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Review of biological, clinical parameters and treatment

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We *know the significance of adenomas about the risk of neoplastic transformation defined as adenoma-carcinoma sequence. Although the majority of adenomas removed are small, it is well recognized that the risk of malignant transformation increases with an increased adenoma size. The term "malignant polyp" refers to an adenoma that macroscopically appears benign, but in which there is an invasion of malignant neoplastic cells within the submucosa through the muscularis mucosae. Malignant Polyps are substantially adenocarcinomas at an early stage; it is estimated that they represent the 0.75-5.6% of all adenomas removed during endoscopic exams. The management of a malignant polyp, diagnosed after an endoscopic removal, is complicated because the presence of residual malignant cells is a possibility. Also the presence of regional lymph nodes metastasis is different in literature and related to different prognostic factors.*
In this review we will analyze the incidence, the most appropriate methods of diagnosis, the biological parameters that characterize the various classes of risk of malignant polyps, in order to choice a correct treatment. The goal should be the improvement of the survival rate, decreasing the likelihood of residual disease evaluating the risk of overtreatment.

KEY WORDS: Adenoma, Adenoma-carcinoma, "Malignant polyp"

Introduction

It is estimated that the prevalence of colonic adenomas in Western people is 21-28% between 50 and 59 years, rising to 40-45% in the population between 60 and 69 years, exceeding 58% in the over 70. [1]
We know the significance of adenomas about the risk of neoplastic transformation defined as adenoma-carcinoma sequence. [2]
Although the majority of adenomas removed are small, it is well recognized that the risk of malignant transformation increases with an increased adenoma size.The endoscopical remotion of adenomas reduces the risk of developing cancer of the colon and rectum. [3]
We can classify the adenomatous polyps according to the degree of dysplasia, (Vienna's Classification) in high or low degree, with the additional category of invasive carcinoma or malignant polyp. [4]
The term "malignant polyp" refers to an adenoma that macroscopically appears benign, with an invasion of malignant neoplastic cells within the submucosa through the muscularis mucosae. [5-8]. An adenocarcinoma is defined as pT1 carcinoma if it invades the submucosa but not the muscularis layer. [9]
Malignant Polyps are substantially adenocarcinomas at an early stage; it is estimated that they represent the 0.75-

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5.6% of all adenomas removed during endoscopic exams [10-14]

The management of a malignant polyp, diagnosed after an endoscopic removal, is complicated because the presence of residual malignant cells is a possibility. Also the presence of regional lymph nodes metastasis is different in literature and related to different prognostic factors.

The therapeutic options include only surveillance when the risk of residual disease is low, or major surgical resection for cases classified as high risk(the real level of risk is often difficult to calculate). [11,15,16]

The endoscopic examination and the endoscopic resection permits a better histopathological evaluation, but the analysis of the biological parameters, that define the risk classification has a particular importance.

In this review we will analyze the incidence, the most appropriate methods of diagnosis, the biological parameters that characterize the various classes of risk of malignant polyps, in order to choice a correct treatment. We will consider the degree of differentiation, depth of invasion of the submucosa, lymph-vascular involvement, the status of endoscopic resection margin, and tumor budding.

Pathology of malignant colorectal cancer

Adenomas an the Adenoma-Carcinoma Sequence

The term "adenoma-carcinoma sequence" is related to the set of evolutionary steps that lead from an adenoma to an adenocarcinoma. The rate of progression of an adenomatous polyp to an invasive form depends on several factor: the size of the polyp, the histological type and the degree of dysplasia.

Polyps larger than 2 cm are more frequently characterized by malignant transformation than polyps smaller than 1 cm.

