Pathologic Issues in the Treatment of Endoscopically Removed Malignant Colorectal Polyps

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Malignant colorectal polyps, treatment, histopathology

Abstract
Endoscopically removed malignant colorectal polyps are early stage cancers for which treatment depends on histopathologic findings. For accurate pathologic evaluation, the polyps should be received in 1 piece because margins cannot be accurately assessed in fragmented polyps. Polyps with grade I or II cancer, no lymphovascular invasion, and a negative resection margin can be successfully treated with endoscopic polypectomy, whereas those with grade III cancer, lymphovascular invasion, or a positive or close margin require definitive surgical resection after endoscopic polypectomy. Potentially new significant parameters for patient management are depth of invasion and tumor budding. The pathology report must be clear and concise, indicating all relevant important parameters. The pathologist must differentiate invasive adenocarcinoma from intramucosal adenocarcinoma and pseudo-invasion. (JNCCN 2007;5:991–996)

Definitive oncologic surgical resection is standard treatment for most colorectal carcinomas. However, treatment decisions of local excision versus surgical resection arise in cases of early colorectal cancer, such as in patients with an endoscopically removed malignant colorectal polyp. The pathology findings in endoscopically removed malignant colorectal polyps are the major determinants of whether endoscopic polypectomy is therapeutic or subsequent definitive surgical resection is necessary. This article focuses on the pathology and its impact on the treatment of these patients.

Definitions
High-grade dysplasia (in situ adenocarcinoma) is a pathologic process that is confined within the basement membrane of the glands. Histologically, both architectural and cytologic changes occur; the former with crypts showing irregular branching, budding, and cribriform change. Cytologically, loss of mucin nuclear hyperchromasia, vesicular nuclei with nucleoli, and stratification of nuclei reaching the lumenal surface of the cell occur. Intramucosal carcinoma is defined as cancer limited to the mucosa where cancer has invaded the lamina propria, eliciting a desmoplastic response. The term invasive colorectal cancer is reserved for cancer that has invaded beyond the muscularis mucosae and into the submucosa. Because the mucosa is devoid of lymphatics only when the cancer has invaded into the submucosa (or beyond), it has the potential to behave in a malignant fashion (metastasize). Invasive cancer must be differentiated from high-grade dysplasia (in situ carcinoma) or intramucosal carcinoma, which no have the potential to metastasize. Lesions (polyps) of high-grade dysplasia or intramucosal carcinoma are cured through complete excision.

Malignant Colorectal Polyps
For the pathologic findings to have any relevant clinical meaning in patient management, the polyp must be received in 1 piece (non-piecemeal fashion) so the specimen can be properly fixed and sectioned and the depth of invasion and status of the margin of resection accurately determined. Guidelines endorsed by the American Society for Gastrointestinal Endoscopy (ASGE)
and American Gastroenterological Association (AGA), and the official statement of the American College of Gastroenterology (ACG) state that these criteria must be met for endoscopic polypectomy to be considered adequate treatment.\textsuperscript{6} Guidelines from the National Comprehensive Cancer Network (NCCN) state that endoscopically removed malignant colorectal polyps that are received fragmented (piecemeal) for which the margins cannot be properly assessed should be treated with a definitive surgical resection.\textsuperscript{9,10} When the specimen is received in a piecemeal fashion, accurately determining the true margin of resection and its relationship to the cancer may be impossible.

Once received in the pathology laboratory, the specimen must be adequately fixed so that proper sectioning is feasible. If the specimen is sectioned before adequate fixation, it may fragment, precluding evaluation of relevant pathologic parameters. The established histologic criteria that determine the proper treatment of endoscopically removed malignant polyps are 1) status of the resection margin, 2) histologic grade, 3) presence or absence of lymphovascular invasion, and 4) the Haggitt system.\textsuperscript{3-7,11-15} Favorable histologic features are 1) a resection margin that is free of cancer, 2) cancer of histologic grade I or II, 3) absence of lymphovascular invasion, and 4) Haggitt levels I through 3. Unfavorable histologic features are cancer at or near the resection margin, cancer of grade III, presence of lymphovascular invasion, or Haggitt level 4. Approximately 40% of endoscopically removed malignant colorectal polyps have favorable histology, whereas 60% will have unfavorable histologic features.\textsuperscript{3,4,12-14}

