Online Submissions: wjg.wjgnet.com
wjg@wjgnet.com
doi:10.3748/wjg.14.5245

World J Gastroenterol 2008 September 14; 14(34): 5245-5253
World Journal of Gastroenterology ISSN 1007-9327

TOPIC HIGHLIGHT

Miguel Angel Muñoz-Navas, Profesor, *Series Editors*

Capsule endoscopy in neoplastic diseases

Marco Pennazio, Emanuele Rondonotti, Roberto de Franchis

Marco Pennazio, Division of Gastroenterology 2, Department of Gastroenterology and Clinical Nutrition, S. Giovanni A.S. Hospital, Via Cavour 31, Turin 10123, Italy
Emanuele Rondonotti, Roberto de Franchis, University of Milan, IRCCS Policlinico, Mangiagalli, Regina Elena Foundation, Gastroenterology and Gastrointestinal Endoscopy Unit, Via Pace 9, Milan 20100, Italy
Correspondence to: Dr. Marco Pennazio, Division of Gastroenterology 2, Department of Gastroenterology and Clinical Nutrition, S. Giovanni A.S. Hospital, Via Cavour 31, Turin 10123, Italy. pennazio.marco@gmail.com
Telephone: +39-11-6333594 Fax: +39-11-6333623
Received: February 15, 2007 Revised: July 26, 2008
Accepted: August 2, 2008
Published online: September 14, 2008

Abstract

Until recently, diagnosis and management of small-bowel 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. Capsule endoscopy (CE) appears to be an ideal tool to recognize the presence of neoplastic lesions along this organ, since it is non-invasive and enables the entire small bowel to be visualized. High-quality images of the small-bowel mucosa may be captured and small and flat lesions recognized, without exposure to radiation. Recent studies on a large population of patients undergoing CE have reported small-bowel tumor frequency only slightly above that reported in previous surgical series (range, 1.6%-2.4%) and have also confirmed that the main clinical indication to CE in patients with small-bowel tumors is obscure gastrointestinal (GI) bleeding. The majority of tumors identified by CE are malignant; many were unsuspected and not found by other methods. However, it remains difficult to identify pathology and tumor type based on the lesion's endoscopic appearance. Despite its limitations, CE provides crucial information leading in most cases to changes in subsequent patient management. Whether the use of CE in combination with other new diagnostic (MRI or multidetector CT enterography) and therapeutic (Push-and-pull enteroscopy) 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.

Key words: Capsule endoscopy; Enteroscopy; Obscure gastrointestinal bleeding; Small-bowel tumors; Polyposis syndromes

Peer reviewer: Klaus R Herrlinger, Hepatology and Endocrinology, Robert-Bosch-Hospital, Auerbachstrasse. 110, D-70376 Stuttgart, Germany

Pennazio M, Rondonotti E, de Franchis R. Capsule endoscopy in neoplastic diseases. *World J Gastroenterol* 2008; 14(34): 5245-5253 Available from: URL: http://www.wjgnet.com/1007-9327/14/5245.asp DOI: http://dx.doi.org/10.3748/wjg.14.5245

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 (Figure 1)[1,9].

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

Table 1 Incidence of small-bowel tumors (modified from Neugut *et al*[11])

Population/area	Ref.	Time interval	Cases of SB tumor	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	1260	8.8

SEER: Surveillance epidemiology and end result.

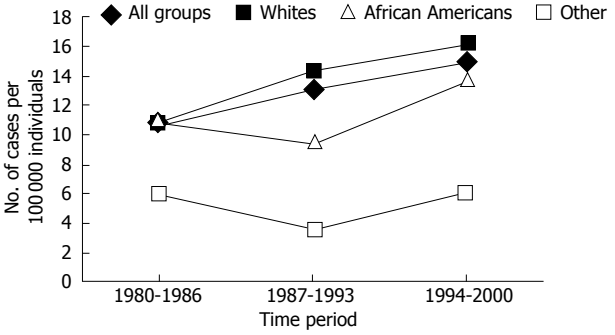

Figure 1 Incidence of small-bowel tumors per race in the Connecticut tumor registry per periods of 7 years since 1980 to 2000[5].

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[1,10,11].

