Chapter 5

Malignant Colorectal Polyps: Diagnosis, Treatment and Prognosis

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1. Introduction

Adenomatous polyps are non-invasive tumours of epithelial cells arising from the mucosa with the potential to become malignant. The adenoma-carcinoma sequence is well known and it is accepted that more than 95% of colon adenocarcinomas arise from adenoma [1]. The World Health Organisation (WHO) classifies adenomas into tubular (<20% villous architecture), tubulovillous and villous (80% villous architecture), with approximately 87% of adenomas being tubular, 8% tubulovillous and 5% villous [2].

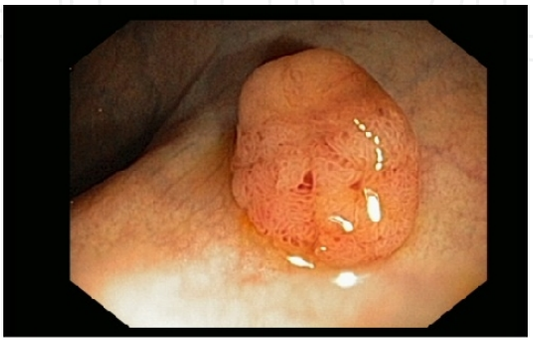

Figure 1. Polyp in colon

Only 5% of adenomas are in danger of becoming malignant. The probability of high grade dysplasia and carcinomatous transformation increases with polyp size, a villous component, when there are many polyps or the age at diagnosis is more than 60 years [2]. The neoplasia is considered to be advanced when polyp size is 1 cm or more, there is a villous component or a high degree of dysplasia. Mixed polyps also have the ability to become malignant, as does hyperplastic polyposis syndrome. More than 25% of advanced polyps are located in the area proximal to the splenic flexure [3].

2. Epidemiology

The prevalence of cancerous polyps in series of endoscopically removed polyps is between 0.2% and 11% [4-6].Currently, screening programs allow the detection and treatment of a great number of adenomas and malignant polyps, and this contributes to a reduction of the mortality by colorectal cancer (CRC) [1,7]. In an asymptomatic population of people over 50 years old who underwent direct colonoscopy, there was a 0.8% prevalence of adenocarcinoma of which 50% were carcinoma “in situ” or in stage I [8,9]. During screening programmes, adenocarcinomas have been detected in between 3% - 4.6% of those who undergo colonoscopy following a positive immunological faecal occult blood test result [10,11].

3. Histology

Carcinoma "in situ", intramucosal carcinoma, high displasia or intraepithelial carcinoma is the stage at which there is no involvement of *the muscularis mucosa.* In general, this tumour stage does not cause metastasis. It is classified as pTis or Stage 0 in the TNM staging system.These terms are defined as non-invasive high grade neoplasia in the Vienna classification [12].Carcinoma in situ or severe displasia or intraepithelial carcinoma corresponds to a carcinoma that is restricted to the epithelial layer without invasion into the lamina propria. Intramucosal carcinoma is a carcinoma characterized by the invasion into the lamina propria.

When the carcinoma spreads to the submucosa, the polyp is considered to have become malignant, being able to spread to lymph nodes or distant sites. The tumours that affect the submucosa are classified as T1 and correspond to Stage I of the TNM staging system. This term is defined as submucosal carcinoma in the classification of Vienna [12].

The term pseudoinvasion refers to the presence of glandular epithelium of the mucosa beneath the muscularis mucosa in colonic polyps. These lesions have no malignant potential and should be management in a similar way to adenomas [13]. However, an inexperienced pathologist can mistake this phenomenon for invasive carcinoma. Pseudoinvasion usually occurs in large polyps (>1 cm), especially those with long stalks, and is most commonly found in polyps of the sigmoid colon. Islands of adenomatous epithelium are displaced through the muscularis mucosa and are found within the submucosa of the stalk. The displaced glandular tissue usually has rounded not infiltrative, contours, carries with it a small

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amount of lamina propria, and is cytologically identical to the overlying adenomatous component. Hemorrhage and hemosiderin depositions, are commonly seen and are a clue to diagnosis. In addition, inflammation and granulation tissue, can be found.Cystic dilatation of the displaced glands with mucin distention is also not uncommon in pseudoinvasion because mucin produced by the entrapped glands has no means of reaching the lumen. Occasionally, rupture of dilated glands occurs with acellularmucin extravasation and there is a subsequent inflammatory response. Distinction from mucinous (colloid) carcinoma is important and can be difficult. Specifically, in mucinous carcinoma, the mucin pools contain malignant cells, a feature lacking in pseudoinvasion.

For these reasons, it is highly recommended that level sections and second opinions, are obtained in cases of polyps with potential pseudoinvasion [14].