The villous type is most subject to malignant transformation (villous architecture > 75%) followed by the tubulovillous (no clear preponderance of one of the two types architectural) and the tubular (tubular architecture> 75 %). In screening programs the reported prevalence of high-grade dysplasia varies between 5% and 15%. [17]

Villous adenomas (5-10%) are sessile and have a wrinkled appearance. [18]

Fearon and Volgenstein demonstrated in the 90s the molecular basis of the adenoma carcinoma sequence, which can be defined as the chromosomal instability way (CIN). The two researchers claimed that at least four genetic alterations are necessary for the evolution of the tumor; typical targets of these changes are tumor suppressor APC, SMAD4 and P53, and the oncogene KRAS. The inactivation of the APC (adenomatous polyposis coli) seems to be the trigger factor to promote the events causing the tumor transformation. The tumor suppressor gene is involved in the transmission pathway mediated by β-catenin and cyclin D1, which leads, with the inactivation of the APC, to β-catenin dysregulation, that causes an uncontrolled cell proliferation, leading to possible, initial, clonal expansion. The remaining agents already listed act, at this point, in a synergistic way by promoting chromosomal instability and tumor progression. [19]

The pathogenetic sequence "adenoma-carcinoma" appears to be: adenoma, increasing degree of dysplasia (mild, moderate and severe), and finally invasive carcinoma and metastatic carcinoma. The process is not, however, unique and unrestrainable, dysplasia does not necessarily progress to cancer. We can identify different degrees of dysplasia in the context of a single adenoma. The three increasing degrees of dysplasia, microscopically evaluated after removal of the polyp are joined together in accord to Vienna's classification in two categories: "low-grade" (mild and moderate) and "high level" (severe).

Low-grade dysplasia (mild): general architecture relatively conserved, with glandular tubules or only slightly elongated and tortuous initial hints at budding, loss of the gradient of cellular differentiation from the base of the crypt to the surface. Elongated nuclei, enlarged, polarized and stratified employing up to 2/3 the thickness of the epithelium.

Low-grade dysplasia (moderate): general architecture relatively conserved, with glandular tubules only slightly elongated or tortuous, initial signs of budding, loss of cellular differentiation gradient from the base of the crypt to the surface. Elongated nuclei, enlarged, polarized and stratified employing up to 2/3 the thickness of the epithelium. Moderate dysplasia has features common to both mild dysplasia to severe dysplasia.

High-grade dysplasia (severe): is a diagnosis that is based on architectural alterations, supported by appropriate cytological alterations. Architectural changes must involve a sufficient number of glands to be identified at low magnification, not just one or two glands: complexity, irregular glandular crowding, obvious branching and budding of crypts, cribriform appearance, back-to-back glands, prominent intraglandular epithelium growth (papillary tufting). Sometimes one of the architectural features can be found in low-grade lesions. In high-grade dysplasia the presence of cytological alterations is therefore necessary: loss of nuclear polarity or layering, with distributed nuclei throughout the thickness of the epithelium, markedly enlarged nuclei, often with dispersed chromatin and prominent nucleoli, atypical mitoses, absence of mucus secretion and prominent apoptosis. It is often defined by some pathologists as "intramucosal colon carcinoma" [20].

Patients with a known diagnosis of adenoma have a risk of developing colon cancer of 4% in 5 years and 14% in 10 years, that is a greatly increased risk compared to the general population. [21]

Malignant Colorectal Polyps

A malignant colorectal polyp is a lesion with invasion of submucosa, through the muscularis mucosae. PT1 adenocarcinoma is characterized by invasion of the submucosa without muscularis propria involvement. [22] This represents 11% of endoscopically removed polyps, adenomas without basal membrane invasion are called polyps in situ. [16]

A higher malignancy incidence has been described in villous adenomas (10-18%) compared with the tubulo-villous (6-8%) and tubular adenomas (2-3%). [23]

The polyp's malignant risk is correlates to the increasing size and patient age. [24,25]

Polyp size is one of the most important risk factors for malignant transformation. In a serie of 5137 adenomas of diameter <5 mm none of them showed malignant tranformation. [26]

There is evidence that large polyp size is correlated with villous morphology and high-grade dysplasia. In a recent study of 13,992 asymptomatic patients undergoing screening, the percentage of high-risk adenoma characters (tight or villous architecture or high-grade dysplasia) was 1. 7% in lesions measuring 1-6 mm, 6.6% in lesions measuring 6-9 mm and 30.6% in those larger than 10 mm. [27,28]

Larger polyps are associated with an increased risk of malignancy (up to 80% of adenomas exceeding 42 mm) [29,30].

