Management of Malignant Adenomas

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Abstract

Keywords

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Most polyps that originate in the colon and rectum are benign. A small subset of polyps will contain a malignancy. Although most malignant adenomas are managed with colonic resection a number can be approached with endoscopic, minimally invasive, and observational techniques. This article reviews the histologic characteristics and adverse risk factors that would portend a poor oncologic outcome and therefore suggest formal colonic resection. Modern endoscopic techniques such as endoscopic mucosal resection and endoscopic submucosal resection are discussed.

Despite the wide availability of several different screening methods for colon neoplasms, approximately 136,830 colorectal malignancies will be diagnosed in the United States this year and there will be 50,310 deaths.¹ The adenoma-carcinoma sequence is integral to our understanding of the pathophysiology of colorectal cancer.² Identification and removal of polyps has led to a new era in cancer prevention. Although most polyps are benign and require little more than a subsequent appointment for surveillance endoscopy, some polyps harbor a malignancy and require more thought and perhaps additional intervention. The focus of this review will be the endoscopic and surgical management of high-grade adenomatous lesions, including malignant adenomas.

Several effective screening mechanisms for the detection of colorectal neoplasms have been developed. These include fecal occult blood testing, flexible sigmoidoscopy, double-contrast barium enema, virtual colonoscopy, optical colonoscopy, and fecal DNA testing. Application of these differing techniques is somewhat dependent on health-care resource settings and philosophies. In the United States, fecal-occult blood testing and optical colonoscopy remain the most common form of colorectal cancer screening. Despite widespread availability of these resources, a significant proportion

of the population has not undergone colorectal cancer screening.³ Although a polyp may have advanced to become an early malignancy, detecting early-stage colorectal cancers provides an opportunity to decrease mortality from the disease. Furthermore, detection of early colorectal malignancies may allow for less invasive methods of management.⁴

Both polyps and early-stage cancers are usually asymptomatic; cancers that have grown large enough to cause symptoms have a much worse prognosis. This contrast highlights the need for screening in asymptomatic persons.

Adenomatous Polyps

Polyps are defined as visible protrusions of the colonic mucosa into the lumen of the colon. The major histologic categories include inflammatory, hyperplastic, hamartomatous, and adenomatous polyps. All polyps have their genesis in the loss of cellular replication control, differentiation, and apoptosis. Such genetic changes result in the phenotypic cellular changes. Adenomatous polyps are differentiated from other types of polyps by the proliferation of glandular tissue. Patients who develop adenomas are at an increased risk of synchronous and metachronous development of colorectal malignancies. When

the adenomatous process has invaded through the muscularis mucosa then the polyp is defined as a malignant process.⁵

All adenomatous polyps typically extend into the lumen of the colon to some extent. This extent can be described as pedunculated (on a stalk) or sessile (flat). Traditionally, adenomatous polyps can be described by their villous component (tubular, villous, and tubulovillous). This subclassification, however, has less clinical impact than other histologic and molecular factors that will be discussed later in the review. Adenomas are identified in 7 to 41% of colonoscopies. Factors implicated in adenoma detection rate include adequate colonic distention and bowel preparation, as well as adequate examination time.⁶ A total of 2 to 5% of the polyps that are removed endoscopically contain a malignancy.⁷ Up to 20% of the polyps that are endoscopically unresectable will contain a malignancy.⁸

There are several endoscopic and histologic factors that affect the probability of progression of an adenomatous polyp to a malignancy. Histologically, polyps are epithelial clusters of dysplastic glands. Histologically, dysplastic cells demonstrate cellular changes that suggest loss of growth and reproductive mechanisms. Adenomatous polyps can be classified by the amount of dysplasia present. Polyps with low-grade dysplasia often show nuclear changes, such as palisading and darkening of the nucleus. Polyps with more severe cellular and nuclear changes are said to have high-grade dysplasia. These changes are often characterized by more irregular nuclei and an even darker appearance of the nucleus. In high-grade dysplasia, the cellular changes are often reminiscent of the changes seen in cells with invasive cancer. However, these cells have not pene-

trated the muscularis mucosa and, therefore, do not represent a malignancy.⁹

Sometimes, the term intramucosal adenocarcinoma is used to describe polyps with high-grade dysplasia that have invaded into the lamina propria. These polyps are also benign and do not have metastatic potential at this stage. Complete endoscopic excision of these lesions is curative. The term, intramucosal adenocarcinoma, should be avoided because it is unclear and often leads to unnecessary confusion and anxiety.⁹