All adenomas have some degree of dysplasia. However, low and high grade dysplasias are artificial subdivisions of a spectrum. There is no definition of “high-grade”. Indeed, the WHO book on tumors of the digestive system, does not contain a list of criteria for high-grade dysplasia in adenomas [15,16]. However in general, high-grade dysplasia entails more substantial changes and includes carcinoma "in situ". Among these changes we consider architectural alteration, often resembling the glandular arrangement of adenomas and cytologic abnormalities, principally cellular and nuclear pleomorphism, nuclear hyperchromatism, loss of nuclear polarity, and marked stratification of nuclei. Other authors have considered as features of high grade displasia: loss of normal glandular architecture, hyperchromatic cells with multilayered irregular nuclei and loss of mucin, high nuclear/cytoplasmic ratio, marked nuclear atypia with prominent nuclei and focal cribriform patterns. Not all these features are necessarily present to the same degree in all dysplastic epithelia, while low-grade dysplasia manifests these same changes but to a lesser degree [15,16].

4. Prognostic factors

Many factors have been associated with a higher probability of residual disease or recurrent carcinoma.

4.1. Morphology

Morphology is described as polypoid (pedunculated or sessil) and nonpolypoid (flat or ulcerated) subtypes according to the Paris classification [17]. The type of polyp and its morphology can guide the endoscopist towards its potential malignancy [2,18,19]. These features include the size, the presence of depressed ulceration, irregular contours, deformity, a short and immobile stalk and the inability to elevate a sessile polyp when a submucosal bleb is formed. In such suspicious lesions, as well as in flat or depressed lesions, diagnosis can be carried out using chromoendoscopy and magnification techniques that can highlight abnormalities of glandular cytoarchitecture and reveal information concerning the extent of submucosal invasion [20,21].

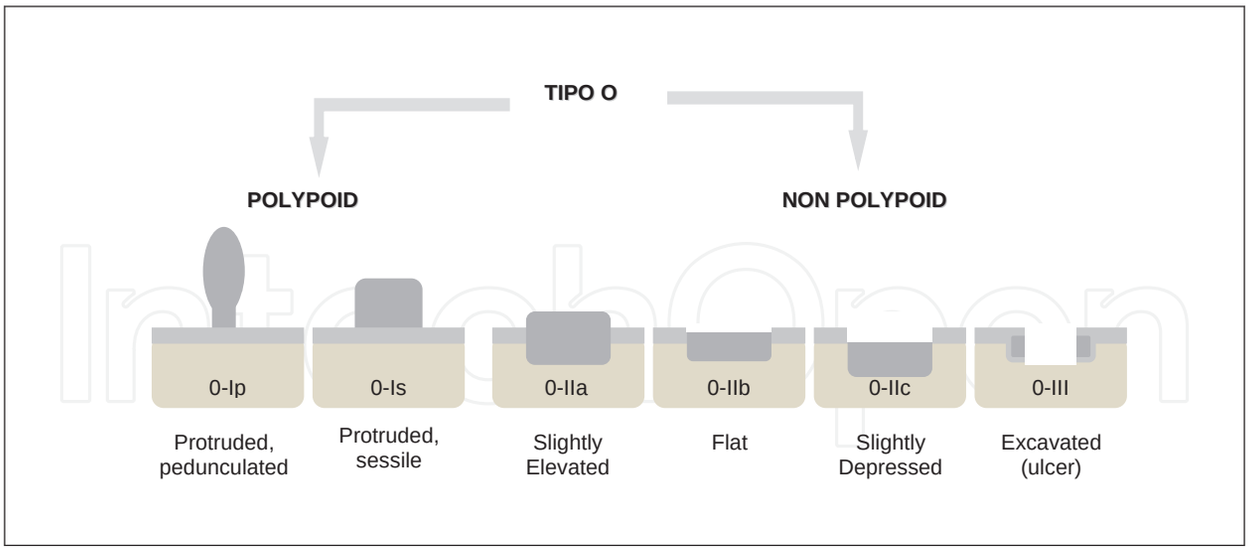

Table 1. The Paris Endoscopy Classification of superficial neoplastic lesions [17]

