

ADENOCARCINOMA IN COLONIC ADENOMAS: DIAGNOSIS AND MANAGEMENT

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Carefully done autopsy studies have shown that the frequency of adenomas is approximately 50% for males and 40% for females in the United States.²⁰ Endoscopic series of colorectal adenomas generally report a lower prevalence of 20-30%.^{6,22} Either way, they are common. Endoscopically resected adenomas have an approximately 5% probability of containing a focus of adenocarcinoma upon histologic examination (Table 1).

TABLE 1: PREVALENCE OF CARCINOMA IN ADENOMAS

| <i>Senior Author</i> | <i>Type of Study</i> | <i>% Adenomas with Carcinoma</i> |
|------------------------|----------------------|----------------------------------|
| Muto ¹⁸ | Surgical | 11 |
| Gillespie ⁶ | Endoscopic | 5 |
| Shinya ²² | Endoscopic | 5 |
| Rickert ²⁰ | Autopsy | 1 |

The literature contains many references to villous adenomas having a higher “malignant potential” than tubular adenomas. Because the original source of this concept came from the world-renowned authority in gastrointestinal pathology, Dr. Basil C. Morson, it became dogma. Dr. Morson’s meaning was that a villous adenoma itself rather than the rest of the patient’s colon is more likely to harbor a focus of carcinoma than a tubular adenoma. Unfortunately, this concept of villous adenomas having a “higher malignant potential” has been misinterpreted to mean that these patients are more likely to have a colorectal carcinoma elsewhere in their colon or are more likely to develop one in their future. The composite literature provides no consensus. Table 2 summarizes data from six different studies analyzing factors that predict an increased risk of developing a future adenoma or carcinoma.

Grade of dysplasia and villous architecture, in particular, lack reproducibility as prognostic features. This relates at least in part to observer variability for these subjective aspects of adenomatous polyps. This further diminishes their utility. One study gained considerable attention regarding the prognostic utility of grade and villous change: that of Atkin et al. from the St. Marks Hospital in London published in the *New England Journal of Medicine*.¹ Their data were not confirmed by prior studies from the same institution (TABLE 2) and this discrepancy was not even mentioned in the Atkin study. Thus, even within one institution, grade and villous change are not reproducible prognostic factors. If anything, size in excess of one centimeter and multiplicity of adenomas are the only factors that seem to have achieved any degree of consensus as

predictors. Based on these data, neither routine grading of dysplasia in colonic adenomas nor their classification as tubular or villous is supported by the composite literature.

TABLE 2: PROGNOSTIC FACTORS FOR FUTURE ADENOMA/CARCINOMA

| <i>Study</i> | <i>Age >60</i> | <i>Size >1cm</i> | <i>Villous or Tubular</i> | <i>Grade of Dysplasia</i> | <i>Number</i> |
|--|-----------------------|-------------------------|-------------------------------|-------------------------------|---------------|
| Morson, 1984 ¹⁶ | NE | + | NE | NE | + |
| Neugut, 1985 ¹⁹ | + | - | - | - | - |
| Lofti, 1986 ¹² | - | - | - | NE | + |
| Williams (St. Marks), 1986 ²⁶ | + | + | - | - | + |
| Atkin (St. Marks), 1992 ¹ | - | + | + | + | + |
| Natl. Polyp Study, 1993 ²⁸ | + | + | - | - | + |

NE = not evaluated

STEPS IN THE MANAGEMENT OF AN ENDOSCOPICALLY RESECTED ADENOMA CONTAINING CARCINOMA

Confirm the Diagnosis of Adenocarcinoma

The first and most important step in managing a patient with an endoscopically resected lesion is a correct diagnosis of invasive carcinoma. This may be challenging because “pseudo-carcinomatous” invasion, or misplaced epithelium within the submucosa or even deeper, is fairly common in colonic adenomas.^{7,17,23} This must be distinguished from adenocarcinoma invading the submucosa (Table 3). Misplaced epithelium is a benign phenomenon that most commonly occurs in large, pedunculated, sigmoid colonic polyps. It is clinically insignificant if the adenoma has been completely excised. In contrast, the presence of submucosal invasion is the diagnostic hallmark of colonic adenocarcinoma with its attendant risk of lymph node or distant metastasis.^{4,9,27} In the colon, in contrast to the esophagus and stomach, there is no risk of metastasis until carcinoma has invaded into the submucosa.^{4,9} Thus, intramucosal epithelial neoplasms of the colon are biologically benign. Because of this, most GI pathologists restrict the term “carcinoma” in the colon to lesions that have invaded into the submucosa. As advocated by the World Health Organization, the terms “carcinoma in-situ” and “intramucosal carcinoma” should be avoided. Use of this terminology in the colon may precipitate unwarranted colectomy for what are biologically benign lesions that are curable by complete endoscopic polypectomy alone. In addition, the diagnosis of carcinoma has strong psychological content for patients and may erroneously impact their insurability.