The literature indicates that endoscopically removed malignant polyps with favorable features can be treated successfully with endoscopic polypectomy alone, whereas those with unfavorable features should undergo definitive surgical resection.\textsuperscript{3,7,11-14} Guidelines from the ASGE, AGA, and ACG state that no further treatment is indicated after resection of an endoscopically resected malignant colorectal polyp if 1) the cancer is not poorly differentiated, 2) no lymphovascular involvement has occurred, and 3) the margin is not involved.\textsuperscript{6} Similar guidelines are published by the NCCN.\textsuperscript{9,10} In a multi-institutional study of 140 cases of endoscopically removed malignant colorectal polyps, 19.7% of cases with unfavorable histology had an adverse outcome compared with 0% with favorable histologic features.\textsuperscript{1} Other investigators have reported an adverse incidence of 0% with favorable histology and an adverse incidence of 11% to 42% with unfavorable histology.\textsuperscript{3,4,12,13} However, in 60% to 80% of cases with unfavorable histology, no residual cancer will be found after definitive surgical resection.

Margins
Tumor at or near the resection margin is a histologic finding that signifies the potential for an adverse outcome (Figures 1 and 2).\textsuperscript{3,7,11-14,16,17} In the author's multi-institutional study, 21.4% of polyps with cancer at or near (<1 mm) the resection margin had an adverse outcome. The literature reports an adverse outcome in 33% of malignant colorectal polyps with cancer at or near the resection margin.\textsuperscript{1} The margin of resection is defined as the actual free edge of the submucosa that contains diathermy change.\textsuperscript{3,4,6,7} Unfortunately, no consensus exists on the definition of a negative margin. A negative (free) margin has been defined as cancer 1) not within the diathermy, 2) greater than 1 high-powered field from the diathermy, 3) greater than 1 mm from the diathermy, or 4) greater than 2 mm from the diathermy.\textsuperscript{3,4,6,12,13,17} The presence or absence of a stalk is irrelevant if the margin is negative. Similarly, reporting of invasion into the stalk has no bearing on the management of these patients.

Grading
The grading system is based on tubule formation (Figures 3 and 4).\textsuperscript{3,8} Grade III cancers show less than
50% gland formation and approximately 5% to 10% of endoscopically removed malignant colorectal polyps are grade III cancer. The grading system takes into account the entire cancer, and isolated clusters of poorly differentiated cancer at the advancing edge of the tumor should not be construed as grade III cancer (see the section on Tumor Budding). Grade III cancers are often associated with other unfavorable histology (positive margin or lymphovascular invasion) and are significantly associated with an adverse outcome compared with grade I and II cancers.\textsuperscript{3,7,14,19,20} In the author’s study, 37.5% of cases of grade III cancer had an adverse outcome compared with 36% of cases reported in the literature.\textsuperscript{1}

**Lymphovascular Invasion**

*Lymphovascular invasion* is defined as invasion of tumor cells into lymphatics or veins. Some investigators feel that this unfavorable histologic feature is significantly associated with an adverse outcome that requires subsequent surgical resection.\textsuperscript{3,11,12,16} However, some have reported that lymphovascular invasion is not a significant independent variable.\textsuperscript{13} The diagnosis of lymphovascular invasion is best made when the tumor cells are away from the main tumor mass (Figure 5). Lymphovascular invasion is often confused with retraction artifact, and therefore the diagnosis of lymphovascular invasion is subjective with poor interobserver variation. Some investigators report that adverse outcome is present only when lymphovascular invasion is associated with other unfavorable histologic findings.\textsuperscript{4,7,17,19} Because of this and high interobserver variation, several groups have not reported lymphovascular invasion or consider it in the algorithm for managing patients with endoscopically removed malignant polyps.\textsuperscript{4,6} Although some recent studies have shown lymphovascular invasion to be associated with an adverse outcome in multivariate analysis,\textsuperscript{16,21,22} others have not found this to be true.\textsuperscript{23}

**Haggitt System**

In the Haggitt system,\textsuperscript{15} the depth of invasion is divided into various levels of invasion defined as level 1: tumor

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**Figure 2** (A) Low-power view of endoscopically removed malignant polyp. Cancer extends to the margin of resection (arrows). (B) High-power view of cancer at the resection margin.