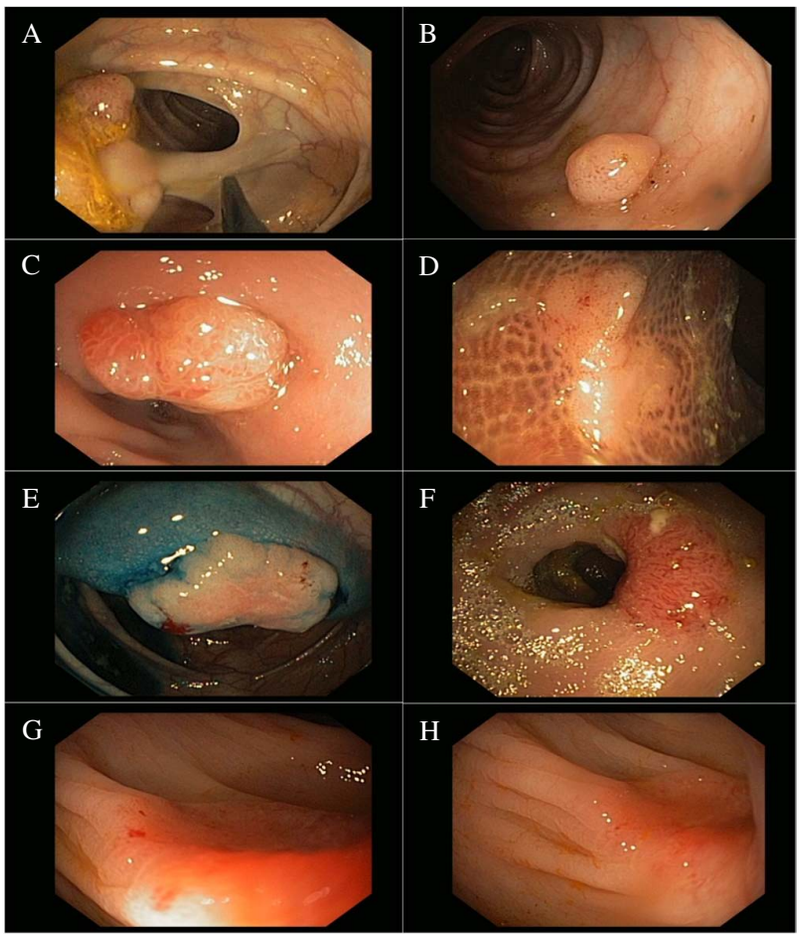

Figure 2. Polyps in colon: Pedunculated polyp 0-Ip (A), sessile polyp 0-Is (B y C), flat polyp 0-IIb (D y F), superficial elevated with central depression 0-IIa + IIc (E) and excavated polyp 0-IIc (G y H).

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Kudo et al. [22] developed the pit pattern classification for colon polyps with six classes of surface pattern depicted by magnifying endoscopy after indigo carmine staining. Class 5 of this pit-pattern classification or an unstructured surface has been shown to correlate well with a diagnosis of malignancy, and can provide important additional information prior to endoscopic treatment. However, endoscopic ultrasound using high frequency transendoscopicminiprobes currently appears to be the most accurate method for defining submucosal or further bowel wall invasion, enabling direct referral for surgical intervention in those cases with deeper infiltration who are at the greatest risk of lymphatic spread [23].

4.2. Type of resection

The success of treatment of a malignant polyp depends on the complete resection by polypectomy or surgical intervention. When en-bloc removal of a polyp is performed, it is possible to assess the depth of infiltration of the tumour cells and whether the margin is affected. Pedunculated malignant polyps are easily removed using a loop snare. However, this technique frequently results in piecemeal removal when applied to sessile and flat malignant polyps. Nevertheless, around one-third of malignant polyps are removed in this way [24]. En-bloc removal is advantageous because it allows full histological evaluation of the complete resection and is associated with lower recurrence rates than piecemeal removal [25]. Endoscopic submucosal dissection (ESD) has been found to be particularly useful for the removal of sessile or flat adenomatous lesions. It has an advantage over other endoscopic techniques in that it allows en-bloc removal of large (>2 cm) colonic lesions. In ESD an electrosurgical cutting device is used to carefully dissect the deeper layers of the submucosa to remove neoplastic lesions in the mucosa. In a meta-analysis it was found that ESD en-bloc resection is achieved in 84.9% of lesions, and clear vertical and lateral margins are achieved in 75.3% of cases [26].

4.3. Level of invasion of adenocarcinoma into the polyp and polypectomy resection margin

Haggitt et al. [27] have assigned levels of invasion to each malignant polyp. In this study, level 1 described invasive adenocarcinoma limited to the polyp head, level 2 included involvement of the neck, level 3 corresponded to adenocarcinoma cells in the stalk, and level 4 to invasion, adenocarcinoma cells infiltrating the submucosa at the level of the adjacent bowel wall. In this system, invasive adenocarcinoma in a sessile polyp by definition had level 4 invasion. However, precise histological evaluation of Haggitt's level may be difficult. Properly marked and orientated specimens are essential.

More recently, some authors have proposed an additional histological classification system based on the grade of cell differentiation at the lesion margins and on the size and depth of invasion of the submucosa. Submucosal invasion has been classified into three types based on the depth of invasion. When less than one-third of the submucosa is invaded the stage is sm1, and if more than two-thirds is invaded the stage is sm3, while stage sm2 is intermediate with invasion of cancer into the middle third. It has been shown that penetration of cancerous cells is associated with a risk of lymphatic spread [29-32]. Research based on large

patient series has shown a 1-3% risk for lymph node metastases in sm1 cancers, 8% in sm2 cancers and 23% in sm3 cancers [29].

