TOPIC HIGHLIGHT

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Non-polypoid colorectal neoplasms: Classification, therapy and follow-up

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Abstract

In the last years, an increasing interest has been raised on non-polypoid colorectal tumors (NPT) and in particular on large flat neoplastic lesions beyond 10 mm tending to grow laterally, called laterally spreading tumors (LST). LSTs and large sessile polyps have a greater frequency of high-grade dysplasia and local invasiveness as compared to pedunculated lesions of the same size and usually represent a technical challenge for the endoscopist in terms of either diagnosis and resection. According to the Paris classification, NPTs are distinguished in slightly elevated (0-IIa, less than 2.5 mm), flat (0-IIb) or slightly depressed (0-IIc). NPTs are usually flat or slightly elevated and tend to spread laterally while in case of depressed lesions, cell proliferation growth progresses in depth in the colonic wall, thus leading to an increased risk of submucosal invasion (SMI) even for smaller neoplasms. NPTs may be frequently missed by inexperienced endoscopists, thus a careful training and precise assessment of all suspected mucosal areas should be performed. Chromoendoscopy or, if possible, narrow-band imaging technique should be considered for the estimation of SMI risk of NPTs, and the characterization of pit pattern and vascular pattern may be useful to predict the risk of SMI and, therefore, to guide the therapeutic decision. Lesions suitable to endoscopic resection are those confined to the mucosa (or superficial layer of submucosa in selected cases) whereas deeper invasion makes endoscopic therapy infeasible. Endoscopic mucosal resection (EMR, piecemeal for LSTs > 20 mm, *en bloc* for smaller neoplasms) remains the first-line therapy for NPTs, whereas endoscopic submucosal dissection in high-volume centers or surgery should be considered for large LSTs for which *en bloc* resection is mandatory and cannot be achieved by means of EMR. After piecemeal EMR, follow-up colonoscopy should be performed at 3 mo to assess resection completeness. In case of *en bloc* resection, surveillance colonoscopy should be scheduled at 3 years for adenomatous lesions ≥ 1 cm, or in presence of villous features or high-grade dysplasia patients (regardless of the size),

while less intensive surveillance (colonoscopy at 5-10 years) is needed in case of single (or two) NPT < 1 cm presenting tubular features or low-grade dysplasia at histology.

Key words: Non-polypoid lesion; Non polypoid tumors; Laterally spreading tumors; Endoscopic mucosal resection; Endoscopic submucosal dissection; Colorectal cancer; Injection

Core tip: Non polypoid tumors (NPTs) are distinguished in slightly elevated (0-IIa, less than 2.5 mm), flat (0-IIb) or slightly depressed (0-IIc). NPTs are usually flat or slightly elevated while depressed lesions show an increased risk of submucosal invasion (SMI). Chromoendoscopy or, if possible, narrow-band imaging technique should be considered for the estimation of SMI risk of NPTs, and the characterization of pit and vascular pattern may be useful to predict the risk of SMI. Endoscopic mucosal resection remains the first-line therapy for NPTs, whereas endoscopic submucosal dissection or surgery should be considered for larger neoplasms presenting SMI.

INTRODUCTION

Colorectal cancer is a major health problem representing the second most commonly diagnosed cancer in women and the third in men[1]. Nowadays, colonoscopy is the most used tool for the early detection of colorectal cancer and the resection of pre-neoplastic lesions in order to prevent advanced and late stage neoplasms. In fact, it's well known that more than 95% of colorectal cancers arise from adenomas (tumors of benign neoplastic epithelium with variable potential for malignancy) and the aim of colonoscopy surveillance is to timely interrupt the "adenoma-carcinoma sequence"[2-5].