Genetics could also play a role in some particular subgroups of patients; subjects affected by familiar adenomatous polyposis, hereditary non-polypoid colorectal cancer, Crohn's disease, celiac disease, Peutz-Jeghers syndrome, and several other diseases must be surveyed for the risk of small intestine tumor[9,12]. A relevant role of genetics has also been described in patients with sporadic gastrointestinal stromal tumors (GISTs) in which four different regions (exon 9, exon 11, exon 13, and exon 17) of the *KIT* gene have found to be mutated[13].

Approximately 40 different histological types of small intestinal tumors have been identified[14]. 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]. 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[15]. 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 hematogenous route[16]. SB metastases from melanoma have been described in 1.5%-4.4% of patients[17,18] with previously removed skin melanoma and in 58% of post-mortem specimens[17].

In the majority of cases, the diagnosis of small-bowel tumors is delayed. This could be due to several factors: (Ⅰ) 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, paraneoplastic syndromes)[19]. Obstruction is also a common presentation; indeed, small-bowel tumors are the third most common cause of small-bowel obstruction in the United States[20]. (Ⅱ) The rare incidence of small-bowel tumors may contribute to the relatively low index of clinical suspicion for their presence.(Ⅲ) 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, 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.

SMALL-BOWEL TUMORS: DIAGNOSTIC TOOLS

Historically the small bowel has been considered a difficult organ to evaluate. For many years, visualization of the small-bowel mucosa and the diagnosis of small-bowel tumors were feasible only in a surgical setting and this organ has been considered a sort of "black box". This situation derived both from the anatomical characteristics of the small bowel and the limitations of available techniques. The length of the small intestine,

the distance between the organ and external orifices (mouth and anus), its sinuousness, its ability to produce huge amounts of fluids and the continuous contractions long hampered accurate inspection of the small-bowel mucosa.

Traditional radiological techniques, including small-bowel follow-through and small-bowel enteroclysis, allow an indirect evaluation of the entire small bowel, however the difficulty to place a specific catheter in the right position (enteroclysis), the low pressure and the dilution of the contrast medium (small-bowel follow-through) contribute to a high miss rate for small and/or flat lesions. Conventional cross-sectional imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), can be helpful in identifying large small-bowel masses or extraintestinal disease, but are unable to provide precise data about the intestinal wall. Endoscopy has the advantage of visualizing intestinal mucosa directly and, above all, of carrying out targeted biopsies. Upper GI endoscopy, when performed to the ligament of Treitz, is suited for identifying duodenal tumors; however, lesions located distally pose a unique diagnostic challenge. Push enteroscopy (PE) is an effective diagnostic and therapeutic procedure which entails the oral insertion of a dedicated enteroscope; however, it only allows thorough examination of the distal duodenum and proximal jejunum to approximately 50-100 cm beyond the ligament of Treitz. Because of its ability to examine the entire small intestine, sonde enteroscopy has been utilized to diagnose small-bowel tumors[21]. However, this technically-challenging procedure has been today completely abandoned. Intraoperative enteroscopy (IOE) is the most complete, but also the most invasive means of examining the small bowel. It is a difficult, time-consuming technique, often traumatic to the bowel, with a substantial risk of complications and even mortality.

The development and the introduction in the clinical practice of the capsule endoscopy (CE) has revolutionized the field of small-bowel imaging, not only opening up this sort of "Pandora's box", but also stimulating the development of other imaging techniques aimed at studying the small bowel.

Magnetic resonance enteroclysis (MRI-enteroclysis) combines the advantages of cross-sectional resonance with those of volume challenge of conventional enteroclysis in the detection and characterization of small-bowel wall abnormalities, such as initial neoplasms. Small-bowel tumors usually exhibit moderate signal intensity on true-FISP images, as opposed to the high signal intensity of the distended lumen and the mesenteric fat. Post-gadolinium 3D FLASH with fat saturation may be the most important sequence for the identification and characterization of small-bowel tumors by their enhancement pattern. The degree of prestenotic dilatation, the peritoneal extension of the neoplasm and associated lymphadenopathy is well visualized in all MRI-enteroclysis sequences[22,23]. The multidetector row computed tomography (MRCT) has the potential to provide high-resolution images and a precise delineation of pathology. The multiplanar reformatted images obtained using MRCT have spatial resolution similar to that of the axial plane without any loss of information. These advantages of MDCT imaging lead to a more accurate demonstration of the site of the tumor and possible complications of underlying small-bowel tumors including small-bowel obstruction, intussusception, perforation and bleeding[24]. The administration of methyl-cellulose as a neutral luminal contrast material in a 4%-15% water-soluble solution or a diluted (1%) barium solution as positive luminal contrast in patients undergoing MRCT results in a computed tomography enteroclysis (CT-enteroclysis). As previously described for MRI-enteroclysis, this technique combines the advantages of enteral volume challenge and the ability of cross-sectional imaging to depict extra intestinal manifestations of the disease[25]. Both MRI enteroclysis and CT-enteroclysis require the placement of a specific catheter into the third part of the duodenum (fluoroscopic monitored), administration of medications (anti-motility agents and sedative medications) and small-bowel preparation with laxatives (PEG-based solutions, 2 to 4 L)[24]. Up to now, there are only few, but promising, publications about the role of these three techniques in the diagnostic algorithm of small-bowel tumors.