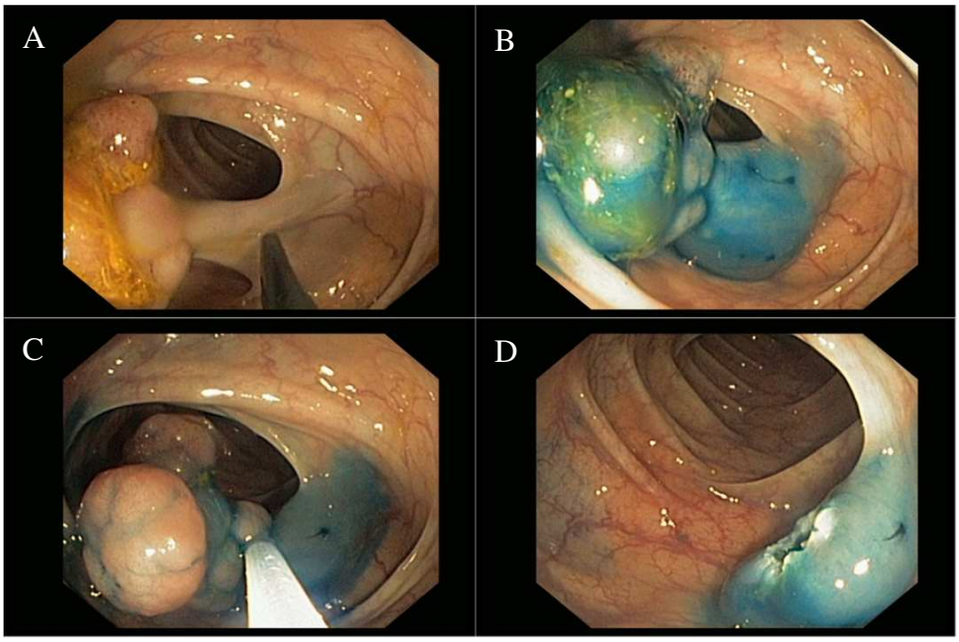

Figure 3. Resection of a pedunculated polyp with an endoscopic snare (A-D).

In sessile polyps, it is essential that the pathologist identifies the stalk or the depth of the diathermy burn. The risk of relapse ranges from 0% to 2% in malignant polyps with a margin of resection greater than 1 mm. If the resection margin is involved, or is less than 1 mm, the percentage of relapse ranges between 21% and 33% [30]. Most authors believe that a resection margin of more than 1 mm is safe and that in such cases the probability of residual disease or recurrent carcinoma is low [4,5,30,31].

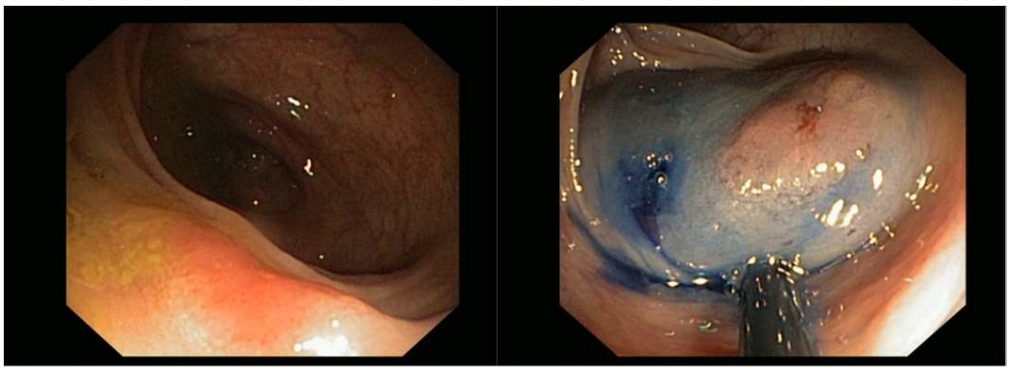

Figure 4. Elevation of a superficial elevated polyp (0-IIb) with Indigo Carmine

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4.4. Stage of differentiation

Four grades were considered [32]:

Grade 1: Corresponded to a well-differentiated intestinal-type adenocarcinoma with well-formed glands and open lumina or with more than 95% glandular differentiation.

Grade 2: Moderately differentiated intestinal-type adenocarcinoma containing solid nests showing only focal glands or with 50-95% glandular differentiation.

Grade 3: Carcinoma is poorly differentiated intestinal–type. Signet ring cell or mucinous adenocarcinoma, composed of hyperchromatic cells arranged into solid sheets and forming absorptive glands, with 5% to 50% glandular differentiation.

Grade 4: Undifferentiated tumours which have less than 5% glandular differentiation.

Undifferentiated carcinoma: Medullary carcinomas with high microsatellite instability.

The prognosis correlates with the histological grade [32]. For example, Grade 3 of differentiation is seen in 5.7 to 9.2% of patients and the risk of residual lesions or relapse in these cases is of the order of 36-38% [30].

4.5. Lymphatic invasion

Lymphatic invasion is defined as tumour cells within a true endothelial-lined channel in the absence of red blood cells [33]. The risk of lymphatic spread has been estimated by histological study of resected specimens. Since lymphatics do not penetrate much beyond the muscularis mucosae, focal cancer that has not invaded through this layer appears to present little or no risk of lymph node spread [34]. The near absence of lymphatics within the mucosa has been proposed as the reason for the observed lack of malignant potential (lymph node metastasis) observed in polyps showing only intramucosal carcinoma. However, this theory has been challenged by studies using more sensitive techniques to detect lymphatic vessels. Studies using the relatively new antibody D2-40, which stains lymphatic but not blood vessel endothelium, have shown that lymphatic present in the stalk and mucosa of adenomas and undergo proliferation, are early invasive cancers. Lymphatic channels are often present near nests of infiltrating tumours in malignant polyps [35,36].

