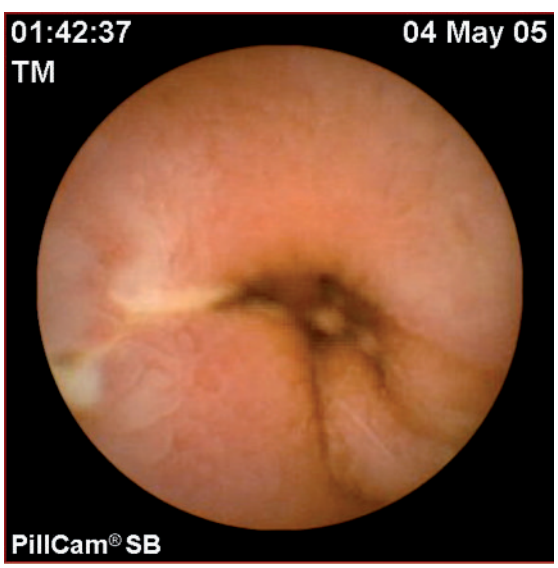

Figure 2
Small bowel ulcers in a patient diagnosed with small-bowel lymphoma

CE while, focusing only on exams addressed to evaluate the small bowel (particularly small-bowel series and/or small-bowel follow-through and/or PE and/or CT-enteroclysis), the mean number of examinations performed per patient ranged between 1 and 2 [30,31,34]. Despite the extensive number of examinations performed before CE, this technique was found to have a positive impact on diagnosis (defined as the capability to identify a neoplasm not shown by other diagnostic techniques or as the ability to provide crucial information leading to change the subsequent patient management) in about 65-80% of cases [33,39]. Urbain *et al.* [33], trying to evaluate the impact of CE on the therapeutic choices of malignant small-bowel tumors, found that CE may influence directly the therapeutic work-up in about 55% of cases by providing information about size, location and appearance of the lesion.

Impact of capsule endoscopy on clinical outcomes

Because the early diagnosis and treatment of cancer usually affects outcome, some Authors [30,31] suggest that the capability of CE to discover small-bowel tumors at an early stage may have an impact on prognosis for patients with these lesions. In addition, several papers revealed that advanced clinical stage and large tumor size contributed to worse prognosis while the identification and subsequent surgical treatment of the primary tumour led to better prognosis [40].

All the papers previously mentioned reported that in patients with small-bowel neoplasm identified by CE, surgery alone or surgery plus chemotherapy is the treatment of choice in about 68-90% of cases [30-32,38,39]. Nevertheless, recent studies [38] showed that the identification of the small bowel tumor with CE can also lead to less invasive procedures such as polypectomy, endoscopic mucosal resection or chemotherapy alone.

Unfortunately, up to now, data about long-term clinical outcomes of small bowel tumors diagnosed by CE are scarce. Bailey *et al.* [31] reported that surgical treatment was performed in 88% of patients with small-bowel tumor, in half of the cases with curative aim: none of the patients who underwent a curative resection developed tumor recurrence at follow-up (ranging from 26 to 51 months). Pasha *et al.* [38] reported that 36% of patients with malignant tumour diagnosed with CE and followed prospectively for more than 24 months remained recurrence free.

Capsule endoscopy for specific small-bowel tumors

Thanks to its capability to identify a small-bowel lesion in most patients with a prior negative diagnostic work-up, several case reports, but also some small series, aimed at evaluating the possible role of the CE in the diagnosis of specific tumors in particular clinical conditions, have been published over the last few years.

In the last few years several papers [41-43] suggested an increased survival for patients with neuroendocrine tumor metastasis when the primary tumor is identified and resected. van Tuyl *et al.* [44], in a prospective descriptive study, evaluated 20 patients with liver metastases, mesenteric metastases or both, originated from a neuroendocrine tumor (NET) with unknown primary location. All these patients had undergone several examinations including small-bowel enteroclysis, abdominal CT, pentetreotide scintigraphy and laboratory tests. In this particular subset of patients, CE showed a diagnostic yield (60%) significantly higher than enteroclysis and CT scan. Pentetreotide scintigraphy had an even higher diagnostic yield than CE but without differentiation between intestinal and mesenteric localization. In this study, the absence of findings at CE in patients with abnormalities at nuclear imaging was interpreted to be related to the presence of NET restricted to the mesentery or to a false-negative CE. On the ground of these data, the Authors suggested that patients with a metastatic NET and an unknown primary tumor should undergo CE. Conversely, in a small retrospective study of 8 patients [45], CE detected NETs of the small bowel with high specificity but slightly lower sensitivity than did CT enteroclysis. It was concluded that CE should not be used as a routine method for diagnosing NET in the small bowel.