It has been estimated that the risk of malignant cells in an adenoma up to 1 cm is <1%, increasing to 10% in adenomas of size up to 1-2 cm and 20-50% in adenomas larger than 2 cm. [31]

A malignant polyp is the earliest form of colorectal carcinoma (pT1 sec. TNM) and has a variable potential to metastasize to the lymph nodes (8-37%). [32] This variability is associated with histological parameters that guide the treatment options (surgical resection vs. follow-up clinical and endoscopic). The parameters are: depth of invasion, endoscopic resection margin status, histological grade of differentiation, tumor budding and lymphovascular invasion.

Serrated Lesions and Serrated Pathways

One of the emerging issues in the screening for colorectal cancer (RCC) context is represented by the interval cancers, better defined as PCCRC (post-colonoscopy colorectal cancer). These are Cancers that occurred in patients who have already undergone a colonoscopy in the past 5 years, they are estimated to be 5% of all RACs, they are mostly right and have a molecular pattern that differs from that of traditional adenomas detected in the 90's by Fearon and Vogelstein.

The most recent studies have enriched the established knowledge with evidence of malignant transformation pathways that are parallel to the classical one. Thanks to the endoscopy techniques as chromoendoscopy and high-resolution endoscopy, and thanks to the improvement of knowledge in the molecular biology on colon cancer, has been highlighted as other colon lesions, which are not the classic adenomatous polyps, can play a role in malignant transformation pathway: hyperplastic polyp, serrated sessile adenoma / serrated traditional adenoma, carcinoma. This is the serrated carcinogenic pathway, which seems to be responsible for a significant proportion of sporadic cancers.

This malignant transformation pathway is in addition to the classical adenoma-carcinoma sequence.

The adjective "serrated", which identifies this kind of lesions, refers to their characteristic phenotypic markers, characterized by the "sawtooth" appearence that can be detected in the gland lumen, due to architectural disorder caused by alterations in the proliferative compartment, which is shifted toward the upper portion of the crypts, with asymmetry between the two emicrypts and goblet or foveolar cells type in the crypt base. The crypts are often dilated and a show irregular shape, sometimes assuming a characteristic "L" or "inverted T" configuration, with serrated appearence, sometimes very prominent, also present in the basal portion of the lesion. This feature is present in hyperplastic polyps, sessile serrated adenomas and traditional serrated adenomas. [33,34]

Previously, these lesions were diagnosed as tight or metaplastic and hyperplastic polyps. Jeremy Jass was the first to demonstrate their malignant potential. [35]

The new classification proposed by Snover et al. [36], on behalf of the WHO divided serrated lesions: hyperplastic polyps, serrated sessile adenomas / polyps without dysplasia, tightened serrated sessile adenomas / polyps with dysplasia (previously called mixed polyps) and traditional serrated adenomas (TSA). (Table I)

In serrated polyps, the adenoma-carcinoma sequence, defined in this case serrated pathway, has tight schedules, thus leading to malignant transformation more quickly; this increased speed will inevitably be the cause of changes in the screening procedures for colorectal cancer prevention. There is a relationship between size and risk of malignancy. [37]

Table I - *Serrated lesions classification*

1. Hyperplastic (metaplastic) polyp
2. Sessile serrated adenoma / polyp without dysplasia
3. Sessile serrated adenoma / polyp with dysplasia (previously called mixed polyp)
4. Serrated traditional adenoma

Classification of Colonic Mucosa Superficial Lesions

The Paris classification of colonic mucosa superficial lesions was drafted in 2002. This classification was sub-

TABLE II - *Paris classification*

Protruded lesions	Flat elevated lesions	Flat lesions
Ip Peduncolated	**0-IIa** Flat elevation of mucosa	**0-IIb** Flat mucosal change
Isp Subpeduncolated	**0-IIa + c** Flat elevation with central depression	**0-IIc** Mucosal depression
Is Sessile	**0-IIa + Is** Flat elevation with raised broadbased nodule	**0-III** Excavated