In the attempt to design a new scope that would allow a large part of the small-bowel mucosa to be visualized, overcoming the limits of PE and IOE, Yamamoto *et al*[25] developed a new method of push-and-pull enteroscopy (PPE) using a double-balloon technique. PPE affords inspection of the entire small bowel, combining the oral and anal approaches, with the advantage of enabling biopsies and endoscopic interventions to be performed in all parts of the small bowel without laparotomy. It is, however, invasive, time-consuming, and requires conscious sedation[26].

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[11]. 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, who can allow 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

Table 2 Summary of CE studies for small-bowel tumors

Study[ref]	Population	Tumor cases (%)	Mean age of patients with tumors (yr)	Malignant tumors (%)	Tumors leading to capsule retention (%)
Cobrin *et al*[28]	562	50 (8.9)	63	48	0
Bailey *et al*[29]	416	27 (6.3)	61	63	3/26 (11.5)
Urbain *et al*[31]	443	11 (2.5)	63	100	0
Estevez *et al*[30]	320	23 (7.8)	63	NA	NA
Schwartz *et al*[32]	NA	87 (NA)	60	60	NA
Pasha *et al*[33]	1000	16 (1.6)	67	86	4/16 (25)
Rondonotti *et al*[34]	5129	124 (2.4)	59	NA	12/124 (9.7)

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

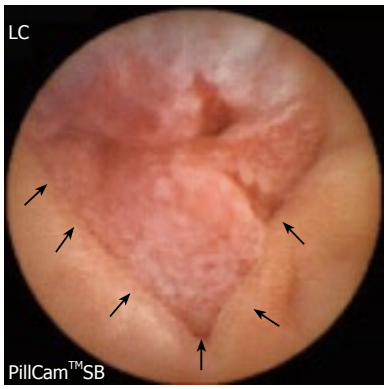

Figure 2 Infiltrating, stenotic, mass (arrows) in the ileum in a patient with hereditary non-polyposis colorectal cancer syndrome. Histology revealed an adenocarcinoma.

practice, some studies have been published[27-32] reporting a frequency of small-bowel tumors higher than previously expected, ranging between 3.6% and 9%. All these studies were retrospective; each of them collected about 350-500 patients undergoing CE, described the frequency of small-bowel tumors in a highly selected group of patients with symptoms (obscure GI bleeding in the majority of cases) and sometimes the diagnosis was based only on the endoscopic images (one study[30] reported 35% of lesions described as tumor without histological confirmation). Two recent studies, coming from the USA and Europe, only published in abstract form[33,34], examined a large population of patients undergoing CE (respectively, 1000[33] and more than 5000[34]) in whom the definitive diagnosis was confirmed by means of tissue sampling (Table 2). They reported a small-bowel tumor frequency only slightly above that reported in previous surgical series, ranging from 1.6% to 2.4%, and also confirmed that the main clinical indication to CE in patients with small-bowel tumors is obscure GI bleeding (in about 90% of cases). Other indications for CE in these two 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*[28] 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[34] and 67 years[33] (Table 2).

Confirming data previously reported in surgical series[9,10] the majority of tumors identified by CE (from 63%[29] to 86%[33]) are malignant neoplasms and the most frequent histological types are adenocarcinomas and carcinoids (in about 20% of cases each[28,29,32]), while GISTs represent the most frequently identified benign neoplasm. Of note, this tumor accounted for more than one third of all collected cases in the large multi-center European study[34]. As far as small-bowel metastases are concerned, these lesions mainly (about 1/3 of cases[34]) derived from previously removed skin melanomas[35], but there are also some papers reporting lesions derived from colorectal cancers[29], from hepatocellular carcinoma or from rare tumors such as seminomas[34].