The degree of cellular dysplasia is associated with the risk of a polyp harboring a colorectal malignancy. In one study, only 6% of the polyps with low-grade dysplasia harbored a malignancy. However, in polyps with high-grade dysplasia the risk of a malignancy was 35%.¹⁰ Patient age is also a factor in the risk of a polyp containing a malignancy. Older patients are more likely to have a malignant polyp. Finally, polyp size is associated with the risk of a polyp harboring a malignancy. Larger polyps are more likely to harbor a malignancy; in one study, less than 2% of the polyps, which were smaller than 1 cm in diameter, had an associated cancer. However, in polyps that were greater than 2 cm in diameter the risk of malignancy was up to 46%.¹¹

Colonoscopic Management of Benign Adenomas

All polyps thought to be adenomas should be removed endoscopically, if technically feasible. Snare polypectomy techniques are beyond the scope of this study; however, a few principles should be observed. First, a complete endoscopic evaluation of the colon should be performed. Proper endoscopic resection

Fig. 1 Depth of invasion in a pedunculated polyp according to Haggitt classification.

typically includes some resection of the submucosa such that accurate histologic assessment of dysplasia and/or invasion can be observed. If there are significant concerns about the size or endoscopic appearance of the polyp, the area should be marked with ink such that it can be identified at a subsequent endoscopic procedure or surgical resection. Finally, any questionable lesions should be reviewed with a pathologist to gain a complete understanding of the polyp histology.

Malignant Adenomas

Management of malignant adenomas is entirely dependent on their level of colonic wall invasion. The extent of invasion is important as it predicts the risk of local recurrence and also the risk of lymph node metastases.⁵ When considering pedunculated polyps, the Haggitt classification system is useful in describing the extent of invasion into the submucosa¹² (► Fig. 1). Haggitt level 1 lesions have adenocarcinoma involving only the head of the polyp. In level 2 lesions, the adenocarcinoma extends into the neck of the polyp. Level 3 lesions are characterized by invasion of the adenocarcinoma into the stalk of the polyp. In level 4 lesions, the cancer invades beyond the stalk into the proper wall of the intestine; however, it is still limited to the submucosa¹² (► Fig. 1).

The Haggitt system is only useful for pedunculated lesions as sessile lesions were not described in his series. Sessile malignant adenomas do not have a stalk and, therefore, can be classified as Haggitt 4 lesions. Another useful classification system for sessile lesions was described by Kudo. Sessile malignant adenomas can be classified as SM1 if the lesion is limited to the upper one-third of the submucosa. SM2 lesions involve the middle third of the submucosa. SM3 lesions involve the lower third of the submucosa¹³ (► Fig. 2).

Pedunculated lesions that are classified as Haggitt level 1 to 3 have very low risk of nodal metastasis. This risk is estimated to be less than 1%.¹² Therefore, Haggitt level 1 to 3 lesions with a margin > 2 mm can be managed endoscopically, if there are no adverse features. Polyps with adverse features are usually candidates for colonic resection. These

adverse features include poor differentiation, lymphovascular invasion, and a close margin (< 2 mm).^{5,13,14}

SM1/SM2 sessile lesions with no adverse features are also associated with a low risk of nodal metastasis. Therefore, these lesions can typically be managed with endoscopic resection.¹⁵ However, if these lesions have adverse features, then they should be managed with surgical resection. Polyps with SM3 invasion or adverse features should typically be offered colonic resection as the risk of a nodal metastasis can be as high as 25%.^{5,13,14}

These recommendations are consistent with National Comprehensive Cancer Network (NCCN) guidelines; however, in practice they can be difficult to follow as submucosal invasion can be difficult to measure with an incomplete specimen, and polyps can be submitted in fragments which can challenge the pathologist's ability to assess the margins and depth of invasion. As a result, the surgeon's final recommendation should incorporate careful pathology review, discussion with the endoscopist, assessment of patient's surgical risk, and a detailed informed consent discussion with the patient.

Surgical Resection

Open colorectal resection was the only surgical choice for the management of advanced colorectal neoplasms until the mid-1990s. Since that time, there has been an explosion in both the application and technical feasibility of laparoscopic colectomy. The laparoscopic approach offers advantages such as less pain, improved cosmesis, and faster return of bowel function.⁵

The traditional indications for surgical management of a malignant adenoma are outlined in ►Table 1.