sequently revised in 2005 and in 2008 finally was integrated between the eastern and western classification with the "Kudo Paris-Japanese classification" drafting [38]. This classification divides superficial lesions in polypoid and not polypoid lesions and defines that polypoid lesions may be pedunculated (0-Ip), sessile (0-Is) or mixed pattern (0-Isp) and that not polypoid lesions are divided between slightly elevated (protrusion <2.5 mm from the surface mucosa), called 0-IIa, completely flat (0-IIb), or slightly depressed (depression <2.5 mm from the surface mucosa) said 0-IIc. However, there are subtypes that are called "mixed forms": elevated and depressed (0-IIa + IIc), depressed and elevated (0-IIa + IIc), and sessile depressed (0-Is + IIc). Macroscopically we can identify three types of lesions that are essentially recognized: polypoid, non-polypoid and depressed. Polypoid lesions grow above the mucosal surface and the volume of the adenomatous component seems to be correlated with the histological grade [39,40]. Depressed lesions require attention because are not so easy to diagnosed and different techniques (EMR) are required for their endoscopic excision. They have demonstred a rapid evolution in malignant lesions no related to the size. The term flat lesions, that is often still used to define any subtype of not polypoid lesion must be better investgated (Table II).

The Biological Parameters

Many factors have been associated with a higher probability of residual disease or recurrenct carcinoma. We refer to the biological parameters that characterize malignant polyps, removed during endoscopic examination, which must be analyzed carefully.
The polyp must be removed and processed correctly, so the pathologist can be put in a correct position to better analyze the removed sample.
Depth of neoplastic invasion within the submucosa, endoscopic resection margin status, histologic grade of differentiation, tumor budding, lymphovascular invasion and differentiation grade.

Submucosal Invasion Level

To classificate the depth of invasion of pedunculated polyps we use Haggitt levels [41], which divide the submucosal invasion in four levels:
– Level 1: Carcinoma invading into the submucosa, but limited to the head of the polyp;
– Level 2: carcinoma invading into the submucosa up to the level of the neck (the junction between the head and stalk) of the adenoma;
– Level 3: Carcinoma invading every part of the stalk;
– Level 4: carcinoma invading the submucosa of the bowel wall below the stalk but above the muscularis propria.
For sessile polyps, which are considered Level 4 by Haggit, we use instead the levels of Kikuchi who consider the invasion of the third superficial (sm1), middle third (sm2) or deep third (sm3) of the submucosa. [42] It is important to emphasize that Kikuchi's system is more difficult to use if there is no muscularis propria in the biopsy; is important to add also that the measurement depends on a recognizable submucosa and on a good polyp orientation in the sample. [43,44]

Resection Margin Status

The importance of ensuring a resection margin free of cancerous tissue is universally recognized, but there is not universal agreement regarding the minimum safe distance between the resection margin line and the cancerous tissue. It is also known that the sample artifacts due to diathermic resection make difficult, for the pathologist, to indicate the possible presence of invasive cells on the resection line. It is particularly difficult to analyze the resection margin of sessile polyps, especially if removed by piecemeal technique. [31] An involved margin has, in the literature, different definitions. There is no consensus about what constitutes a "negative margin", which has been defined in different ways: the absence of malignant tissue within the margin of resection, diathermy [45],> 1mm from the edge [46] and more

than 2mm from the sidelines. [47,48] Current European guidelines recommend that the neoplastic cells presence less than 1 mm from the resection margin is considered as an involved margin. [31]

Differentiation Grade

The cancer differentiation grade is divided into G1 and G2 for low grade and G3 for high grade. Possible anaplastic component, even minimal, is equivalent to G4. The well-differentiated carcinomas have well-formed glands with a percentage of more than 95% differentiation, poorly differentiated carcinomas may even reach 50% of differentiated glandular tissue. The majority of carcinomas are classified as moderately differentiated and are localized in the middle, between the two categories described above. A lower level of differentiation correlates better with metastatic disease compared to more differentiated forms. [49,50]

Lymphovascular Invasion

Lymphovascular invasion is defined as the presence of visible tumor cells within the endothelial lumen in the absence of erythrocytes. [51] The lymphovascular invasion (whose prevalence ranges between 3.5% and 39%) [52] in a malignant polyp is strongly associated with the risk of lymph node involvement with a consequent worsening prognosis.

