Adverse Histologic Features in Colorectal Nonpedunculated Malignant Polyps With Nodal Metastasis

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Abstract: Tumor differentiation, lymphovascular invasion, margin status, polyp shape, and size are important parameters of malignant polyps (pT1) indicating possible node metastasis, which justifies a surgery. However, the size, margin, and lymphovascular invasion are often unknown or difficult to assess in a piecemeal polypectomy from a nonpedunculated malignant polyp. The aim of the study was to identify adverse histologic features in nonpedunculated malignant polyps associated with an increased risk of nodal metastasis, which may warrant a colectomy procedure. A total of 24 node-positive and 18 node-negative nonpedunculated malignant polyps and their corresponding subsequent resection specimens from 2005 to 2018 were reviewed. Cases with node metastasis were more often positive for high-grade tumor budding (70.8% vs. 16.7%; $P = 0.0005$), poorly differentiated clusters (54.2% vs. 22.2%; $P = 0.0369$), and both high-grade tumor budding and poorly differentiated clusters (45.8% vs. 11.1%; $P = 0.0160$) compared with controls without nodal metastasis. High-grade tumor budding, poorly differentiated clusters, and combined high-grade tumor budding and poorly differentiated clusters increased the risk of nodal metastasis, with odds ratio of 12.1, 4.1, and 14.3, respectively. Furthermore, nodal metastasis could be seen in subsequent colectomy specimen even in completely excised malignant polyps with adverse histologic features. Our findings indicate that high-grade tumor budding and poorly differentiated clusters are important adverse histologic risk features in predicting lymph node metastatic potential. These histologic features should be reported and it may warrant a colectomy when they are present.

Key Words: colorectal carcinoma, malignant polyp, tumor budding, poorly differentiated clusters, colectomy

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The advent of colonoscopic screening has been associated with a significant reduction of colorectal carcinoma (CRC) incidence and cancer-related mortality through the early detection and removal of adenomatous polyps.[1,2] The adenoma-carcinoma sequence is a well-established and accepted concept of CRC carcinogenesis, and adenomas are the precursors in about 70% of all CRCs.[3] Therefore, it is not surprising that adenomatous polyps sometimes contain areas of early submucosal invasive adenocarcinoma (pT1), namely "malignant polyps," in polypectomy specimens. The shape of adenomatous polyps can be pedunculated or nonpedunculated (sessile/flat). A pedunculated pT1 malignant polyp is often relatively easy to be removed completely through endoscopic polypectomy with <3% risk of incomplete resection. However, incomplete resection rate can be up to 10.8% in nonpedunculated piecemeal resection of pT1 malignant polyps.[4] Because of the potential for incomplete resection after polypectomy and the risk of concurrent or subsequent lymph node metastasis, the management for malignant polyps identified at endoscopic polypectomy (polypectomy alone vs. definitive surgical resection) remains controversial. Much of the decision-making for surgical resection of malignant polyp is based on the previously reported unfavorable pathologic findings including tumor at or near (within 1 mm) the margin, and/or poor tumor differentiation and/or lymphovascular invasion.[5–7] More recent studies have shown that malignant polyp size, tumor budding, poorly differentiated clusters, and depth of submucosal invasion are also important pathologic risk factors to predict lymph node metastasis of pT1 CRCs.[8–12]

However, in daily pathology practice, the size of the polyp, margin status, lymphovascular invasion, or depth of invasion are often unknown or difficult to assess in a piecemeal polypectomy specimen from nonpedunculated (sessile/flat) adenomatous polyps. The evaluation of tumor budding and/or poorly differentiated clusters in a polypectomy specimen can be easily achieved but often overlooked in a regular pathology examination. The aims of this study were (1) to retrospectively review malignant polyps with subsequent surgical colectomy confirmed pT1 invasive adenocarcinoma with or without lymph node metastasis for tumor differentiation, high-grade tumor budding, and poorly differentiated clusters, and (2) to

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asses if these easily recognized pathologic features portend an increase in nodal metastasis potential indicating colectomy.

MATERIALS AND METHODS

The pathology database was searched to identify pT1N0 and pT1N1 or greater (pT1N≥1) CRCs arising from nonpedunculated (sessile/flat) malignant polyps from 2005 to 2018. Patients with previous or synchronous colonic adenocarcinoma, familial adenomatous polyposis, or inflammatory bowel disease were excluded from this study. CRCs arising from pedunculated malignant polyps, sessile serrated adenomas, and malignant polyps with identifiable lymphovascular invasion were also excluded from the study. The pedunculated polyp was defined as the identification of a definite stalk by histologic examination or endoscopic description. Malignant polyps without corresponding subsequent colectomies were excluded and only nonpedunculated (sessile/flat) malignant polyps with corresponding subsequent resection specimens were included in this study.

