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## **Practice parameters for early colon cancer management: Italian Society of Colorectal Surgery (Società Italiana di Chirurgia Colo-Rettale; SICCR) guidelines**

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### **Abstract**

Early colon cancer (ECC) has been defined as a carcinoma with invasion limited to the submucosa regardless of lymph node status and according to the Royal College of Pathologists as TNM stage T1 NX M0. As the potential risk of lymph node metastasis ranges from 6 to 17 % and the preoperative assessment of lymph node metastasis is not reliable, the management of ECC is still controversial, varying from endoscopic to radical resection. A meeting on recent advances on the management of colorectal polyps endorsed by the Italian Society of Colorectal Surgery (SICCR) took place in April 2014, in Genoa (Italy). Based on this material the SICCR decided to issue guidelines updating the evidence and to write a position statement paper in order to define the diagnostic and therapeutic strategy for ECC treatment in context of the Italian healthcare system.

### **Keywords**

Early colon cancer Endoscopic resection Tattooing Submucosal invasion Lymphovascular invasion Lymph node harvesting

Early colon cancer (ECC) has been defined as a carcinoma with invasion limited to the submucosa regardless of lymph node status and according to the Royal College of Pathologists as TNM stage T1 NX M0 [1]. As the potential risk of lymph nodes metastasis ranges from 6 to 17 % [2] and the preoperative assessment of lymph nodes metastasis is not reliable, the management of this pathology is still controversial varying from endoscopic to radical resection [2–4].

The introduction and progressive development of colorectal cancer screening programs and the improved endoscopic techniques have led to an early detection of colonic lesions and have increased the number of patients who can undergo definitive and radical endoscopic treatment [5].

Nevertheless, the advantage of less invasive endoscopic procedures is counterbalanced by the well-described risk of lymph node metastasis. It is therefore of great importance that some factors have been associated both with lymph node metastasis and recurrent colonic disease, poor differentiation, tumour budding, depth of submucosal invasion, lymphovascular invasion, technique of endoscopic removal and, finally, the significance of lymph node clearance that is strictly related to surgical lymph node harvesting. The evaluation of these factors should lead to targeted surgery for lesions associated with a high risk of local recurrence or lymph node metastases.

Between 2012 and 2013 the European Society for Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN) and the Japanese Society for Cancer of the Colon and Rectum (JSCCR) produced clinical practice guidelines on early colon cancer and the Association of Coloproctology of Great Britain and Ireland (ACPGBI) edited a position paper on the management of the malignant colorectal polyp [6–9]. A meeting on recent advances on the management of colorectal polyps endorsed by the Italian Society of Colorectal Surgery (SICCR) took place in April 2014, in Genoa (Italy) [10, 11]. Based on this material the SICCR decided to issue guidelines updating evidences and to write a position statement paper in order to define the diagnostic and therapeutic strategy for ECC treatment in the context of the Italian healthcare system. A number of Italian experts in the field were selected and interacted telematically with a Delphi method [12]. A literature search was conducted by searching PubMed, Embase and The Cochrane Library databases, for each single topic, with the aid of the patient, intervention, comparator/control, outcome (PICO) search strategy [13]. The evidence of the outcomes has been organized according to the latest Oxford classification [14].

## **Endoscopic resection**

*Endoscopic resection is a safe and effective alternative to surgery for the removal of superficial neoplastic lesions confined to the mucosa or invading less than 1 mm in the submucosal layer (m/sm1). These lesions have a negligible risk of lymph node metastases and are therefore amenable to curative local endoscopic treatment [EL:II; GoR:A].*

Colonoscopic removal of precancerous lesions reduces dramatically both the incidence of and mortality from colorectal cancer (CRC) [15, 16]. Curative endoscopic resection (ER) is indicated for neoplastic lesions confined to the mucosal layer or invading less than 1 mm into the submucosal layer (m/sm1), without vascular or lymphatic spread (V-/L-), well differentiated or moderately well differentiated, without ulceration and with low budding grade [8, 17, 18]. Non-polypoid lesions account for about one-fourth of precancerous lesions [19–21]. Lesions with a depressed component, non-granular type laterally spreading tumours and granular type laterally spreading tumours with large nodules are associated with a higher rate of submucosally invasive carcinoma [22].