**Figure 3** Grade II adenocarcinoma. Tumor forms glands. Compare with Figure 4.

**Figure 4** Grade III adenocarcinoma. Tumor grows in a solid sheet-like pattern and there is no gland formation. Compare with Figure 3.
limited to the head of the polyp; level 2: tumor at the neck of the polyp; and level 4: tumor at the submucosa of the bowel wall below the stalk of the polyp. Using this system, endoscopically removed malignant polyps invading to levels 1 through 3 can be safely treated using polypectomy alone if the tumor is grade I or II and no lymphovascular invasion is present. However, Haggit level 4 cannot be determined from endoscopically removed pedunculated polyps and questions have been raised about the use of this system for sessile polyps.\textsuperscript{12}

**Polyp Configuration**

Whether malignant colorectal polyps with a sessile configuration can be successfully treated with endoscopic removal is controversial. In a review of 31 studies consisting of 1900 cases of endoscopically removed malignant colorectal polyps, Hassan et al.\textsuperscript{11} found that a positive margin was significantly associated ($P < .0001$) with the sessile configuration (56.8%) compared with the polypoid configuration (18.7%). The literature seems to indicate that endoscopically removed sessile malignant polyps and questions have been raised about the use of this system for sessile polyps.\textsuperscript{12}

**Polypoid Carcinoma**

A polypoid carcinoma is a polyp consisting entirely of cancer with no evidence of associated adenoma. The term \textit{polypoid carcinoma} is firmly entrenched in the literature and clinicians are often concerned that it may indicate a more aggressive lesion. Studies have shown that polypoid carcinomas are biologically no more aggressive than adenomas with invasive cancer and can be managed using the same histologic criteria as invasive cancers arising in adenomas.\textsuperscript{3,7,13,19,20}

**New Potential Histopathologic Parameters**

**Depth of Invasion**

Investigators recently measured the actual depth of cancer invasion into the submucosa. Ueno et al.\textsuperscript{16} found a 0% incidence of lymph node metastasis in malignant colorectal polyps that had invaded to a depth of less than 2000 µm, provided that the margin was negative, the cancer was grade I or II, and no lymphovascular invasion was present. Kitajima et al.\textsuperscript{22} reported a 0% incidence of lymph node metastasis in sessile lesions with a depth of invasion less than 1000 µm and pedunculated polyps with a depth of invasion less than 3000 µm, provided no lymphatic invasion was present.

**Tumor Budding**

\textit{Tumor budding} is defined as isolated single cancer cells or small clusters (< 5 cells) at the advancing edge of the cancer. A tumor is positive for budding when 5 or more buds are present per 20× power field.\textsuperscript{16,24} Multivariate analysis has shown that tumor budding is significantly associated with an adverse outcome (lymph node metastasis or local recurrence) in T1 cancers.\textsuperscript{11,14}

Although promising as predictors of adverse outcome in endoscopically removed malignant colorectal polyps, these studies of depth of invasion and tumor budding have included cases that were treated initially with polypectomy or surgical resection. Future studies of patient cohorts who underwent endoscopic polypectomy as initial treatment are needed to validate the significance of these markers.

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\textsuperscript{1} Morson et al.\textsuperscript{6} have specifically commented that the presence or absence of a stalk is largely irrelevant if the margin is negative.

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\textit{Figure 5} (A) Low-power view of lymphovascular invasion (arrows). (B) High-power view showing cancer in a lymphovascular channel lined with endothelial cells.
Pathology of Malignant Colorectal Polyps

The Pathology Report

The pathology report should indicate all relevant and important parameters, including:

1. Whether invasive cancer is present (invasive vs. intramucosal cancer)
2. The status of the resection margin; whether cancer is at or close to (and the distance) the resection margin
3. The presence or absence of lymphatic or venous invasion
4. The histologic grade

Examples of reports include 1) invasive adenocarcinoma grade III arising in the background of a tubulovillous adenoma. The cancer is close to the resection margin (< 1 mm). There is no evidence of lymphovascular invasion. Another example is 2) invasive adenocarcinoma grade II arising in the background of a tubular adenoma. The cancer is more than 1 mm from the resection margin. No lymphatic or venous invasion is present.

Summary

The established histopathologic criteria for managing patients with endoscopically removed malignant colorectal polyps only apply to complete polypectomy (i.e., non-piecemeal). NCCN guidelines recommend that patients be treated with definitive surgical resection when the specimen is fragmented or the margins cannot be readily assessed. If the specimen was received fragmented, the pathology report should indicate this with an added comment that, because of the nature of the specimen, the status of the true resection margin cannot be determined.

Early stage colorectal cancer (pT1) in the form of endoscopically removed malignant colorectal polyps can be successfully treated with endoscopic polypectomy.

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References


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