The nonpedunculated (sessile/flat) malignant polyps and their corresponding subsequent colectomy specimens were reviewed. The cauterized edge/margin status, differentiation grade of the invasive adenocarcinoma, tumor budding, and poorly differentiated clusters of the malignant polyps were reviewed and recorded. The corresponding subsequent colectomy specimens were only reviewed for residual tumor status and lymph node metastasis. Malignant polyps with N0 designation were used as the control group. World Health Organization criteria were used to classify tumor differentiation into low grade (tumors with >50% glandular formation) and high grade (tumors with <50% glandular formation).[13] A positive margin was defined as carcinoma present at the submucosal margin or obscured by cautery artifact or a piecemeal specimen such that completeness of polypectomy could not be accurately assessed. Tumor budding was defined as single to clusters of <5 tumor cells at the tumor invasive front (Fig. 1A). After selecting 1 field where tumor budding was the most intensive, the number of buds was determined by counting the number of tumor buds under an objective lens with a magnification of ×20 (0.785 mm^2). The grade of tumor budding was defined as follows: low grade: 0 to 4 buds and high grade: ≥5 buds.[9,12,14] The poorly differentiated cluster was defined as clusters of ≥5 tumor cells that lacked a gland-like structure at the tumor invasive front[11,12,14,15] (Fig. 1B). After selecting 1 field where poorly differentiated cluster was the most intensive, the number of tumor cell clusters was determined by counting the tumor cell clusters under an objective lens with same magnification as tumor budding. The grade of poorly differentiated cluster was defined as follows: low grade: 0 to 4 tumor cell clusters and high grade: ≥5 tumor cell clusters.

A χ^2 analysis or the Fisher exact test was used to characterize the relationship between categorical variables and to calculate odds ratio and *P*-values. Sensitivity and specificity were calculated for different morphologies and their combinations.

RESULTS

Clinical Characteristics of Malignant Polyps

A total of 42 nonpedunculated (sessile/flat) malignant polyps with corresponding subsequent resection specimens were identified (Table 1). Of the 42 cases, 24 cases (11 female:13 male, average age, 62 y) showed lymph node metastasis (node-positive) with pN1 in 22 cases and pN2 in 2 cases. Eighteen cases (11 female:7 male, average age, 68 y) without lymph node metastasis (pN0, node-negative) were identified as the control group. Malignant polyps with lymph node metastasis (pN≥1) were more commonly seen in the left colon compared with pN0 control group, but there was no statistical difference (17/24, 71% vs. 9/18, 50%; $P=0.2097$). Positive margins were present in 18 (75%) of the 24 nodal positive and 15 (83.3%) of the 18 nodal negative malignant polyps ($P=0.7083$). Of note, 6 of the malignant polyps in the nodal positive group showed lymph node metastases, although