*Thorough assessment by means of high-definition endoscopy coupled with magnification chromoendoscopy is useful to predict the depth of cancer invasion in high-risk non-polypoid lesions [EL:I; GoR:B].*

*The macroscopic appearance of the lesion with evident ulceration of the surface, a failed lifting of the lesion or the presence of a mucosal or vascular invasive pattern on magnified inspection are specific markers of invasive neoplasia and should prompt the endoscopist to desist from any attempt at endoscopic treatment [EL:II; GoR:B].*

The most important pre-procedural step is estimating the depth of invasion of a lesion and by proxy the risk of lymph node metastases. Meticulous evaluation of the morphology of the lesion using the Paris classification [23], mucosal pattern using the Kudo classification [24] and vascular pattern using the National Institute for Health and Care Excellence (NICE) classification [25] dictates indications and treatment choice for larger colorectal lesions.

At magnifying chromoendoscopy, classification of pit patterns has been strictly associated with the risk of submucosal (or deeper) cancer. Pattern V appears to predict a substantially higher risk of invasive cancer (20–30 % for V irregular and >90 % for V non-structured) as compared with

patterns II–IV [26–31]. An irregular/sparse or severely irregular vascular pattern has been shown to be highly predictive of massive submucosal invasion with a sensitivity and specificity of 95 and 81 %, respectively [32, 33]. The predictive capability of magnifying chromoendoscopy is clinically relevant only when applied to lesions with a potential for invasion, such as non-polypoid lesions with a depressed component (0–IIc) [15, 19, 21] or non-granular or nodule-mixed laterally spreading tumours [20, 21, 34].

Other macroscopic predictors of deep invasion at colonoscopy are fold convergence, expansive appearance, an irregular surface contour, a demarcated depressed area, a >1 cm nodule or the non-lifting sign, i.e. inability to raise the lesion after submucosal injection [35–37]. A positive non-lifting sign could in theory be an indication for endoscopic submucosal dissection (ESD), especially when it is related to fibrosis from a previous biopsy or previous attempts at ER [38].

*A primary strategy of colonoscopy and endoscopic mucosal resection (EMR) performed by an experienced endoscopist should be considered a first-line therapy for removal of large, non-invasive, sessile or laterally spreading colon adenomas, with some advantages over alternatives including surgery or ESD that are more resource intensive and carry greater risks of morbidity and mortality [EL:II; GoR:B].*

*Following piecemeal EMR of large sessile or flat colorectal lesions the first surveillance colonoscopy should be done at 2–6 months [EL:II; GoR:B].*

The aim of any endoscopic resection is to achieve an oncologically radical excision with both lateral and vertical margins free of neoplasia (R0). Larger sessile or non-polypoid lesions can be challenging to remove endoscopically and may require more advanced techniques, such as EMR and ESD [17, 18]. The size of the lesion is considered the guiding criterion in selecting en bloc EMR versus piecemeal EMR versus ESD. EMR is effective in removing en bloc lesions of up to 20–25 mm, and, in piecemeal fashion, larger lesions, avoiding surgery in over 90 % of patients [34, 39–48]. Piecemeal EMR is burdened with higher local adenoma recurrence rates (6–23 %) [49, 50]. Independent risk factors for early recurrence after piecemeal EMR are lesion size >40 mm, the use of argon plasma coagulation during the original resection and the occurrence of intraprocedural bleeding [51]. To overcome this problem, ESD using electrosurgical dissecting knives was developed to allow en bloc resection, irrespective of the lesion's size. ESD is recognized for its effectiveness in large, complete, en bloc resections and lesions with precise pathological assessments [52–56]. A number of meta-analyses of retrospective or non-randomized studies consistently show that ESD achieves higher rates of en bloc resection (>90 %) and curative R0 resection (>85%), as well as a lower rate of local recurrence (<3 %) compared to EMR. Nonetheless, ESD is much more time consuming than EMR, there is a twofold higher rate of additional surgery and the rate of procedure-related complications is higher with a fivefold increased risk of perforation [57–61], suggesting that the indications for ESD should be rigorously determined.