In the last years, an increasing interest has been raised on non-polypoid colorectal tumor (NPT) and in particular on laterally spreading tumor (LST). LST is a large flat neoplastic lesion tending to grow laterally along the surface of the bowel[6,7]. By definition, LSTs show a diameter beyond 10 mm[8-10]. LSTs and large sessile polyps have a greater frequency of high-grade dysplasia (HGD) and local invasiveness as compared to pedunculated lesions of the same size and usually

Table 1 Paris classification of superficial colorectal lesions

Polypoid type[1]	Pedunculated (0-1p)
	Sessile (0-1s)
	Mixed (0-1sp)
Non-polypoid type	Slightly elevated (0-IIa)
	Flat (0-IIb)
	Slightly depressed (0-IIc)
Mixed types	Elevated and depressed (0-IIa + IIc)
	Depressed and elevated (0-IIc + IIa)
	Sessile and depressed (0-1s + IIc)

[1]Elevated more than 2.5 mm above the mucosal layer.

represent a technical challenge for the endoscopist either in terms of diagnosis and of resection. That is why the term "advanced mucosal neoplasia" (AMN) has been recently proposed for these two classes of lesions[11].

MORPHOLOGY AND CLASSIFICATION

The morphology of colonic lesions depends on the direction of proliferation growth.

Following this, two main macroscopic types may be recognized: superficial lesions (type 0) and advanced cancers (type 1-5)[12].

According to the Paris classification (Table 1), lesions with superficial appearance (category 0) are distinguished in: polypoid type [elevated more than 2.5 mm above the mucosal layer: pedunculated (0-1p), sessile (0-1s) or mixed (0-1sp)], non-polypoid [slightly elevated less than 2.5 mm (0-IIa), flat (0-IIb) or slightly depressed (0-IIc)] and mixed types.

The threshold of 2.5 mm, which corresponds to the height of a closed biopsy forcep, is quite arbitrary and not really reliable because many flat lesions are not homogeneous in their whole surface.

Non-polypoid lesions are usually flat or slightly elevated and tend to spread laterally while in case of depressed lesions, cell proliferation growth progresses in depth in the colonic wall, thus leading to an increased risk of submucosal invasion (SMI) even for smaller lesions. In the colon and rectum, slightly elevated and flat NPTs are commonly classified together since they are not so easily distinguishable and because true flat masses (0-IIb) are rarely found in this intestinal tract. Among non-polypoid tumors, type 0-IIa (slightly elevated) is by far the most frequent[12].

NPTs (flat or depressed) may be found throughout the colon unlike polypoid cancers which are more frequent in the left part[13,14].

The distinction among the different subtypes is not always easy to capture, hence the local endoscopist and pathologist expertise plays a pivotal role in the diagnostic algorithm[15,16].

As aforementioned, flat colorectal neoplasms equal to or larger than 10 mm are called LSTs.
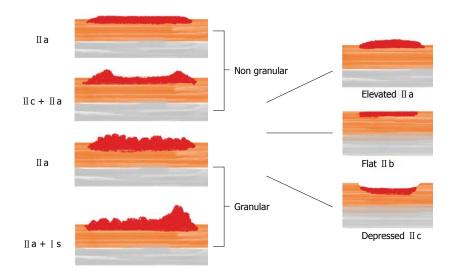
Figure 1 Subtypes of non polyploid tumors according to Paris classification (see the text for the details). Flat non polyploid tumors (NPTs) ≥ 1 cm are called laterally spreading tumors (LSTs). The morphological subclassification of LSTs is represented on the left.

Table 2 Categories of pit pattern at the surface of the colonic mucosa

Non neoplastic	I : Normal mucosa
	II : Enlarged regular stellar crypts
Neoplastic, adenomatous	IIIL: Elongated, sinuous crests
	IIIS: Narrowed round and irregular pits
	IV: Branched or gyrus-like crests
Neoplastic, cancer	Vi: Irregular surface
	VN: Amorphous surface

The categories are classified in reference to prediction of histology and treatment decision.

LSTs are divided into the granular (LST-G) and non-granular type (LST-NG) based on their detailed endoscopic appearance during chromoendoscopy with indigo carmine dye spraying[13,17]. The LST-G type is composed of conglomerates of nodules forming a flat broad-based mass (thus the term "granular") while this characteristic is lacking in the latter group (LST-NG)[13,18].

NPTs have a higher risk of local invasiveness than polyploid tumors, regardless the size[13,14]. While the larger is the polyploid lesion the higher is the risk of SMI, not all the NPTs show a so strict correlation between size and local invasiveness.