Small-bowel tumors appear at CE as masses or polyps in about 70%-80% of cases[28-34] and as ulcers (sometimes actively bleeding) or stenoses in 20%-30% of cases (Figure 2). Unfortunately, it is very difficult to identify pathology and tumor type based on the capsule endoscopic appearance of lesions[36]. These tumors are mostly located in the jejunum, 40%-60% of cases, in the ileum, 25%-40% of cases, and less frequently in the duodenum, in 15%-20% of cases[28-34]. The location of the majority of lesions in the mid-small bowel 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%[29,32] examinations before 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[28,29,32]. 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[31,34]. Urbain *et al*[31], 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.

Because the early diagnosis and treatment of cancer usually affects outcome, some authors[28,29] 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. 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 85%-90% of the cases[28-30,33,34] but, to date, there is only one published paper describing the follow-up of these patients. Bailey *et al*[29] 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 (range, 26-51 mo). These authors also reported that none of the patients with benign tumors discovered by CE and treated according to CE findings had recurrence of either overt or occult obscure GI bleeding at follow-up (3-51 mo).

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.

Van Tuyl *et al*[37], 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[38], 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[35] 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*[39] 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 gastrointestinal 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[40,41], is a rare condition; however, since the introduction of CE and PPE in clinical practice, a few reports[42,43] have been published on this topic. LP is defined as polypoid mucosal involvement of long segments of the GI tract by neoplastic lymphoid cells[40]. 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[44]. 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 PPE approach).

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[45,46] showing that CE is a useful tool in the assessment of complicated

celiac disease, especially in patients with refractory celiac disease type Ⅱ[45].

CAPSULE ENDOSCOPY: RISKS AND LIMITATIONS IN PATIENTS WITH SMALL-BOWEL TUMORS

Several papers[47-49] 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, for example, due to the duration of battery life (about 8 h), the capsule allows an evaluation of the entire small bowel only in 75%-85%[47,49] of cases. In addition, sometimes the presence of fecal debris, particularly in the distal small bowel, can hamper the accurate visualization of the small-bowel mucosa.

Among general limitations, capsule retention is certainly the more 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[50,51]. 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. However, although capsule retention at the site of the lesion has been described in 10%[29,34] to 25%[33] of these patients (Table 2), most authors consider this situation as a minor complication. In fact, although some case reports describing possible acute obstructions due to capsule retained at the site of the tumor[52,53] exist, none of the 15 patients with capsule retention described in large published series[29,33,34] developed acute small-bowel obstruction. In these patients the subsequent surgical intervention, allowing capsule retrieval, was planned basically to treat the tumor (or because of symptoms persistence) 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[54] and that PPE can also allow capsule retrieval when surgical intervention is contraindicated or not feasible[55]. In addition, the recently developed Patency capsule[56] (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 insufflation and of remote orientation. This issue has recently been highlighted in papers addressed to study patients with small-bowel inherited polyposis syndromes[57,58] 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[58]. The ingestion of "reference granules" of mesalazine 15-20 min before CE has recently been proposed to increase the accuracy of the procedure[59].

Table 3 Frequency of capsule retention in patients undergoing capsule endoscopy (modified from Pennazio[50])

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	10-25
Suspected small-bowel obstruction	21

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[60], or we can refer to the localization system[61]; 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[33] 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[30,62-64] reported patients with negative CE in whom further examinations showed small-bowel tumors (false negative capsule endoscopy). Lewis *et al*[63], 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 missing findings. 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), but unfortunately all these are indirect indicators and often

are completely lacking.

Pasha *et al*[33] 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[30], can significantly influence the subsequent management; in fact a positive CE requires further invasive examinations (PPE 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.

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 (Figure 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[57,58,65,66] showing that this tool seems to be superior to small-bowel follow-through[57]. 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[50]. 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[57,58]. The coupling of CE with PPE and polypectomy may offer an ideal follow-up and treatment method for these patients, possibly avoiding surgery[67].

The role of CE is less clear in familial adenomatous polyposis (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*[68] 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. For these reasons, CE is not presently recommended when the diagnosis of FAP is well established, but it may be considered as a part of surveillance for patients with severe duodenal polyposis (Spigelman stage Ⅲ-Ⅳ; Figure 4)[65,66]. Moreover, in FAP patients with known mesenteric desmoids, caution is recommended before performing CE for the possible risk of capsule retention.