As far as small-bowel metastases are concerned, Prakoso and Selby [46] performed a retrospective analysis of a prospective database identifying 13 patients with previous or recurrent malignant melanoma referred for CE. The indication for CE were overt GI bleeding in three patients, anemia in six, abnormal imaging in two, abdominal pain in one, and one patient had positive fecal occult blood test. In these patients CE was able not only to show small-bowel metastases (in 5 patients) but also to provide a different possible explanation of symptoms in three other patients (NSAID-related ulcers, artero-venous malformation or aphtoid lesions). The Authors concluded that since the optimal investigation for the detection of small-bowel metastases in patients with melanoma has still to be determined, CE can be considered an ideal method to do so because it appears to be more sensitive than small-bowel follow-through and CT scan.

Flieger *et al.* [47] explored the potential contribution of CE to the diagnosis and staging of gastrointestinal lymphomas describing capsule endoscopic features of these tumors. They studied with CE a total of 27 consecutive patients with newly diagnosed gastro intestinal lymphoma: 20 patients with histologically confirmed gastric lymphoma and seven patients with intestinal lymphoma. All seven patients with primary intestinal lymphomas were found to have pathological findings at CE (ulcerations, nodules or villous atrophy), while 5 of the 20 patients with gastric lymphoma had pathological findings in the small bowel (including abnormal villi, white nodules or villous atrophy). In this study, the Authors found that CE is able to identify pathological intestinal findings in patients with gastrointestinal lymphoma more frequently than previously thought and suggest that knowledge of small-bowel involvement can lead to changes in the therapeutic strategy in individual cases.

Lymphomatous polyposis (LP) first described by Cornes in 1961 [48,49] is a rare condition, however, since the introduction of CE and balloon-assisted enteroscopy (BAE) in clinical practice, a few reports [49,50] have been published on this topic. LP is defined as polypoid mucosal involvement of long segments of the GI tract by neoplastic lymphoid cells [49-51]. For many years LP has been considered the macroscopic appearance of the mantle cell lymphoma, but it has recently been suggested that it can be also the macroscopic manifestation of mucosa-associated lymphoid tissue (MALT) lymphoma and follicular B cell lymphoma [52]. In patients with LP, CE is a valuable tool because it may recognize the presence of nodules, evaluate the extent of the small-bowel involvement and drive further investigations (i.e. the decision about the BAE approach). In a recently published paper Akamatsu *et al.* [53] suggested that, in patients with diagnosis of follicular lymphoma, a complete evaluation of the entire small bowel before starting the treatment is mandatory in order to discover multifocal lesions; this should be achieved by CE or BAE.

Another peculiar clinical condition is represented by patients with refractory celiac disease. It is known that these patients have an increased risk to develop small-bowel neoplasms, mainly enteropathy associated T-cell lymphoma (EATL). However, in this particular subgroup of patients CE is aimed at identifying not only a malignant neoplasm but also some other possible complications such as ulcerative jejunitis. To date, two papers have been published on this topic [54,55] showing that CE is a useful tool in the assessment of complicated celiac disease, especially in patients with refractory celiac disease type II [54].

Interestingly Ronchi *et al.* [56] reported an increased prevalence (14%) of small bowel tumours detected by CE in patients with acromegaly. Although this study seems to be noticeably biased (there was no histological confirmation of lesions identified by CE) it opens up a new frontier in the field of cancer prevention-surveillance in patients with increased risk of malignancies.

Capsule endoscopy: risks and limitations in patients with small-bowel tumors

Several papers [57-58] described risks and limitations related to the use of CE in everyday clinical practice. Some limitations can be present in any procedure performed regardless of the clinical indication (“general limitations”); these limitations are mainly related to the technical characteristics of the device or to the anatomical structure of the small bowel: i.e. due to the length of the small bowel, the capsule allows an evaluation of the entire small bowel only in 75-85% of cases [57,59]; in the recently published systematic review the overall completion rate was 83.5% while in patients undergoing CE because of small bowel tumors it was 85.6%. In addition, sometimes, the presence of fecal debris, particularly in the distal small bowel, may hamper the accurate visualization of the small-bowel mucosa.