Detecting lymphatic invasion by expert pathologists using light microscopy is difficult. There are no recognized guidelines for establishing the presence of lymphatic invasion (for example, the number of sections or immunostains needed to identify lymphatic vessels). For example, in a study in which five pathologists assessed the lymphatic invasion of 140 malignant polyps, they agreed (4 out of 5 observers) on only 17 cases [37].The intra and inter-observer variability in the interpretation of samples received among even the most expert histopathologists can be high and often leads to diagnostic uncertainties [37]. The use of immunohistochemistry for D2-40 may help identify lymphatic channels. However, its use is not yet routine, and technical issues such as loss of a suspicious focus in level sections limits the usefulness of special stains in this setting. The presence of lymphatic invasion has been proposed by some researchers as an indication for colectomy. However, few malignant pol-

yps with lymphatic invasion have been reported, and most of them have had positive margins, grade 3 invasive adenocarcinoma (as defined above), or both [5].

4.6. Vascular invasion

The presence of vascular invasion is defined as cancer in an endothelial-lined channel surrounded by a smooth muscle wall [35]. However, it is difficult to recognise it. Vascular markers (CD31, CD34 and factor VIII) may help. These markers strongly stain blood vessel endothelium, and to a lesser extent lymphatic endothelium [14].The prevalence of venous invasion in malignant polyps varies greatly, ranging from 3.5% to 39% [37].Often venous invasion is associated with lymphatic invasion and/or tumours which have a resection margin of less than 2 mm and/or are poorly differentiated. In contrast, Talbot et al. [38] observed that venous invasion was not associated with poorer prognosis.

4.7. Risk of residual disease or recurrent carcinoma in favourable and unfavourable histology

Favourable histology is defined as grade 1 or 2 differentiated adenocarcinoma in which carcinoma cells are at least 1 mm from a clearly visualized margin, resection is carried out en bloc and there is an absence of vascular or lymphatic invasion.

Unfavourable histology is defined as polyps with biopsy margin ≤1 mm, tumour within the cauterized region constitutes a positive margin, piecemeal removal, poorly differentiated tumour (grade 3) or lymphatic or vascular invasion.In these cases, surgical resection is indicated because of the increased risk of lymph node metastasis or residual disease [14]. On the other hand, in the absence of unfavourable features, polypectomy is considered curative. Sometimes, specimens do not lend themselves to proper analysis for any reason (piecemeal removal or poor orientation) result in a default decision to resect.

In 1995, Volk et al [5] reviewed 20 studies in which 858 malignant polyps were analysed. They observed residual disease or recurrent carcinoma in 89 patients (10%). However, there were relapses or tumours in the area of the resection in only 8 (1%) patients with favourable histological criteria. Subsequent studies have also reported an incidence of less than 1% [37,39]. Only one study described incidence higher than 5% in malignant polyps with favourable histology [40] and the study itself has been widely criticized from subsequent reviews [5]. By contrast, in malignant polyps with unfavourable histology, the risk of relapse or residual lesions ranges between 10% and 39% [5,14,29,39].

4.8. Marking with India Ink

In 1975, Ponsky and King [41] published the first case in which marking with India ink was used with the purpose of locating the polyp during the surgical procedure. Sometimes to locate the base of the polyp after polypectomy or during surgery is extremely difficult.

All the endoscopicallyunresectable polyps in patients in whom surgery would be considered, should be tattooed. Endoscopicallyresectable polyps that could have become malig-

nant should also be tattooed. Among the criteria that should hint the endoscopist about the presence of malignancy in the polyps is size, an irregular surface or a flat or excavated morphology [2,18,42,43].

The size of the polyp is an important factor that indicates malignancy [42,44-46]. The probability of dysplasia could be up to 38,5% in those larger than 1 cm [47].The flat or ulcerated lesions have a higher risk of high-grade dysplasia or carcinoma [22,48-50]. The probability of cancer or severe dysplasia increases from 4% in small flat lesions, up to 6% in small polyps, 16% in large polyps and 29% in long, flat lesions, and up to 75% in depressed lesions [51].

However, tattooing in suspicious polyps at first colonoscopy, in our experience is still low, 17.6%. We study a retrospective series that include 74 patients. Our endoscopists usually marked large polyps, polyps resected in a fragmented manner and polyps with proximal location. However, in a multivariate analysis only proximal location was significant associated with marking. It is known that flat polyps, with a greater potential for malignancy, are most frequently located in the right colon [37,39]. In our series, 16.2% of the polyps were proximal; of these, 58.3% were marked; on the other hand, only 9.7% of the distal polyps were marked. The factors that could have a greater influence when it comes to marking proximal polyps more frequently was their potential to become malignant in this location and the difficulty of finding the polypectomy scar in subsequent controls or in surgery.