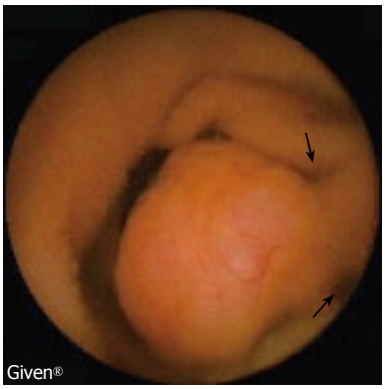

Figure 3 Small sessile, plaque-like, polyp (arrows) in the distal duodenum in a patient with familial adenomatous polyposis.

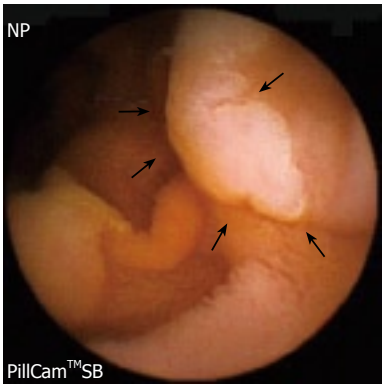

Figure 4 Pedunculated jejunal polyp (arrows denote stalk) in a patient with Peutz-Jeghers syndrome.

CONCLUSION

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 (PPE) 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.