Lesions greater than 20–25 mm with central depression or non-granular LST or granular LST >40 mm may in principle be treated with en bloc ESD. Also, residual/recurrent adenoma after incomplete resection or in the presence of post-biopsy fibrosis or scar tissue may necessitate ESD [62, 63]. In the colon ESD is more technically challenging because of less space, difficult positioning, thinner bowel wall, and the presence of colonic folds. Recent data from large prospective studies show that not only can piecemeal EMR achieve low rates of recurrence, but also that recurrence is not really a significant clinical problem [51, 64]. In fact, the residual or recurrent tissue is usually unifocal, diminutive and easily treated endoscopically. If the initial EMR is successful and there is no submucosally invasive cancer in the resected specimens, over 98 % of the patients will be adenoma free and have avoided surgery on follow-up [51, 65]. Piecemeal EMR does not preclude surgery, which is always possible in the very few cases where recurrence is not manageable endoscopically.

The optimal timing of surveillance colonoscopy following piecemeal EMR of large sessile lesions is at 2 and 6 months [18, 66]. This time interval is sufficient for recurrent or residual adenoma to become apparent, and in most cases, it is usually still small and thus easily treatable.

## **Tattooing**

*Endoscopic tattooing is recommended to mark a lesion or a polypectomy site for future surgical identification. This relatively inexpensive and potentially simple addition to colonoscopy should become routine practice, particularly in the era of laparoscopic colon cancer resection [EL:III; GoR:A].*

Endoscopic tattooing is an effective means to enable subsequent endoscopic and surgical localization of luminal colonic lesions [67]. A retrospective review of 341 consecutive patients undergoing elective surgical resection for CRC showed that the repeat preoperative endoscopy rate was 40.5 %. The most common reasons for re-endoscopy included tattooing of the lesion (45.5 %), surgical planning (35.5 %), and repeated therapeutic attempts (9 %). Independent predictors of re-endoscopy included planned laparoscopic procedures ( $p = 0.011$ ), and the absence of a tattoo on the first colonoscopy ( $p = 0.010$ ) [68]. A variety of substances have been tried for endoscopic tattooing, including India ink, methylene blue, indigo carmine, and indocyanine green. The advent of a prepackaged sterile carbon particle suspension (SPOT, GI Supply, Camp Hill, PA, USA) has greatly enhanced the accessibility and ease of use of endoscopic tattooing [67]. The tattoo must be placed at a distance from the lesion, unless it is certain that the patient will have surgery and EMR and ESD are not therapeutic options. Tattooing is recommended only downstream from the lesion in all cases, with one injection placed in line with the lesion, and one or two additional injections performed, one of which should be on the opposite side of the lumen [67]. Carbon particles are not biologically inert and have been associated with rare cases of peritonitis resulting from transmural injection. Much of this risk can be mitigated by the use of the saline solution bleb test injection method (pre-injection of normal saline solution to find the submucosal plane) [69, 70]. Recent evidence supports the hypothesis that tattooing may enhance staging accuracy by increasing the lymph node yield per surgical specimen, which is an important quality marker with survival implications [71].

## **Resection margin**

*The presence of a deep resection margin  $<1$  mm after endoscopic polypectomy of the colon is associated with a high risk of residual tumour and recurrence or lymph node metastases and should lead to radical surgery. When the resection margin is  $<1$  mm from cancer cells, the patient should undergo radical colonic resection provided that the patient is fit for surgery. A resection margin  $<1$  mm from a dysplastic area an intense endoscopic follow-up should be recommended [EL:II; GoR:B].*

Many authors have reported that the risk of residual tumour, recurrences or lymph node metastases in patients who underwent endoscopic polypectomy with a resection margin  $>1$  mm in absence of any other adverse factor is  $<2$  % [72–74] and that a resection margin  $>2$  mm leads to a very low possibility of residual disease [75–79]. Most studies considered a margin  $<1$  mm as similar to an involvement of the actual margin both in terms of recurrences and residual disease or lymph node metastases, with a recurrence rate ranging between 21 and 33 % [75, 80]. Similar recommendations regarding quality assurance in colorectal cancer pathology were reported by the consensus of expert opinion produced by the International Agency for Research on Cancer [81]. The involvement of lateral margins in residual disease should elicit further endoscopic treatment if the resection falls on a dysplastic area, while it is an indication for immediate surgery even in case of a clear deep margin if the resection falls on a neoplastic area [76, 78, 80, 81].