Tumor Budding

Tumor budding is defined as the cancer cells presence, isolated or in small groups, (less than 5 cells) in the stroma on the tumor advancement front. According to Ueno et al. (2004) evaluated an area of 0.785 square mm with 20 x objective, a carcinoma is classified as negative (less than 5 outbreaks) or positive (more than 5 outbreaks). Studies on pT1 cancer have shown that the tumor budding presence was significantly associated with lymph node metastasis and other adverse outcomes. [53-57]

Risk Assessment and Treatment

The analysis of biological risk parameters is fundamental to choose between a follow-up endoscopy without resection of the affected segment of colon (for polyps at low risk) and a resection of the colon associated with regional lymphadenectomy (for malignant polyps that are classified in a high-risk class).
The adverse outcome in a malignant polyp is defined as residual cancer in a resected sample and local recurrence or metastatic disease diagnosed during the period of follow-up [47].

Resection Margin

The cancer presence on or near the resection line, increases the risk of an adverse outcome.Boenicke et al. [59] reported that the concurrent presence of involved resection margin and sessile morphology is an important risk factor for lymph node metastases after complete endoscopic malignant polyp removal. They observed 105 patients with malignant polyp that underwent polypectomy, only 39 of these showed infiltrated resection margin and then underwent surgical resection. Local recurrence at the original malignant polyp site was noted in three patients while the presence of lymph node metastases in eight patients (7.6%). They thus concluded that incomplete tumor removal and lymphatic infiltration showed a significant correlation with lymph node metastases presence, but not with residual disease presence.
Is generally accepted that the risk of lymph node metastasis, recurrence or residual tumor was <2% in malignant polyps removed where the resection margin free from cancer is > 1mm and there are no additional histological adverse features. [48,54,59] Cooper et al. [46] reported that when a pathologist finds invasive elements in the resection margin, or when the distance between invasive elements and the margin is <1 mm, the percentage of recurrence rises to 33%. It is also widely recognised that a negative margin for malignant cells of more than 2 mm has a low probability of residual cancer. [46, 60-63] The majority of studies have shown that a clearance <1 mm has the same clinical meaning of a cancer on the margin [46,47,59] and should be considered as an indication for further intervention. When the margin is involved or the distance is <1 mm, the relapse rate rises from 21% to 33% [46]. Further endoscopic options are limited for malignant polyps showing a resection margin involved. However, for rectal polyps with an uncertain or involved resection margin, local excision is a reasonable therapeutic option if there are no other histological characters that increase the level of risk.The CD10 positivity in some experience was associated to an higher risk of lymphnode metastases.[64]
If the deep margin is clear but, the lateral margin shows residual adenoma, further local excision is a reasonable therapeutic option (if there are no other characters histological risk). If further local excision is not possible, surgery should be considered for surgical resection, consistent with the patient's condition. This surgery should be performed as soon as possible rather than waiting to find the recurrence, a delayed surgery shows a significantly worse outcome [59,60,62].

Depth of Invasion

Studies conducted by Haggitt and his colleagues concluded that all pedunculated polyps with a depth of invasion that is less than level 4 (invasion of malignant cells

within the submucosa below the base of the peduncle), represent a group with a very low level of risk of local recurrence or locoregional lymph node metastases [41,65]. It has been established, on this basis, that this group of pedunculated lesions, in absence of other histological feature with adverse prognostic meaning, can be treated only with endoscopic resection, being risk of a negative outcome of the disease almost 0%. Nascimbeni *et al.* [66] have reviewed a number of studies that claimed that the incidence of lymph node involvement in malignant pedunculated polyps, resected endoscopically, with levels of invasion of Haggit 1, 2 and 3 was <1%. Matsuda et al. [67] analyzed data from 384 hospitals in Japan about malignant pedunculated polyps removed endoscopically, reported that an invasion of the only polyp head (haggit 1 and 2) correlated with 0% of lymph node metastases, while 6.2%, among those that were characterized by invasion of the stalk (Haggitt 3 and 4), showed the presence of lymph node metastases. Thus concluding that endoscopic treatment alone was sufficient for levels 1 and 2 of Haggitt, being related to a minimal risk of locoregional recurrence. Kikuchi et al. 42 determined the classification of sessile malignant polyps and reported risks of lymph node metastases in different levels of depth; these range was from 0.5% in level SM1 to 14.4% in level SM3. The majority of sessile polyps is today classified according to the Kikuchi classification that redefines the sessile polyps, previously included in the Level 4 Haggitt. Nascimbeni et al. [66] confirmed that the invasion of the inferior third of the submucosa is a feature at higher risk of developing lymph node metastases. The frequency of lymph node metastases described was 23% in the SM3 Kikuchi group.Lesions that are limited to levels SM1 and SM2, in absence of other adverse prognostic characteristics (such as the absence lymphovascular infiltration, poor differentiation or free margin <2mm), can be treated with endoscopic resection alone. Pedunculated malignant polyps classified as level 4 Haggitt, sessile polyps SM1 or SM2 associated with unfavorable histological features and all sessile polyps SM3 should be considered for surgical resection. However Kim et al. [68] have highlighted as an accurate classification of the submucosal invasion level is complicated in endoscopic mucosal sample that do not include the muscolar layer. For rectal malignant polyps the situation is more complex because the majority are sessile polyps (pedunculated lesion are unusual in the rectum) and full-thickness excision is often performed. Groups of patients in which a TEMS for pT1 carcinoma has been performed, showed a great variability in the local recurrence incidence, from 2% to 24% [64,69-71]. When total mesorectal excision (TME) for pT1 carcinoma has been performed, lymph node involvement has been found in 2-23% of cases [64,72,73]. The radical resection of a pT1 tumor does not guarantee a curative outcome, in fact, the 1. 7-6.0% of patients develop local recurrence within 5 years after surgery [72-74].