REFERENCES

1 **Neugut AI**, Jacobson JS, Suh S, Mukherjee R, Arber N. The epidemiology of cancer of the small bowel. *Cancer Epidemiol Biomarkers Prev* 1998; **7**: 243-251
2 **Rossini FP**, Risio M, Pennazio M. Small bowel tumors and polyposis syndromes. *Gastrointest Endosc Clin N Am* 1999; **9**: 93-114
3 **DiSario JA**, Burt RW, Vargas H, McWhorter WP. Small bowel cancer: epidemiological and clinical characteristics from a population-based registry. *Am J Gastroenterol* 1994; **89**: 699-701
4 **Ross RK**, Hartnett NM, Bernstein L, Henderson BE. Epidemiology of adenocarcinomas of the small intestine: is bile a small bowel carcinogen? *Br J Cancer* 1991; **63**: 143-145
5 **Weiss NS**, Yang CP. Incidence of histologic types of cancer of the small intestine. *J Natl Cancer Inst* 1987; **78**: 653-656
6 **Gabos S**, Berkel J, Band P, Robson D, Whittaker H. Small bowel cancer in western Canada. *Int J Epidemiol* 1993; **22**: 198-206
7 **Chow JS**, Chen CC, Ahsan H, Neugut AI. A population-based study of the incidence of malignant small bowel tumours: SEER, 1973-1990. *Int J Epidemiol* 1996; **25**: 722-728
8 **Severson RK**, Schenk M, Gurney JG, Weiss LK, Demers RY. Increasing incidence of adenocarcinomas and carcinoid tumors of the small intestine in adults. *Cancer Epidemiol Biomarkers Prev* 1996; **5**: 81-84
9 **Hatzaras I**, Palesty JA, Abir F, Sullivan P, Kozol RA, Dudrick SJ, Longo WE. Small-bowel tumors: epidemiologic and clinical characteristics of 1260 cases from the connecticut tumor registry. *Arch Surg* 2007; **142**: 229-235
10 **Blanchard DK**, Budde JM, Hatch GF 3rd, Wertheimer-Hatch L, Hatch KF, Davis GB, Foster RS Jr, Skandalakis JE. Tumors of the small intestine. *World J Surg* 2000; **24**: 421-429
11 **Kala Z**, Valek V, Kysela P, Svoboda T. A shift in the diagnostics of the small intestine tumors. *Eur J Radiol* 2007; **62**: 160-165
12 **Ashley SW**, Wells SA Jr. Tumors of the small intestine. *Semin Oncol* 1988; **15**: 116-128
13 **Miettinen M**, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Arch Pathol Lab Med* 2006; **130**: 1466-1478
14 **O'Riordan BG**, Vilor M, Herrera L. Small bowel tumors: an overview. *Dig Dis* 1996; **14**: 245-257
15 **Lowenfels AB**. Does bile promote extra-colonic cancer? *Lancet* 1978; **2**: 239-241
16 **Gill SS**, Heuman DM, Mihas AA. Small intestinal neoplasms. *J Clin Gastroenterol* 2001; **33**: 267-282
17 **Das Gupta TK**, Brasfield RD. Metastatic melanoma of the gastrointestinal tract. *Arch Surg* 1964; **88**: 969-973
18 **Reintgen DS**, Thompson W, Garbutt J, Seigler HF. Radiologic, endoscopic, and surgical considerations of melanoma metastatic to the gastrointestinal tract. *Surgery* 1984; **95**: 635-639
19 **Talamonti MS**, Goetz LH, Rao S, Joehl RJ. Primary cancers of the small bowel: analysis of prognostic factors and results of surgical management. *Arch Surg* 2002; **137**: 564-570; discussion 570-571
20 **Fitzgibbons RJ**, Filippi CJ, Quinn TH. Inguinal hernias. In: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Pollock RE. Schwartz's Principles of Surgery. 8th ed. New York: McGraw-Hill, 2005: 230-246
21 **Lewis BS**, Kornbluth A, Waye JD. Small bowel tumours: yield of enteroscopy. *Gut* 1991; **32**: 763-765
22 **Semelka RC**, John G, Kelekis NL, Burdeny DA, Ascher SM. Small bowel neoplastic disease: demonstration by MRI. *J Magn Reson Imaging* 1996; **6**: 855-860
23 **Gourtsoyiannis N**, Papanikolaou N, Grammatikakis J, Prassopoulos P. MR enteroclysis: technical considerations and clinical applications. *Eur Radiol* 2002; **12**: 2651-2658
24 **Ramachandran I**, Sinha R, Rajesh A, Verma R, Maglinte DD. Multidetector row CT of small bowel tumours. *Clin Radiol* 2007; **62**: 607-614
25 **Yamamoto H**, Kita H, Sunada K, Hayashi Y, Sato H, Yano T, Iwamoto M, Sekine Y, Miyata T, Kuno A, Ajibe H, Ido K, Sugano K. Clinical outcomes of double-balloon endoscopy for the diagnosis and treatment of small-intestinal diseases. *Clin Gastroenterol Hepatol* 2004; **2**: 1010-1016
26 **May A**, Nachbar L, Schneider M, Ell C. Prospective comparison of push enteroscopy and push-and-pull enteroscopy in patients with suspected small-bowel bleeding. *Am J Gastroenterol* 2006; **101**: 2016-2024
27 **de Franchis R**, Rondonotti E, Abbiati C, Beccari G, Signorelli C. Small bowel malignancy. *Gastrointest Endosc Clin N Am* 2004; **14**: 139-148
28 **Cobrin GM**, Pittman RH, Lewis BS. Increased diagnostic yield of small bowel tumors with capsule endoscopy. *Cancer* 2006; **107**: 22-27
29 **Bailey AA**, Debinski HS, Appleyard MN, Remedios ML, Hooper JE, Walsh AJ, Selby WS. Diagnosis and outcome of small bowel tumors found by capsule endoscopy: a three-center Australian experience. *Am J Gastroenterol* 2006; **101**: 2237-2243
30 **Estevez E**, Gonzalez-Conde B, Vazquez-Iglesias JL, Alonso PA, Vazquez-Millan Mde L, Pardeiro R. Incidence of tumoral pathology according to study using capsule endoscopy for patients with obscure gastrointestinal bleeding. *Surg Endosc* 2007; **21**: 1776-1780
31 **Urbain D**, De Looze D, Demedts I, Louis E, Dewit O, Macken E, Van Gossum A. Video capsule endoscopy in small-bowel malignancy: a multicenter Belgian study. *Endoscopy* 2006; **38**: 408-411
32 **Schwartz GD**, Barkin JS. Small-bowel tumors detected by wireless capsule endoscopy. *Dig Dis Sci* 2007; **52**: 1026-1030
33 **Pasha SF**, Sharma VK, Carey EJ, Shiff AD, Heigh RI, Gurudu SR, Erickson PJ, Post JK, Hara AK, Fleischer DE, Leighton JA. Utility of video capsule endoscopy in the detection of small bowel tumors. A single center experience of 1000 consecutive patients. Proceedings of the 6th International Conference on Capsule Endoscopy, 2007 June 8-10; Madrid, Spain, 2007: 45
34 **Rondonotti E**, Pennazio M. Small bowel tumors detected by capsule endoscopy (VCE): preliminary data from the ECEG (European Capsule Endoscopy Group) database. *Gastroint Endosc* 2007: **65**: AB90-AB371
35 **Prakoso E**, Selby WS. Capsule endoscopy in patients with malignant melanoma. *Am J Gastroenterol* 2007; **102**: 1204-1208
36 **Pennazio M**. Small-intestinal pathology on capsule endoscopy: tumors. *Endoscopy* 2005; **37**: 1008-1017
37 **van Tuyl SA**, van Noorden JT, Timmer R, Stolk MF, Kuipers EJ, Taal BG. Detection of small-bowel neuroendocrine tumors by video capsule endoscopy. *Gastrointest Endosc* 2006; **64**: 66-72
38 **Johanssen S**, Boivin M, Lochs H, Voderholzer W. The yield of wireless capsule endoscopy in the detection of neuroendocrine tumors in comparison with CT enteroclysis. *Gastrointest Endosc* 2006; **63**: 660-665
39 **Flieger D**, Keller R, May A, Ell C, Fischbach W. Capsule endoscopy in gastrointestinal lymphomas. *Endoscopy* 2005; **37**: 1174-1180
40 **Cornes JS**. Multiple lymphomatous polyposis of the gastrointestinal tract. *Cancer* 1961; **14**: 249-257
41 **Yatabe Y**, Nakamura S, Nakamura T, Seto M, Ogura M, Kimura M, Kuhara H, Kobayashi T, Taniwaki M, Morishima Y, Koshikawa T, Suchi T. Multiple polypoid lesions of primary mucosa-associated lymphoid-tissue lymphoma of colon. *Histopathology* 1998; **32**: 116-125
42 **Higuchi K**, Komatsu K, Wakamatsu H, Kawasaki H, Murata M, Miyazaki K, Oikawa K, Ohwada M, Nanjo H, Otaka M, Watanabe S, Komatsu K. Small intestinal follicular lymphoma with multiple tumor formations diagnosed by double-balloon enteroscopy. *Intern Med* 2007; **46**: 705-709