## **Submucosal invasion**

*Measurement of depth of submucosal invasion, according to the Haggitt or Paris classification, is highly predictive of the risk of lymph node metastases, whereas there are no other adverse factors, the risk of lymph node metastases is low for pedunculated polyps with malignancy confined to the head or the upper part of the stalk (Haggitt 1, 2, 3) and for sessile or flat lesions with submucosal invasion <1 mm (Paris sm1). [EL:II; GoR:B].*

The recent interest in the classification of submucosal invasion in clinical practice is due to the consideration of the superficial depth of tumour invasion as a surrogate for nominal lymph node metastasis risk and as a general criterion for identifying patients eligible for local endoscopic resection.

According to many authors, after endoscopic resection, the rate of lymph node metastasis in malignant pedunculated polyps with Haggitt level of invasion 1, 2, 3 was <1 % [82–85], whereas the rate of node invasion was 6.2 % in patients with polyp stalk invasion [85]. Similarly, with regard to malignant sessile polyps, the reported risk of lymph nodes metastasis ranges from 1 % in sm1 to up to 15 % in sm3 lesions (according to the Paris classification) [23]. Therefore, it is generally accepted in clinical practice that patients with malignant cells below the base of stalk of pedunculated polyps (Haggitt level 4) and patients with sessile polyps and an sm2 or sm3 level of submucosa invasion, even in absence of other adverse factors, should undergo colon resection [9]. Likewise, in the review and meta-analysis by Beaton, nodal involvement for a cancer with a submucosal depth of invasion between 1 and 2 mm ranged from 1.3 to 4 %, whereas lymph node metastasis occurs in 12–18 % of patients with submucosal invasion depth of >2 mm [86]. The 2010 guidelines of the Japanese Society for Cancer of the Colon and Rectum provided a literature review in addition and expert consensus opinion leading to similar results [8]. Numerous studies combined the risk of lymph node metastasis of pedunculated and non-pedunculated lesions, which is not supported by classification systems, so that results from many studies are difficult to analyse and interpret. Mou in a meta-analysis on the risk of lymph node metastases in non-pedunculated (sessile and non-polypoid) T1 cancers reported that even for patients with a submucosal invasion depth <1 mm the risk of lymph nodal metastases was not zero (rate 1.9 %), whereas for patients with an invasion depth >1 mm the rate was 14.6 % [87]. Searching the literature produced two meta-analyses on this issue [86, 87] and few studies including more than 200 patients, with a number of low-quality studies reporting on less than 100 patients. Moreover, very few studies reported the average number of lymph nodes collected, a bias for the studies.

## **Lymphovascular invasion**

*Lymphovascular invasion is related to an increased risk of lymph node metastasis. When lymphovascular invasion is detected, surgery should be recommended [EL:II; GoR:B].*

There are difficulties in assessing lymphovascular invasion in colorectal malignant polyps, due both to technical problem and not agreed protocols, as a consequence inter-observer variation is high [9], thus being a bias in the related analyses. Moreover, some authors have demonstrated that lymphatic vessels are more represented in the superficial submucosal layer (sm1) rather than in the deepest (sm3) [88, 89].

Kitajima, first, demonstrated with a multivariate analysis that lymphatic invasion is an independent risk factor for lymph node metastasis [72]. Accordingly, in many studies lymphovascular invasion was found to be significantly associated to the risk on lymph nodal metastases [2, 84, 85, 90–93]. Beaton in his meta-analysis confirmed this finding in four papers including more than 200 patients; moreover, this association was proven even by analysing independently both lymphatic invasion and vascular invasion [2, 4, 72, 86, 93–101].