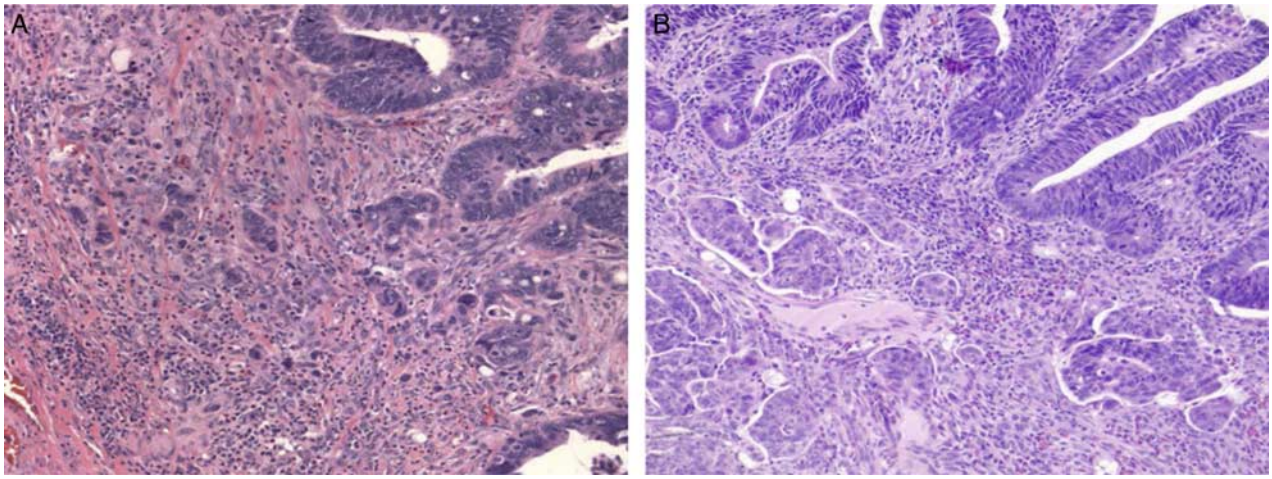

FIGURE 1. Malignant polyp. A, Malignant polyp with high-grade tumor budding and poorly differentiated clusters are also seen (hematoxylin and eosin). B, Malignant polyp with high-grade poorly differentiated clusters (hematoxylin and eosin).

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TABLE 1. Clinical Features of Nonpedunculated Malignant Polyps

			n (%)					
	N = 42, n (%)	Age (y)	Female	Male	Left Colon	Right Colon	Positive Margin	No Residual Tumor in Colectomies
pT1N0	18 (42.9)	68 (48-84)	11 (61.1)	7 (38.9)	9 (50)	9 (50)	15 (83.3)	2 (11.1)
pT1 N≥1	24 (57.1)	62 (40-82)	11 (45.8)	13 (54.2)	17 (70.8)	7 (29.1)	18 (75)	6 (25)

there were no residual tumors in subsequent colectomy specimens (Table 1).

Pathologic Features of the Invasive Adenocarcinoma in the Malignant Polyp

As seen in Table 2, of the node-positive malignant polyps, the invasive adenocarcinomas were low grade in 87.5% (21/24) of the cases. Of the node-negative malignant polyps, the invasive adenocarcinomas were all low grade (18/18). There was no statistical difference in tumor differentiation grade between node-positive and node-negative malignant polyps ($P = 0.1196$). As compared with the node-negative malignant polyps, node-positive malignant polyps showed significant high-grade tumor budding (17/24, 70.8% vs. 3/18, 16.7%; $P = 0.0005$). Similarly, node-positive malignant polyps showed a significantly higher number of high-grade poorly differentiated clusters (13/24, 54.2% vs. 4/18, 22.2%; $P = 0.0369$). Of the malignant polyps with high-grade poorly differentiated clusters, 84.6% (11/13) of them were associated with high-grade tumor budding. Malignant polyps with nodal metastasis were more often positive for both high-grade tumor budding and poorly differentiated clusters (11/24, 45.8% vs. 2/18, 11.1%; $P = 0.0160$) compared with controls without lymph node metastasis. Prior studies have shown that cribriform architectural pattern is one of the adverse histologic features in pT1 CRCs associated with lymph node metastasis.[8,12] However, there was no significant difference in the presence or absence of cribriform architectural pattern in malignant polyps with or without nodal metastasis (15/24, 62.5% vs. 9/18, 50%; $P = 0.5328$). Of the 24 node-positive malignant polyps, 21 had mismatch repair protein status assayed by immunohistochemical stains (MLH1, PMS2, MSH2, and MSH6) showing that 19 (90.5%) demonstrated intact expression indicating microsatellite stable and 2 (9.5%) demonstrated loss of expression (both were MLH1 and PMS2 loss) indicating microsatellite instability (MSI)-high. Of the 18 node-negative malignant polyps, 17 had mismatch repair protein status assayed by immunohistochemical stains and 1 had MSI status assayed by polymerase chain reaction showing that 13 (72.2%) were microsatellite stable and 5 (27.8%) were MSI-high. There was no significant difference regarding the MSI of malignant polyps with or without lymph node metastasis ($P = 0.2155$).

Pathologic Features of the Invasive Adenocarcinoma in the Malignant Polyp Associated With Nodal Metastasis

We have shown above that malignant polyp with nodal metastasis were more often positive for high-grade tumor budding, high-grade poorly differentiated clusters, and both high-grade tumor budding and poorly differentiated clusters compared with malignant polyps without nodal metastasis. We next performed logistic regression analysis to correlate these adverse histologic features with the risk of lymph node metastasis. Of the malignant polyps with high-grade tumor budding, high-grade poorly differentiated clusters, and both high-grade tumor budding with high-grade poorly differentiated clusters, there were significant increases of the risks of lymph node metastasis, with odds ratio of 12.1 (2.747 to 45.89), 4.14 (1.121 to 13.72), and 14.3 (2.571 to 74.26), respectively. The sensitivity, specificity, positive, and negative predictive values of these 2 histologic features and combination to predict lymph node metastasis is seen in Table 3.