The use of a 2 mm before negative margin threshold can be considered controversial. Some authors report adequate oncologic outcomes in patients with negative margins smaller than 2 mm.¹⁶ A recent retrospective study from the United Kingdom reported on 21 patients with malignant polyps, with less than 1 mm margin, who were treated with observation. None of these patients developed recurrence after a rather limited mean follow-up of 3.2 years.¹⁵ A larger study by

Fig. 2 Depth of invasion in a sessile polyp according to Kudo classification.

Table 1 Indications for surgical management of malignant adenomas

Piecemeal excision
Inability to assess the resection margin
Resection margin less than 2 mm
Evidence of lymphovascular invasion
Pedunculated lesion with Haggitt level 4 invasion
Sessile lesion with Haggitt level 3 invasion

the northern region colorectal cancer audit suggested that a negative resection margin was associated with the absence of recurrence.¹⁷ In a recent population-based study using the linked Surveillance, Epidemiology, and End Results Program (SEER) Medicare database 5-year survival in patients undergoing surgery for colon, polyps containing invasive carcinoma was higher than in the group undergoing polypectomy for similar polyps (75 vs. 62%). This difference, however, did not meet the statistical significance with a hazard ratio of 1.15 (95% confidence interval: 0.98–1.33).¹⁸

Endoscopic Mucosal Resection

Endoscopic mucosal resection (EMR) was first described for the management of tumors of the esophagus and stomach.^{19,20} EMR differs from standard polypectomy in which the technique produces a deeper submucosal resection margin. Because the colon wall is thinner than the stomach or esophagus, EMR in the colon is more technically difficult. Indications for EMR include large adenomas or small early cancers confined to the upper layer of the submucosa.²¹ Typically, this type of procedure is performed to avoid a colonic resection. A recent prospective trial reported on 514 lesions treated with EMR. This technique was successful 89% of the time. Risk factors for failure of the technique were location near the ileocecal valve, difficult position, and a previous attempt at EMR by another endoscopist.²² With this technique, local recurrence can be as high as 13%. Risk factors for recurrence include lesions greater than 2 cm in size, piecemeal excision, and evidence of a positive margin.²³

Endoscopic Submucosal Resection

Endoscopic submucosal dissection (ESD) involves removal of polypoid lesions using a high-frequency electrosurgical generator which is threaded through a colonoscope. A hyaluronic acid and dextrose solution is injected underneath the polyp. The solution is designed to elevate the submucosa from the muscular layer of the colon wall. Specialized tools can be inserted through the colonoscope to perform the resection. The mucosa is incised and the dissection is carried into a deep submucosal layer. A recent review compared the EMR to ESD. This review found recurrence rates to be higher in the EMR group (14 vs.

2%). Procedure times, however, were longer in the ESD group. Complication rates were similar in both the groups.²⁴

It is important to note that even though these techniques remove the primary lesion, is still important to estimate the risk of lymph node involvement. Neither ESD or EMR can adequately treat or stage lymph node metastasis. In addition, both these techniques are technically challenging and are only offered in selected centers.²¹ The technical difficulty will likely limit their widespread applicability.

Combined Laparo-Endoscopic Treatment

There are several recent reports regarding the laparoscopic-assisted endoscopic polypectomy (LAEP). This technique involves laparoscopic mobilization of the colon to make polypectomy easier. This technique offers several advantages; the polypectomy site can be manipulated to guide a polyp in a difficult location toward the snare. In addition, if a perforation or thermal injury is noted, this can be oversewn or repaired. A leak test can also be performed to ensure that the repair is technically sound.^{5,21} Cruz et al recently reported on their experience of using a multimodal approach for the management of difficult polyps that included LAEP, EMR, and laparoscopic colectomy. Out of 123 patients, 55 (45%) underwent LAEP or EMR. A total of 76% of the patients in this group were ultimately managed without laparoscopic colectomy.²⁵

Conclusion

Malignant adenomatous polyps are challenging endoscopic and surgical problems. The most important step in their management is determining the depth of invasion, as this will predict the risk of local recurrence and lymph node metastasis. Patients with malignant polyps with clear margins > 2 mm and the absence of adverse features can be offered close surveillance. A variety of new techniques, including EMR, LAEP, and ESD, can be used to achieve these margins. In patients with close or indeterminate margins and/or adverse features, formal colectomy with adherence to oncologic principles is suggested.

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