Among general limitations, capsule retention is certainly the most feared one because it can significantly modify the subsequent management of the patient. It is generally recognized that the frequency of capsule retention is mostly dependent on the clinical indication to CE (Table 3), ranging between 0% in healthy subjects to 21% in patients with intestinal obstruction [60,61]. Patients with small-bowel tumors, which frequently appear as lesions protruding into the small-bowel lumen or as stenoses, in both cases capable of narrowing the lumen of the small bowel, have a high probability to develop capsule retention. The recent systematic collection of Liao *et al.* [62] reports a retention rate in patients undergoing CE for small bowel tumors of 2.1%, which is closely similar to that observed in patients examined for obscure GI bleeding. However, in the larger studies especially focused on small bowel tumors, capsule retention seems to be a frequent situation that can occur in 10-17% of patients (table 2). Nevertheless most Authors consider this situation as a minor complication (Zmora *et al.* defined this as a "fortunate" complication [63]). In fact, although possible acute obstruction due to capsule retained at the site of the tumor has been reported [64-65], this is an extremely rare event and does not represent a contra-indication in itself to CE. In these patients the subsequent surgical intervention, allowing capsule retrieval, was planned basically to treat the tumor rather than to retrieve the capsule. We must also keep in mind that surgical intervention aimed to retrieve the capsule can be done in a laparoscopic way [66] and that BAE can also allow capsule retrieval when surgical intervention is contraindicated or not feasible [67,68]. In addition, the recently developed Patency capsule [69] (Given Imaging, Yoqneam, Israel) can be used in selected patients as a screening method to prevent capsule retention.

The capsule can also have some problems in sizing lesions because of the shape of its dome, its magnification capability, the lack of air insufflated and of remote orientation. This issue has recently been highlighted in papers addressed to study patients with small-bowel inherited polyposis syndromes [70-71] in which the authors found that MRI seems to be more accurate and reliable than CE in the estimation of location and size of polyps [71]. The ingestion of "reference granules" of mesalazine 15-20 minutes before CE has recently been proposed to increase the accuracy of the procedure [72].

Another general limitation, that can be critical in the field of small-bowel tumors, is the accurate localization of the lesion along the small bowel. To estimate the location of a lesion we can correlate the time when the lesion appears to the small-bowel transit time divided in three equal thirds [73], or we can refer to the localization system [74]; both these systems are time-consuming, depend on some reference points established by the reader, are not suitable when the capsule does not reach the ileo-cecal valve during examination time and the localization software is reliable only considering a two dimension plan. Despite all these obvious limitations, in one large study [39] the capsule was able to correctly estimate the location of the lesion in a surprisingly high percentage of patients (about 85%).

Unfortunately, in the field of small-bowel neoplasms, in addition to these general limitations there are some other related to the intrinsic characteristics of these lesions ("tumor-related limitations").

Several studies [75-77] reported patients with negative CE in whom further examinations showed small-bowel tumors (false negative capsule endoscopy). Lewis *et al*. [76], analyzing data from an industry-maintained trial database, found that in about 1.5% of patients with small-bowel tumors CE was completely negative. These authors estimated that the miss rate of CE in neoplastic diseases can reach 18.9%. Although this percentage is substantially lower than that reported in the same paper for other diagnostic techniques (63.2%) it remains still alarming, especially if one keeps in mind the clinical relevance of these miss findings. In addition, recent reports showed a relatively low sensitivity of CE when compared with CT enterography [78]. Obviously, there are several reasons contributing to that miss rate but probably the crucial one is related, in this particular subset of patients, to the fact that sometime it is arduous, on the ground of CE findings, to discriminate masses from bulges. A bulge is defined as a round smooth, large base protrusion in the lumen having an ill defined edge on the surrounding mucosa; it can be a prominent normal fold or the luminal expression of intestinal loop angulation and stiffness, and sometimes it can be virtually indistinguishable from a small submucosal tumor. Some visual clues may help distinguishing masses from bulges (i.e. changes in mucosal characteristics, presence of bridging folds, of transit abnormalities, of repetitive images, and of synchronous lesions). Recently, Shyung *et al.* [79] proposed, on the ground of these visual clues, a simple scoring system to distinguish masses from bulges. Unfortunately this has not been validated yet in clinical practice. Moreover, in everyday clinical practice, these indicators are often completely lacking.

Pasha *et al.* [38] described 51 patients with polypoid lesions revealed at CE that were not confirmed at further examinations (false positive capsule endoscopy). This problem, highlighted also in other studies [32], can significantly influence the subsequent management: in fact a positive CE requires further invasive examinations (BAE or surgical interventions). For this reason the final interpretation of a finding identified by CE must be done taking into account not only the endoscopic images but also the patient's clinical history and other diagnostic examinations performed. On the other hand, as largely discussed, CE has some technical and practical limitations; therefore, mainly in the field of small bowel neoplasm, it should be complementary to other diagnostic techniques such as CT enterography or BAE.

Capsule endoscopy in inherited polyposis syndromes

On the ground of its own technical characteristics (i.e. high-quality endoscopic images of the whole small bowel, no need for radiations) and of the patients' acceptance, CE has also been

proposed in patients with inherited polyposis syndromes for both surveillance over time and in case of symptomatic disease.