DISCUSSION

For several decades, since the advent of colonoscopy, the question has arisen of how to manage a colonic malignant polyp containing a component of invasive adenocarcinoma. The main consideration is the risk of concurrent lymph node metastasis, and thus the need for subsequent colonic resection of the involved colonic segment and removal of the regional lymph nodes. Studies from the 1980s and 1990s have proposed 3 histologic criteria with predictive value for lymph node metastasis in malignant polyps including positive margin, poor tumor differentiation and lymphovascular invasion.[6,16–21] On the basis of the early years' data, these criteria are widely accepted and followed by many pathologists, endoscopists, oncologists, and surgeons to warrant a colectomy in a patient

TABLE 2. Pathologic Features of Malignant Polyp

	n (%)											
	Tumor Grade		TB		PDC		TB+PDC		Cribriform		MSI	
	Low	High	Low	High	Low	High	No	Yes	No	Yes	MSI-High	MSS
pT1N0	18 (100)	0 (0)	15 (83.3)	3 (16.7)	14 (77.8)	4 (22.2)	16 (88.9)	2 (11.1)	9 (50)	9 (50)	5 (27.8)	13 (72.2)
pT1 N≥1	21 (87.5)	3 (12.5)	7 (29.2)	17 (70.8)	11 (45.8)	13 (54.2)	13 (54.2)	11 (45.8)	9 (37.5)	15 (62.5)	2 (9.5)	19 (90.5)
P	0.1196		0.0005		0.0369		0.0160		0.5328		0.2155	

MSS indicates microsatellite stable; PDC, poorly differentiated clusters; TB, tumor budding.

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TABLE 3. Adverse Pathologic Features for Lymph Node Metastasis in Malignant Polyps

	High-TB (%)	High-PDC (%)	TB+PDC (%)
Odds ratio	12.14 (2.747-45.89)	4.14 (1.121-13.72)	14.30 (2.571-74.26)
Sensitivity	83.3	77.8	86.7
Specifity	70.8	54.2	68.8
PPV	68.2	56.0	72.2
NPV	85	76.5	84.6

NPV indicates negative predictive value; PDC, poorly differentiated clusters; PPV, positive predictive value; TB, tumor budding.

with a malignant polyp. In recent years, many studies have identified the quantitative depth of submucosal invasion as a potential predictor of lymph node metastasis in early CRCs and malignant polyps.[22] A "level" system, dividing the submucosa into upper (sm1), middle (sm2), and lower (sm3) thirds, and even an absolute depth of invasion measurements have been proposed.[23–25] These adverse histologic factors are ideal to evaluate a complete intact endoscopic excision specimen or a pedunculated polyp with stalk. However, in reality, many malignant polyps are nonpedunculated (sessile/flat) and an intact endoscopic excision cannot be achieved. The specimens are often received piecemeal for pathologic examination and the depth of invasion, margin status, and lymphovascular invasion cannot be accurately assessed. In the current study, near 80% (33/42) of the malignant polyp cases received for histologic evaluation showed tumor present in at least one of the cauterized edges/margins or obscured by cautery artifact. Furthermore, lymph node metastases were identified in malignant polyps, even when there were no residual tumors in subsequent colectomy specimens. These findings indicate that a piecemeal polypectomy specimen with at least 1 positive cauterized edge/margin or margin status obscured by cautery artifact is not uncommon, and lymph node metastasis can be seen in a malignant polyp which has been completely excised through polypectomy. Thus, finding and using other adverse histologic features in these malignant polyps can aid to decide further management with endoscopic excision alone or a surgical colectomy.