LST-Gs with homogeneous surface have a low risk (< 2%) of SMI no matter their size is, whereas LST-Gs with mixed-size nodules have a higher risk of SMI (7.1% for lesions < 20 mm and 38% for those > 30 mm)[19]. Even higher is the risk of SMI for LST-NGs, particularly in those presenting a thinner center (LST-NGs with pseudo-depression): 12.5% in case of size < 20 mm and 83.3% for diameters > 30 mm[13].

Depressed lesions are rare (1%-6% of all NPTs) but present the highest overall risk of SMI: 27%-35.9%[13]. Figure 1 graphically describes the three main types of NPTs and the subclassification of LSTs.

ENDOSCOPIC DIAGNOSIS

The detection of a superficial lesion in asymptomatic patients undergoing complete colonoscopy is a frequent event ranging from 10% to 60%[12,20-22].

In a Japanese series, the rate of NPTs was 42% (10.948 out of 25.862 superficial neoplastic lesions identified)[23]. The proportion was lower, although still significant, in another Japanese series (27%: 2711/12811)[24]. In the United States and Western countries, the proportion of NPTs is highly variable ranging from 9.35% to 31.4%[25,26].

NPTs may be frequently missed by inexperienced endoscopists, thus a careful training and precise assessment of all suspected mucosal areas should be performed.

Chromoendoscopy or, if possible, narrow-band imaging (NBI) technique should be considered for the estimation of SMI risk of NPTs. NBI, by using light filters to narrow the bandwidth of the endoscope's light aimed at selective evaluation of the area of interest, is able to recognize and better define the vascular and pit-pattern, both indicators of malignancy[27,28]. For instance, irregular and sparse vascularization and loss of epithelial crests are related to evolved lesions[29].

The microarchitecture of pits, epithelial crests, or ridges (so called "pit pattern") has been extensively described by Kudo *et al*[29]: three main categories of pit patterns are described: (1) nonneoplastic (I and II); (2) neoplastic adenomatous (III and IV); or (3) neoplastic cancer (V)[29,30] (Table 2). Type IV is the most common among AMNs and is usually related to large NPT-Gs and implies tubule-villous histology.

With regard to vascularization, irregular multi-branched microvessels alternated to avascular areas are predictor of higher risk of SMI[31]. A more detailed description of vascular patterns detectable at the surface of colonic mucosa is summarized in Table 3.

Table 3 Categories of vascular pattern at the surface of colonic mucosa	
Non neoplastic	Normal: Well-delineated capillaries surrounding pits opening
	Faint: Poor visibility of capillaries around enlarged pits
Neoplastic, adenomatous	Network: Vessels organized in a large and regular mesh
	Dense: Enlarged vessels of regular size at top of elongated crests
Neoplastic, cancer	Irregular: Enlarged vessels of irregular diameter and diverging directions
	Sparse: Poor distribution of irregular vessels with diverging directions

The categories are classified in reference to prediction of histology and treatment decision.

Even if no single feature is absolutely specific for SMI, the presence of more than 1 high-risk characteristic correlates to more invasive lesions[32].

LST-Gs account for 60%-80% of the cases *vs* 20%-40% of LST-NGs, whereas depressed NPTs (those at higher risk of SMI) represent 1% to 6% of the total number of superficial colorectal lesions[7,14,33,34]. Most studies reported the majority of NPTs in the proximal colon (55.7%-80%)[33,34], which differs from two Chinese series wherein 65%-75% of non polypoid lesions were located in the distal colon[7,35].

IMPORTANCE OF NPTS DETECTION IN PATIENTS WITH INFLAMMATORY BOWEL DISEASES

It's well known that patients with long-lasting inflammatory bowel disease (IBD) colitis have a higher risk of developing colorectal cancer than the general population[36-39].

Even if the vast majority of colitic dysplasia is endoscopically visible, colonoscopic surveillance remains challenging as the dysplasia can have a varied endoscopic appearance ranging from lesions appearing identical to sporadic adenomas to plaques, nodular mucosa, puckering of the mucosa, villiform mucosa, strictures, and broad-based masses with indistinct lateral margins. Dysplastic areas detected within inflamed or previously inflamed mucosa show a more aggressive behavior and tend to progress more rapidly than sporadic adenomas in non-inflamed mucosa[40-42]. Thus, all lesions suspected to be dysplastic should be removed promptly.