We agree with other authors [52-57] that tattooing is one of the best methods for tumor location, either if the patient is following-up by colonoscopy or is undergoing for surgical resection [42,58].

5. Treatment

Prior to removal of the polyp, it is difficult to know whether the polyp is malignant or not. Some features, as we have mentioned earlier, can give some indication of the degree of malignancy. Regardless of the morphological characteristics, a polyp is normally removed when detected.

Polypectomy should be performed en bloc, since this is essential to establish and define favourable or unfavourable histological criteria. In just a few cases, only polyp biopsies are performed, such a lack of coagulation data, polyp could be difficult to remove at that point in time, or the patient being on antiplatelet drugs or anticoagulants.

The indication for a malignant polyp with sessile morphology, regardless of favourable histological criteria, is surgery [10], especially in patients younger than 50 years old, who tend to present fewer surgical complications [59]. Surgical treatment is recommended for malignant polyps with pedunculated morphology which have unfavourable histological criteria (partial polyp resection, poorly differentiated carcinoma, vascular or lymphatic invasion, or lesions ≤1 mm from the polypectomy) [10]. On the other hand, for malignant polyps with pedunculated morphology but with favourable histological criteria, polypectomy is considered to be curative (Figure 7). Non-invasive high grade neoplasia regardless of their mor-

phology, are considered to be cured with polypectomy. Indeed, according to some authors, polyps harbouring "in situ" or "intramucosal" cancer should not be regarded or treated as malignant polyps [59].

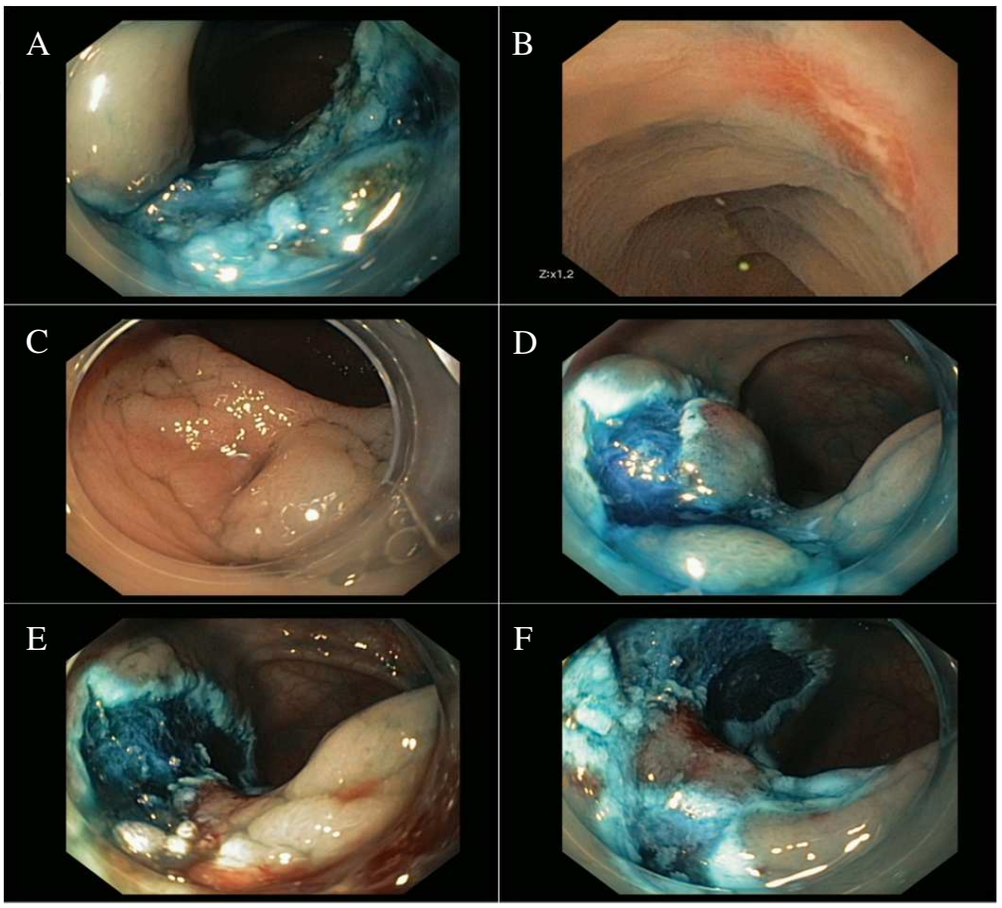

Figure 5. Endoscopic Mucosal Resection in a 0-IIa + Is polyp in colon (A-E), with control of the base after one month (F).

However, until now in many pathology reports were not reported histological criteria. For example at the University of Minnesota between 1987 and 2000, 83% of the reports are not angiolymphatic vessel invasion, 69% not reported the depth of invasion by cancer cells and 22% no stated the degree of tumour differentiation [60]. Beside the agreement among experienced pathologists was poor with respect to histological grade of differentiated carcinoma and angiolymphatic vessel invasion [60].