Tumor budding is a recognized prognostic factor in CRCs and many other tumors. Tumor budding reflects a complex interplay between tumor cells and extracellular matrix. It is believed that tumor budding represents the initial phase of tumor invasion and is a "surrogate indicator" of the ability of the cancer cells to detach from the main tumor, infiltrate the extracellular matrix, penetrate the lymphatic vessels to reach the regional lymph nodes and portend a poor prognosis.[26] Sohn et al[27] showed that tumor budding was highly predictive of lymph node metastasis (14.6%) with an odds ratio of 69.5 in cases of pedunculated or semipedunculated submucosal invasive CRCs. In a large meta-analysis of assessing the prognostic value of tumor budding in pT1 CRCs, encompassing 41 studies with a total of 10,137 patients, Cappellesso et al[10] reported that tumor budding was significantly associated with lymph node metastasis in pT1 CRCs, with an odds ratio value of 6.44. The findings in our current study through evaluation of the nonpedunculated malignant polyps are consistent with previous studies and tumor budding should be histologically reported in any endoscopically removed malignant polyps to direct more appropriate patient management. The most recent American Gastroenterological Association (AGA) guidelines for early CRCs has adopted and advocated the evaluation and reporting of tumor budding in all endoscopic resection specimens by an expert gastrointestinal pathologist.[2]

Similarly, while poorly differentiated clusters are closely associated with poor prognosis in CRCs, the presence of poorly differentiated clusters was also identified as an independent risk factor for nodal metastases in early pT1 CRCs.[11] Although poorly differentiated clusters and tumor budding are distinguished by being defined as ≥ 5 and <5 tumor cells, the 2 entities likely belong in the same spectrum of dedifferentiated biological features.[28] Micropapillary carcinoma, a subtype of CRC, has been reported as an aggressive variant of carcinoma associated with frequent lymphovascular invasion and poor outcome.[29–31] Studies have shown that micropapillary pattern and poorly differentiated clusters represent the same biological phenomenon as tumor budding in CRCs,[32,33] and thus counting micropapillary pattern as poorly differentiated clusters have been proposed.[34] Although many studies have demonstrated the poor tumor differentiation based on World Health Organization grading system is one of the adverse histologic features to predict lymph node metastasis in pT1 CRCs, our current study does not show correlation of tumor differentiation with or without lymph node metastasis. The reason for this is possibly due to the limited sample size or the piecemeal specimens from endoscopic malignant polyp which may not represent the entire invasive carcinoma component. However, consistent with prior studies, our findings confirmed the close relationship of the presence of poorly differentiated clusters and lymph node metastasis in malignant polyps. Furthermore, in view of the World Health Organization grading system, grading of CRC based on the counting of poorly differentiated clusters more likely reflects the biological aggressiveness of the tumor and more accurately predicts prognosis.[35,36] Accordingly, grading CRC based on the number of poorly differentiated clusters has been proposed.[35,37] Konishi et al[28] demonstrated that grade of poorly differentiated clusters and tumor budding were strongly correlated. In our current study we also found the close relationship between poorly differentiated clusters and tumor buddings: 84.6% of the malignant polyps with high-grade poorly differentiated clusters were associated with high-grade tumor budding, and malignant polyps with nodal metastasis were more often positive for both high-grade tumor budding and high-grade poorly differentiated clusters compared with controls without nodal metastasis. As the similarity of poorly differentiated clusters and tumor budding, it seems rather arbitrary to use a cutoff of 5 cancer cells per cluster to define whether it is tumor budding or poorly differentiated clusters, proposals that tumor budding or poorly differentiated clusters could

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potentially be combined as a novel dedifferentiation marker at the invasive front in CRCs.[14,28] Our prior study[38] and current findings support the notion of this combination. Malignant polyps with both tumor budding and poorly differentiated clusters showed higher odds ratio in predicting lymph node metastasis comparing to the presence of tumor budding or poorly differentiated clusters alone.

The present data exhibit some limitations. The first is that this is a retrospective study. More comprehensive prospective studies are required to assess these adverse histologic features in malignant polyps. A second limit is that only malignant polyps with subsequent colectomies were included in this study. Cases with adverse histologic features such as high-grade tumor budding or poorly differentiated clusters but without subsequent colectomy, or cases with well-differentiated carcinoma, negative margin, and absence of lymphovascular invasion, but unknown status of tumor budding or poorly differentiated cluster and without subsequent colectomies were not included in this study. The selection bias of cases in this study may skew the results. The third weakness is that the number of cases in this study is small, a multi-institutional larger cohort will better define the risk of adverse histologic features in predicting lymph node metastasis.

In summary, our data showed nodal metastasis can be seen in nonpedunculated polyps with both low-grade and high-grade tumor differentiation in the absence of knowledge of polyp size, orientation, depth of submucosal invasion, and lymphovascular invasion, as well as completely excised malignant polyps with adverse histologic features. High-grade tumor budding and poorly differentiated clusters are important adverse histologic risk factors in predicting lymph node metastatic potential. These adverse histologic features should be evaluated and reported, and a colectomy procedure may be warranted especially when both histologic risk features are present.

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