Lymphovascular Invasion

In a multivariate analysis of outcome in a group of patients who underwent surgical resection Kitajima et al. [54] have shown that lymphatic invasion was an independent risk factor for lymph node involvement.
The retrospective study done by Hassan et al. [16] on 1900 patients with malignant polyp shows the presence of lymphovascular invasion in 18% of polyps. The presence of lymph node metastases was recorded in 35% of polyps in which there was lymphovascular invasion and in 7% of cases in which it was absent. Eighty-three of the 268 polyps had lymphovascular invasion as the only adverse risk character. In the group in which this parameter was found to be the only one that was present there was a very low risk of metastatic disease (0.5%), but lymph node metastases were present in 7% of patients. The lymphovascular invasion then appears to be an independent risk factor for the presence of lymph node metastases.
The presence of lymphovascular invasion turns out to be a parameter of intermediate risk and should lead to take into account, during the discussion with the patient, the surgical resection.

Cancer Differentiation

Hamilton et al. [75] reported that the risk of residual disease and lymph node metastases is closely correlated with the histological grade of the tumor. A lack of differentiation is an unusual finding in colorectal malignant polyps, being present in 4-7.2% of cases [16,76]. It is generally acknowledged that a lack of differentiation in a malignant colonic polyp is associated with a high risk of residual disease or lymph node involvement [6,11,48,58,77]. However, a lack of differentiation is rarely found as an isolated histological feature, usually shows up associated with other adverse features. Cooper et al. [78] observed that the high level of risk in poorly differentiated carcinomas correlated with other adverse prognostic factors, such as the free margin <1 mm or infiltrated margin.

Combination of Factors

The malignant polyp presents more than one risk factor. Kitajima et al. [64] reported that the presence of lymph node metastasis was related to pedunculated polyps in which the depth of invasion was greater than 3000 uM under the muscularis mucosa and there was also lymphovascular invasion. Even Hassan et al. [16] observed the combination of various factors. The polyps were classified into low-risk (n = 375) when there were no adverse histological characters, and high risk (n = 268) with at least one adverse risk factor present (resection margin involved, lymphovascular invasion or poor differentia-

TABLE III - *Indications for treatment*

Biological parameter	Endoscopic resection (low-risk malignant polyps)	Surgical resection (high-risk malignant polyps)
Differentiation grade	High	Poor
Clear resection margin	> 1 mm	< 1 mm
Lymphovascular invasion	Absent	Present
Infiltration level (haggitt)	1,2	3,4
Level of infiltration (Kikuchi)	SM1, SM2	SM3
Tumor budding	< 5 NESTS	> 5 NESTS