Random sampling is ineffective in detecting dysplastic areas, especially in the case of NPTs. Chromoendoscopy with targeted biopsy significantly improves surveillance efficacy (the increase was about 7% in a recent meta-analysis)[43], while NBI failed to show a clear superiority over high-definition white light colonoscopy in the detection of dysplasia in IBD patients[44-48].

Raised dysplastic lesions within an area of current or previous inflammation have been termed dysplasia-associated lesions/masses (DALMs). Until recently these have been considered an indication for colectomy because of their reported higher risk of cancer[49].

DALMs appear as well-circumscribed, sessile or pedunculated polyps and should be promptly and radically treated by means of endoscopic resection (contextually biopsies should be taken from the normal-looking mucosa surrounding the polypectomy margins in order to detect further areas of dysplasia). If a timely and appropriate endoscopic therapy is performed, the overall rate of progression to cancer of adenoma-like DALMs is very low (only 2.4% in a recent review)[50].

If the radical resection of the lesion is not feasible, or if dysplastic foci in the adjacent mucosa are detected, then colectomy is mandatory[51,52].

Although the polypoid aspect is predominant, however, as well as in the general population, some lesions are minimally elevated (less than 2.5 mm in height), completely flat or even depressed in morphology.

Non-polypoid lesions can be more difficult to detect and distinguish from the surrounding inflamed mucosa and a particularly careful endoscopic assessment is required.

Once a NPT is detected, the therapeutic approach is the same as that previously described for DALMs but *en bloc* resection is mandatory (when infeasible, surgery remains the sole option)[53-58].

ENDOSCOPIC THERAPY

According to the aforementioned characteristics (superficial aspect, pit and vascular pattern) and the predicted risk of SMI, the proper therapeutic indication should be considered.

Lesions suitable to endoscopic resection are those confined to the mucosa (or superficial layer of submucosa in selected cases) whereas deeper invasion makes endoscopic therapy infeasible[59].

In the last years, a number of resection techniques for the management of AMNs have been described; among them, inject-and-cut endoscopic mucosal resection (EMR) is the most common[59,60]. More recently, endoscopic submucosal dissection (ESD) has been developed to improve the "*en bloc*" resection rate of AMNs.

Saline is the most commonly used injection solution worldwide[59]. Submucosal epinephrine-saline solution injection has been shown to be an effective method for the complete endoscopic polypectomy, especially in flat or sessile lesions and is widely used because of

its simplicity, low cost, and wide availability[61]. On the other hand, a number of studies have raised concerns about its efficacy in preventing post-procedural haemorrhage due to the short-lasting period of mucosal elevation following epinephrine injection[62].

Consequently, other substances (such as sodium hyaluronate, hydroxypropyl methylcellulose and glycerol), have been tested because of their ability to create a longer lasting submucosal cushion as a result of their viscous properties. In doing so, such substances enable lengthier procedures and increase the rate of *en bloc* resection, even for large lesions; however, despite the promising results of the aforementioned reports, their efficacy in preventing post-polypectomy bleeding (PPB) is still matter of debate[63,64].

An ideal submucosal injection solution should be inexpensive, readily available, non-toxic, easy to prepare and inject and should provide a long-lasting submucosal cushion.

Succinylated gelatin seems to fulfil these criteria but a recent randomized control trial, while showing a significant improvement of efficacy outcomes, failed to find a decreased PPB and perforation rate after gelatin submucosal injection as compared to saline[65]. Our group has recently published a retrospective propensity-score comparison of 306 patients treated with submucosal epinephrine injection and 306 with polidocanol injection for the endoscopic resection of LSTs or sessile lesions ≥ 20 mm, reporting a significantly lower PPB rate in the polidocanol group[66]. However, further confirms provided by randomized trials are warranted to identify the ideal injection solution.

The inject-and-cut EMR consists in simple pre-defined steps: at first, the solution is injected into the submucosa at one edge of the lesion with a disposable injection needle to create a submucosal cushion for safety purposes and better resection. While the assistant injects the solution, the endoscopist tangentially stabs the colonic wall. After the submucosal injection, a disposable electrosurgical snare is placed over the elevated tissue and gently pressed against the mucosa, while closing until resistance was felt. The lesion is then cut using an electrosurgical unit providing blended current[9,67-70].