43 **Esaki M**, Matsumoto T, Nakamura S, Suekane H, Ohji Y, Yao T, Iida M. Capsule endoscopy findings in intestinal follicular lymphoma. *Endoscopy* 2007; **39** Suppl 1: E86-E87

44 **Kodama T**, Ohshima K, Nomura K, Taniwaki M, Nakamura N, Nakamura S, Kohno S, Yamamoto J, Karube K, Yamasita Y, Shirakusa T, Kikuchi M. Lymphomatous polyposis of the gastrointestinal tract, including mantle cell lymphoma, follicular lymphoma and mucosa-associated lymphoid tissue lymphoma. *Histopathology* 2005; **47**: 467-478

45 **Daum S**, Wahnschaffe U, Glasenapp R, Borchert M, Ullrich R, Zeitz M, Faiss S. Capsule endoscopy in refractory celiac disease. *Endoscopy* 2007; **39**: 455-458

46 **Culliford A**, Daly J, Diamond B, Rubin M, Green PH. The value of wireless capsule endoscopy in patients with complicated celiac disease. *Gastrointest Endosc* 2005; **62**: 55-61

47 **Ho KK**, Joyce AM. Complications of capsule endoscopy. *Gastrointest Endosc Clin N Am* 2007; **17**: 169-178, viii-ix

48 **Cheifetz AS**, Lewis BS. Capsule endoscopy retention: is it a complication? *J Clin Gastroenterol* 2006; **40**: 688-691

49 **Rondonotti E**, Herrerias JM, Pennazio M, Caunedo A, Mascarenhas-Saraiva M, de Franchis R. Complications, limitations, and failures of capsule endoscopy: a review of 733 cases. *Gastrointest Endosc* 2005; **62**: 712-716; quiz 752, 754

50 **Pennazio M**. Capsule endoscopy: where are we after 6 years of clinical use? *Dig Liver Dis* 2006; **38**: 867-878

51 **Cave D**, Legnani P, de Franchis R, Lewis BS. ICCE consensus for capsule retention. *Endoscopy* 2005; **37**: 1065-1067

52 **Strosberg JR**, Shibata D, Kvols LK. Intermittent bowel obstruction due to a retained wireless capsule endoscope in a patient with a small bowel carcinoid tumour. *Can J Gastroenterol* 2007; **21**: 113-115

53 **Lin OS**, Brandabur JJ, Schembre DB, Soon MS, Kozarek RA. Acute symptomatic small bowel obstruction due to capsule impaction. *Gastrointest Endosc* 2007; **65**: 725-728

54 **Dominguez EP**, Choi Y, Raijman IL, Sweeney JF. Laparoscopic approach for the retrieval of retained video capsule endoscopy. *JSLS* 2006; **10**: 496-498