TABLE IV - *Influence of single biological parameters on degree of risk*

Biological parameter	Degree of risk
Resection margin< 1 mm	++++
Resection margin 1-2 mm	+
Peduncolated haggitt level 4	++++
Sessile: Kikuchi 2	++
Sessile: Kikuchi 3	++++
Poor differentiation	+++
Mucinous tumor	+
Tumor budding	+
Lympho-vascular invasion	++

tion). Among the 375 low-risk, 295 did not undergo surgical resection (recurrence in one case). Eighty were treated surgically and in 4 cases was detected nodal disease. In only one case out of 375 occurred metastatic disease. In the high-risk group were identified residual disease in 21% of cases, recurrence in 9%, lymph node metastases in 11% of cases and metastatic disease in 9% of patients. Nivatvongs et al. [50] by observing a group of 151 patients with endoscopically removed malignant polyp that subsequently underwent surgical resection showed that, of these, 23% of the polyps had evidence of lymphovascular invasion, 31% [11] of which were associated with lymph node involvement and showed the level Haggitt 4 of invasion into submucosa. Malignant polyps are thus divided into low, intermediate and high risk. Biological parameters are used to make this division. The most important of these characteristics is the presence of a free resection margin > 1 mm, followed by the depth of infiltration of malignant cells in the submucosa. These two characters are related, as well as levels Haggitt 1-3 polyps are more likely to be excised with a clear resection margin compared to level 4 of Haggitt polyps or those of sessile morphology. The level of differentiation and the presence, or absence, of lymphovascular invasion were similarly prognostic factors, but both are most often found in deeply invasive malignant polyps. It should be added that an isolated lymphovascular invasion in the absence of other adverse prognostic indicators, can be found and defines an intermediate risk of lymph node metastases. (Tables III and IV)

The low-risk polyps have a low probability of experiencing a negative outcome, while the polyps with at least one character of high risk are characterized by a risk of persistence of disease that can reach 50% depending on the number of adverse prognostic characters. Between these two groups is the intermediate risk which represents the biggest challenge in the decision of subsequent therapeutic interventions.

Conclusions

The management of malignant colonic polyps remains a challenge for the multidisciplinary team that takes care of colorectal pathology. The introduction of screening programs for the early detection of colorectal cancer on a large scale and the increasing use of colonoscopy to investigate Gastrointestinal symptoms, have considerably increased the diagnosis frequency of malignant polyps (pT1 the TNM classification).

It is necessary that every patient who is diagnosed with a malignant polyp is considered by the multidisciplinary team of the colorectal cancer and an estimate of the risk of residual disease must be made. The risk is not absolute, but increases with the number of negative prognostic characters that are found. The class of risk is calculated combining the various biological parameters, from low to very high. The risk class will lead to the most appropriate treatment that can range from an endoscopic resection to a major surgical intervention.

In conclusion a wide adherence to screening programs, a correct endoscopic examination, a proper collection and treatment of adenomas displayed, but especially the evaluation of the class of risk, in order to appropriate treatment, is fundamental for the prevention, and thus the reduction of colorectal cancer mortality.

Riassunto

Conosciamo il significato di “adenoma” riguardo al rischio di una trasformazione neoplastica secondo la nota sequenza adenoma-carcinoma. Nonostante che la maggioranza degli adenomi asportati siano di piccole dimen-

sioni, è ben noto che il rischio di trasformazione maligna aumenta con l'accrescersi del volume dell'adenoma. Il termine "polipo maligno" si riferisce ad un adenoma che si presenta macroscopicamente come benigno, ma in cui vi è una invasione di cellule maligne nel contesto della sottomucosa al di là della *muscularis mucosa*.
I polipi maligni sono sostanzialmente adenocarcinomi in uno stadio precoce, e di stima che rappresentino il 0,75-5,6% di tutti gli adenomi asportati durante gli esami endoscopici.
Il trattamento del polipo maligno, diagnosticato dopo la sua asportazione endoscopica, è reso complicato dalla possibile presenza di cellule neoplastiche residue nella sede di asportazione. Anche la presenza di metastasi nei linfonodi regionali è considerata in modo differente in letteratura e posta in relazione con differenti fattori prognostici.
In questa revisione vengono analizzati l'incidenza, i metodi diagnostici più appropriati, i parametri biologici che caratterizzano le vari classi di rischio dei polipi maligni, per poter scegliere il trattamento corretto nel singolo caso. le finalità sarebbero quelle di migliorare il tasso di sopravvivenza, di diminuire la probabilità di malattia residua pur valutando il rischio di un trattamento eccessivo.

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