Lesions larger than 20 mm are not usually amenable of *en bloc* resection, thus piecemeal resection is required[15]. In case of suspected residual tissue after resection, application of argon plasma coagulation (APC) may burn residual areas thus decreasing the risk of recurrence[71].

There is no unequivocal consensus on the pro-phylactic application of clips on the resection site after removal of AMNs: in fact, the promising efficacy in preventing PPB of this technique reported in a recent retrospective study still needs confirmation[72].

Recent refinement of ESD instruments and skills has lead to its application in the treatment of large colorectal lesions as an alternative to EMR. While in other fields of gastrointestinal endoscopy ESD has been proven superior to EMR[73], the indications for colorectal ESD, however, are relatively few even at experienced centers because most colorectal neoplasms are benign and can be resected using piecemeal EMR with minimal risk of recurrence[74].

During ESD, after submucosal injection, a marginal resection is performed to isolate the lesion with 3 or 4 mm surrounding normal mucosa. The submucosa under the lesion is injected further and then the ESD knife dissects through the submucosal layer to resect the lesion *en bloc*[74-80].

In conclusion, EMR (piecemeal for LSTs > 20 mm, *en bloc* for smaller neoplasms) remains the first-line therapy for NPTs. ESD in high-volume Centers or surgery should be considered for large LSTs for which *en bloc* resection is mandatory and cannot be achieved by means of EMR: namely, LST-G whole nodular type, LST-NG pseudo-depressed or other types with type V pit pattern areas which cannot be resected *en bloc* with a snare[81,82].

If the pathologic analysis of the specimen reveals the presence of adenocarcinoma and the lesion is limited to the mucosa (so called "carcinoma *in situ*"), there is no indication to surgery provided that the endoscopic resection has been radical. In contrast, adenocarcinomas with invasion into the submucosa show a 6% to 12% risk of lymph node metastasis[83,84], hence in Western countries they are commonly referred to surgery. As further studies have shown that well-differentiated adenocarcinomas with submucosal invasion within 10 mm without lymphatic or vascular involvement have small, if not nil, risk of lymph node metastasis[85], in Japan, NPTs with these features are treated by means of endoscopic resection.

Bleeding, abdominal pain and perforation are the most frequent and serious complications, in particular after endoscopic removal of AMNs[82]. All these adverse events are more frequently reported after ESD, hence this technique should be considered only in highly-experienced Centers.

FOLLOW-UP

Follow-up recommendations for NPTs are exactly the same as those proposed with regard to polypoid lesions[86-89].

After piecemeal EMR, follow-up colonoscopy should be performed at 3 mo to assess resection completeness and remove any residual or recurrent lesion[89]. If a residual or recurrent lesion is recognized, it should be treated accordingly. Once complete removal has been established, subsequent surveillance needs to be individualized based on the endoscopist's judgment[89,90].

In case of *en bloc* resection, surveillance colonoscopy should be scheduled at 3 years for adenomatous lesions ≥ 1 cm, or in presence of villous features or high-grade

dysplasia patients (regardless of the size)[90].

Usually, less intensive surveillance (colonoscopy at 5-10 years) is needed in case of single (or two) NPT < 1 cm presenting tubular features or low-grade dysplasia at histology[90].

However, in the real life, under certain circumstances (such as dubious radicality, need to treat margins with argon after resection, excised margin defined as not assessable by the pathologist), follow-up may be even stricter[90].

CONCLUSION

NPTs are commonly found during screening colonoscopy and usually represent a diagnostic and therapeutic challenge for the endoscopist, which should provide a careful characterization and classification of all diagnosed NPTs[50,91-94]. Chromoendoscopy and NBI are useful tools for the detection of non-polypoid lesions and should be routinely applied in the clinical practice. Pit pattern and vascular pattern features may accurately predict and assess the risk of SMI[95-99]. EMR represents the first line therapy in case of lesions confined into the mucosa, whereas patients with superficial SMI should be offered ESD (in highly-experienced Centers) or surgery.

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