Endoscopic submucosal dissection (ESD) has emerged as a possible technique to successfully resect malignant colonic polyps en bloc [26,61]. The technique makes it possible to treat and cure large (>2 cm) sessile and flat polyps enabling pathological evaluation in most patients, also can be an alternative to surgery for older patients and for those suffering from associated conditions that contraindicate surgery.

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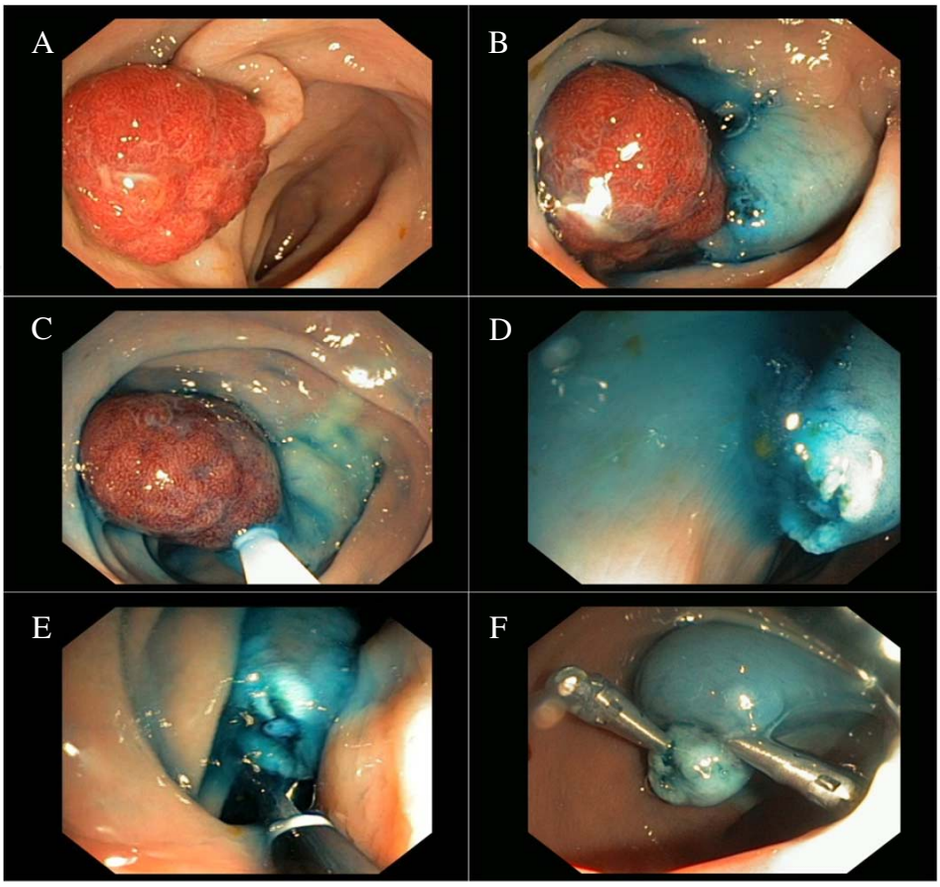
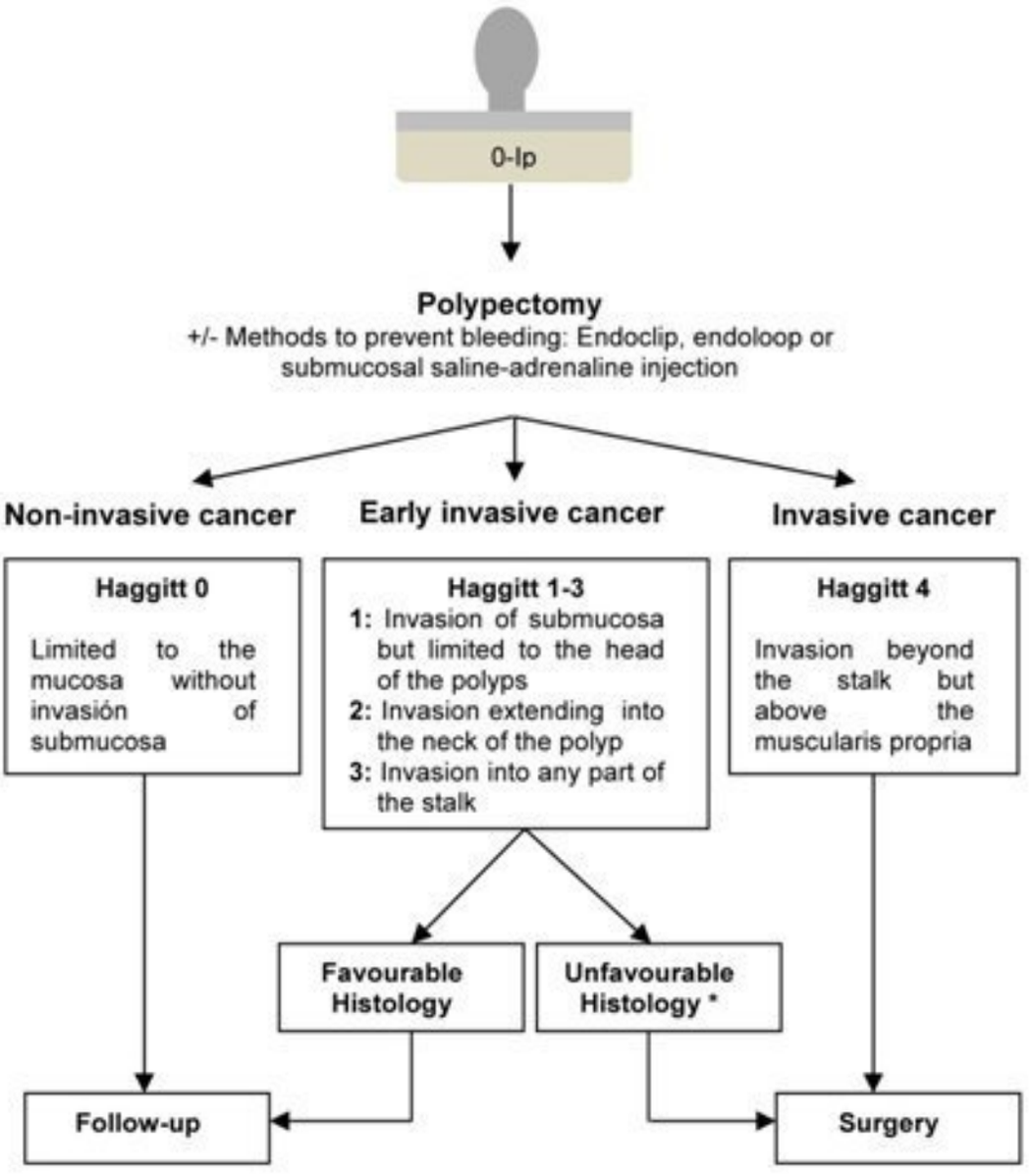