## **Histological differentiation**

*Poor differentiation is a less common feature, frequently associated with other adverse factors and related to a high risk of lymph nodes metastases. When a malignant polyp is found to be with a poor differentiation grading, patient should be considered for colic resection, provided that the patient is fit for surgery [EL:II; GoR:B].*

Poor differentiation is found in a small proportion of colorectal malignant polyp, with a rate ranging between 4 and 7.2 % [47, 102, 103], and being frequently associated with other adverse factors [9, 86]. It is generally accepted that poor differentiation is related to high risk of residual disease and lymph node metastasis [9, 47, 75, 86, 104–106]. In a meta-analysis of 13 studies, polyps with poor differentiation were associated with a higher risk of lymph node metastasis than well differentiated or moderately differentiated, whereas well differentiated ones were associated with a low risk as compared with the other two grades [2, 4, 72, 85, 90–92, 94–101, 107–110]. Similar results were confirmed by a subset analysis of papers reporting more than 200 cases [2, 72, 85, 107].

### **Tumour budding**

*Tumour budding is related to an increased risk of lymph nodes metastasis, although it is difficult to assess the actual impact as single adverse factor. When tumour budding is detected as a single adverse feature, surgery should be recommended [EL:II; GoR:B].*

The impact of tumour budding in T1 colon cancer was evaluated in 11 studies that demonstrated the association with lymph node metastasis [11, 72, 90, 93, 97, 98, 101, 109–114]. However, since the tumour budding frequently occurs in association with other adverse features and since the number of cases reported in the analyses was small, it is difficult to detect the actual impact as a single adverse factor in colon cancer.

### **Lymph node harvesting**

*The number of nodes removed is an independent factor for better staging, with a strong correlation with survival. When a colon resection is performed, the number of lymph nodes collected should be  $\geq 12$ . [EL:II; GoR:B].*

In recent population studies conducted in the USA and Europe, it has been reported that the “magic” number of 12 lymph nodes examined is rarely achieved in district or community hospitals which fail to hit the target in 33–60 % of the cases [115–118]. The national report card concluded that only the Comprehensive Cancer Centers were compliant with 92 % of patients with more than 12 lymph nodes retrieved, thus stressing the importance of a multidisciplinary team (MDT) approach and of developing of pooled experience [119]. The number of nodes examined has frequently been reported as an independent positive prognostic factor with a strong correlation with survival [120–122]. Hoenberger considered the lymph node harvest as a surrogate marker of surgical quality reporting a significant difference in survival between node-positive and node-negative patients with a cut-off point of 29 lymph nodes examined [123]. Similar results were reported by Choi with a significant difference in survival when a minimum of 21 nodes were examined; above this number there was no differences [124]. Although there is no consensus on what should be the cut-off point, it makes sense to conclude that the more lymph nodes are retrieved and examined the better will be the quality of care [125]. Finally, the lymph node ratio has been reported to be an independent prognostic factor with a better correlation to the outcome than node positivity has, but, due to the lack of randomized trials it cannot be considered a standard quality assurance indicator [125, 126].

An analysis from a large database in the USA demonstrated a median harvest of one node in patients who underwent colon resection for malignant polyps [127]. Gill, in the analysis of data of the Northern Colorectal Cancer Audit Group in UK on management of malignant colorectal polyp reported that the median lymph node yield was 9.0, reflecting current practice over a range of experience and hospital size from district general hospitals to tertiary referral centres [74].



Benhaim reported that the total number of lymph nodes examined after salvage colectomy for endoscopically removed malignant polyps varies and, in most cases, is less than the recommended 12 [128]. Particularly, a lower number of lymph nodes were collected in the polypectomy patients as compared to those who underwent colon resection for more invasive cancer (mean: 11.6 vs. mean: 26.3, respectively). Gelos explained this phenomenon with the reduced inflammatory reaction in ECC that could account for the more difficult observation of micro-metastatic-lymph nodes by the pathologist [118, 129]. Although many studies deal with this issue, few papers on colorectal malignant polyps have an adequate median volume of collected lymph nodes to analyse, by stratification of results, the actual impact of lymph node recruitment on early colon cancer staging and define the actual cut-off value.

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