In Peutz-Jeghers syndrome (PJS) the polyps are chiefly located in the small bowel (Fig. 3) and may give rise to complications in the form of intussusception, bleeding and obstruction of the intestine, depending on the number and size of the polyps present, as well as to small-bowel malignancy. Several studies have explored the possible diagnostic role of CE in these patients [70,71,80,81] showing that this tool seems to be superior to small-bowel follow-through [70]. Unfortunately, the same studies also underlined that CE (as discussed above) is not reliable for accurate sizing of polyps. At the present time it is suggested that CE should be performed at diagnosis in all patients with PJS, as the primary surveillance modality every 2-3 years from the age of 10, and as part of the investigation of patients with symptoms [60]. Additional information to evaluate the size and location of polyps, which is useful for planning the appropriate therapeutic strategy, can be provided by CT/MRI [70,71]. The coupling of CE with BAE and polypectomy may offer an ideal follow-up and treatment method for these patients, possibly avoiding surgery [82], or allowing for better locating the small bowel lesions when a laparoscopic approach is planned [83-85].

The role of CE is less clear in familial adenomatous polyposes (FAP). CE may miss duodenal/periampullary polyps due to a quick passage of the device in the descending duodenum. In a recently published prospective study, Wong *et al.* [86] compared CE with push enteroscopy and with lower GI endoscopy in 32 patients with FAP. They showed that, in a defined segment of the small bowel, CE diagnosed significantly fewer small-bowel polyps than standard endoscopy, showed only fair agreement with PE in determining polyp counts, and was fairly inaccurate in determining the size of the largest polyp and also in detecting large polyps. Recently Katsinelos *et al.* [87] described a similar situation in a small series of patients with FAP. Although duodenal adenomatous polyps were found in 64.3% patients, and jejunal and ileal polyps in 50% and in 57.1% of patients, respectively, the identification of the ampulla of Vater was not achieved with CE and, importantly, the findings of CE had no immediate impact on the further clinical management of FAP patients.

For these reasons, CE is not presently recommended when the diagnosis of FAP is well established. Although CE has been suggested for surveillance of patients with severe duodenal polyposis (Spigelman stage III°-IV°) [80], the association of advanced distal adenomas with the severity of the duodenal polyposis remains controversial [88,89] and, therefore, the role of CE in FAP requires to be further clarified by large prospective studies. Iaquinto *et al.* [90], suggested that another possible criterion to select patients with FAP for CE is to stratify them according to the APC germline mutation. Moreover, in FAP patients with known mesenteric desmoids, caution is recommended before performing CE for the possible risk of capsule retention. Regarding another genetic disorder, a recent prospective study showed that CE may detect curable early or advanced neoplasia with a better reproducibility than CT enteroclysis in asymptomatic individuals

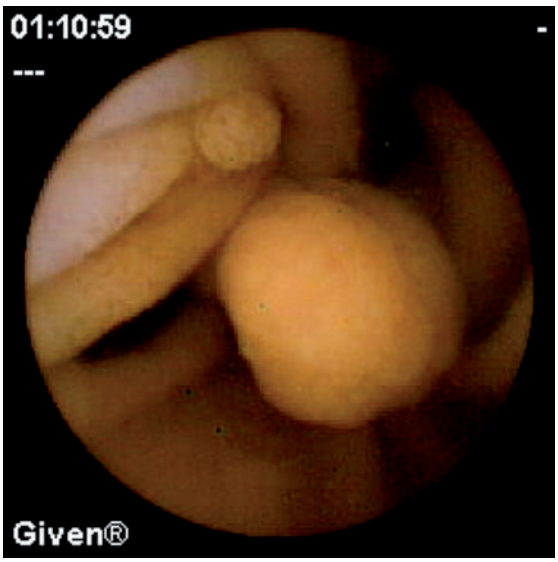

Figure 3
Pedunculated jejunal polyp in a patient with Peutz-Jeghers syndrome

with Lynch syndrome [91]. The clinical utility of systematic small-bowel screening in these patients should be accessed through large prospective studies.

Conclusions

Small-bowel tumors are a small but significant proportion of GI neoplasms. Using new diagnostic modalities, their frequency has been shown to be slightly superior than previously thought. Until recently, diagnosis and management of these tumors were delayed by the difficulty of access to the small bowel and the poor diagnostic capabilities of the available diagnostic techniques. An array of new methods has recently been developed, increasing the possibility of detecting these tumors at an earlier stage. Despite its limitations, CE plays a pivotal role in this setting. Whether the use of CE in combination with other new diagnostic (MRI or multidetector CT enterography) and therapeutic (BAE) techniques will lead to earlier diagnosis and treatment of these neoplasms, ultimately resulting in a survival advantage and in cost savings, remains to be determined through carefully designed studies.

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