Figure 6. Polypectomy of pediculated polyp 0-Ip. Submucosal injection was performed using indigo carmine (A,B), polypectomy was made with electrosurgical knives (C), After polypectomy, a large non bleeding vessel was visualized (D) and cauterized using coagulation forceps (E) and obliterated with an endoclip (F) to reduce the risk of delayed bleeding

An exception to these guidelines is patients with malignant polyps, with sessile or flat morphology, that are located in the rectum. The occurence of distant metastases is correlated to T-stage and, after radical resection of T1 tumours, the 5-year rate of metastases is about 10% [62], similar to other locations of malignant polyps. About 50% of the local recurrences following local resection are curable if the patients are included in an intensive follow-up programme. Local resection should be offered to patients whenever the individually calculated risk of short-term mortality after major surgery exceeds twice the additional risk of local recurrence added by local procedures. An adequate preoperative evaluation of the patient's general health is essential before deciding the modality of treatment for the individual T1 rectum cancer patient.

In recent years, various serum markers been identified in an effort to establish which patients could benefit from surgical treatment and from a more strict follow up. These markers include metalloproteinase 7, vascular adhesion proteins, vascular endothelial growth factors and cytokeratins [63-66]. The majority of markers have been studied in patients operated on for colon cancer with infiltration of the lamina propria (equivalent to or higher than T2), so these results cannot readily be extrapolated to malignant colorectal polyps.



* Biopsy margin ≤ 1 mm, piecemeal removal, poorly differentiated tumour, lymphatic or vascular invasion

Figure 7. Therapeutic algorithm of pedunculated (0-Ip) polyps.

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6. Follow-up

In cases of non-invasive high grade neoplasia and malignant polyps with pedunculated morphology and favourable histological criteria, it is recommended that a colonoscopy be carried out three months after taking the biopsy [1,43].If this is normal, a further check-up is advised after one year, three years and five year [43]. Some authors suggest that if the results within three months are negative, subsequent monitoring should be the same as that offered to patients with non-malignant adenomas [35,44]. However, recent studies estimate that 11.8% of patients who have undergone polypectomy will develop a metachronic advanced adenoma and 0.6% an invasive carcinoma. Associated risk factors include age, number of polyps (5 or more), size (greater than 1 cm), villous architecture, proximal location, and being male. Smoking, body mass index, family history of CRC, and degree of dysplasia were not found to be associated with higher risks of advanced adenoma or cancer [45].

There have been reports of cases of malignant pedunculated polyps with unfavourable histological criteria which, despite no findings of residual carcinoma in the intestine wall or lymph node involvement, are found on follow up to have distant metastasis, even five years after surgery [4,5].

7. Conclusion

En brief, the adenoma-carcinoma sequence is well known and polypectomy has proven to reduce the incidence of CRC. However, the success of treatment depends on the complete resection and the future follow up of the base of polypectomy.

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