55 **Tanaka S**, Mitsui K, Shirakawa K, Tatsuguchi A, Nakamura T, Hayashi Y, Sakamoto C, Terano A. Successful retrieval of video capsule endoscopy retained at ileal stenosis of Crohn's disease using double-balloon endoscopy. *J Gastroenterol Hepatol* 2006; **21**: 922-923

56 **Spada C**, Shah SK, Riccioni ME, Spera G, Marchese M, Iacopini F, Familiari P, Costamagna G. Video capsule endoscopy in patients with known or suspected small bowel stricture previously tested with the dissolving patency capsule. *J Clin Gastroenterol* 2007; **41**: 576-582

57 **Brown G**, Fraser C, Schofield G, Taylor S, Bartram C, Phillips R, Saunders B. Video capsule endoscopy in peutz-jeghers syndrome: a blinded comparison with barium follow-through for detection of small-bowel polyps. *Endoscopy* 2006; **38**: 385-390

58 **Caspari R**, von Falkenhausen M, Krautmacher C, Schild H, Heller J, Sauerbruch T. Comparison of capsule endoscopy and magnetic resonance imaging for the detection of polyps of the small intestine in patients with familial adenomatous polyposis or with Peutz-Jeghers' syndrome. *Endoscopy* 2004; **36**: 1054-1059

59 **Racz I**, Janoki M, Kovacs V. Measurement of small-bowel polyp size in patients with Peutz-Jeghers syndrome by using reference granules during video capsule endoscopy. *Endoscopy* 2007; **39** Suppl 1: E41

60 **Biagi F**, Rondonotti E, Campanella J, Villa F, Bianchi PI, Klersy C, De Franchis R, Corazza GR. Video capsule endoscopy and histology for small-bowel mucosa evaluation: a comparison performed by blinded observers. *Clin Gastroenterol Hepatol* 2006; **4**: 998-1003

61 **Fischer D**, Schreiber R, Levi D, Eliakim R. Capsule endoscopy: the localization system. *Gastrointest Endosc Clin N Am* 2004; **14**: 25-31

62 **Mehdizadeh S**, Ross A, Gerson L, Leighton J, Chen A, Schembre D, Chen G, Semrad C, Kamal A, Harrison EM, Binmoeller K, Waxman I, Kozarek R, Lo SK. What is the learning curve associated with double-balloon enteroscopy? Technical details and early experience in 6 U.S. tertiary care centers. *Gastrointest Endosc* 2006; **64**: 740-750

63 **Lewis BS**, Eisen GM, Friedman S. A pooled analysis to evaluate results of capsule endoscopy trials. *Endoscopy* 2005; **37**: 960-965

64 **Chong AK**, Chin BW, Meredith CG. Clinically significant small-bowel pathology identified by double-balloon enteroscopy but missed by capsule endoscopy. *Gastrointest Endosc* 2006; **64**: 445-449

65 **Schulmann K**, Hollerbach S, Kraus K, Willert J, Vogel T, Moslein G, Pox C, Reiser M, Reinacher-Schick A, Schmiegel W. Feasibility and diagnostic utility of video capsule endoscopy for the detection of small bowel polyps in patients with hereditary polyposis syndromes. *Am J Gastroenterol* 2005; **100**: 27-37

66 **Burke CA**, Santisi J, Church J, Levinthal G. The utility of capsule endoscopy small bowel surveillance in patients with polyposis. *Am J Gastroenterol* 2005; **100**: 1498-1502

67 **Ohmiya N**, Taguchi A, Shirai K, Mabuchi N, Arakawa D, Kanazawa H, Ozeki M, Yamada M, Nakamura M, Itoh A, Hirooka Y, Niwa Y, Nagasaka T, Ito M, Ohashi S, Okamura S, Goto H. Endoscopic resection of Peutz-Jeghers polyps throughout the small intestine at double-balloon enteroscopy without laparotomy. *Gastrointest Endosc* 2005; **61**: 140-147

68 **Wong RF**, Tuteja AK, Haslem DS, Pappas L, Szabo A, Ogara MM, DiSario JA. Video capsule endoscopy compared with standard endoscopy for the evaluation of small-bowel polyps in persons with familial adenomatous polyposis (with video). *Gastrointest Endosc* 2006; **64**: 530-537

S- Editor Zhong XY **L- Editor** Rippe RA **E- Editor** Lin YP