Regardless of these definitional issues for adenocarcinoma of the colon, it can frequently be challenging to distinguish between benign misplaced epithelium within the submucosa or deeper and adenocarcinoma invading the submucosa or deeper.^{7,17,23} The most useful histologic features in this differential are: 1) the rounded appearance of the glands on low power in benign, misplaced epithelium vs. the irregular, angulated and infiltrative appearance of invasive adenocarcinoma; and 2) the presence of lamina propria surrounding the dysplastic glands in misplaced epithelium vs. the characteristic

desmoplastic stroma that develops in response to submucosal invasion of colonic adenocarcinoma. This second feature is the more important criterion. Direct comparison of obvious benign lamina propria in a given polyp to any potential desmoplastic stroma may be very helpful. The appearance of lamina propria will vary from patient to patient and even from different colonic locations within the same patient, and so too will desmoplasia, so that direct internal comparison provides valuable information and in the great majority of cases will permit this distinction.

Both of the above listed features (glandular architecture and stroma) may be obscured by cautery artifact, inflammation, erosion and ulceration. The orderly and grouped appearance of the glands may be disrupted by these confounders, as may the nature of the surrounding stroma, which usually appears more cellular and desmoplastic-like with cautery or erosion/ulceration. An important aide to differentiating ulcer stroma from true desmoplasia is stromal vascularity. Ulcer stroma is granulation tissue composed in large part of capillaries. True desmoplasia on the other hand is usually hypovascular.

In addition to the above two main criteria in the differential of benign versus malignant, hemosiderin deposits and dense collagen tend to be common in association with benign misplaced epithelium and are very unusual if only invasive adenocarcinoma is present. Hemosiderin deposition and fibrosis are probably related to chronic trauma and torsion of the polyp stalk with associated hemorrhage and herniation of epithelium into the submucosa. Benign misplaced epithelium is most common in large, pedunculated sigmoid adenomas, probably because of the increased likelihood of stalk formation in and torsion of polyps from this region of the colon, due to the more solid nature of the stool here in comparison to the more proximal colon.

Benign misplaced epithelium, as well as invasive adenocarcinoma, may both be associated with acellular mucin pools within the submucosa (Table 3). As a practical rule, acellular mucin collections in these lesions have the same biologic significance as the associated epithelium. That is, if the associated epithelium consists of benign misplaced glands with accompanying lamina propria, then the mucin pools are also benign. If the associated epithelium is that of invasive adenocarcinoma, then the mucin pools should be regarded as part of the malignant process.^{5,7,9,17,23}

TABLE 3: CARCINOMA VERSUS BENIGN MISPLACED EPITHELIUM

| <i>Feature</i> | <i>Misplaced Epithelium</i> | <i>Adenocarcinoma</i> |
|-----------------------------------|-----------------------------|-----------------------|
| Lamina propria around glands | + | - |
| Desmoplasia around glands | - | + |
| Hemosiderin & dense fibrosis | + | - |
| Mucous lakes | + | + |
| High-grade dysplasia | + | + |
| Rounded low power appearance | + | - |
| Infiltrative low power appearance | - | + |

Benign misplaced epithelium may develop in gastrointestinal tract pathologies other than adenomatous polyps. These include Peutz-Jeghers' polyps, inverted hyperplastic polyps, colitis cystica profunda in association with idiopathic inflammatory bowel disease or radiation-induced injury, solitary rectal ulcer syndrome, and other forms of gastrointestinal prolapse.^{5,23} It should be noted that benign misplaced epithelium, with or without associated acellular mucin pools, may rarely extend beyond the submucosa to involve deeper wall structures, including the muscularis propria and even into the pericolonic adipose tissue.

The subsequent steps after determining that there is true submucosal invasion are discussed in detail below. Briefly, the pathologist also evaluates the depth of the invasion within the polypectomy specimen. A histologic grade is assigned and the lesion is scrutinized for evidence of lymphatic or blood vessel invasion. The completeness of resection is then evaluated by noting the status of the margin and finally, an estimate of the risk of metastasis can be provided through synthesis of these composite microstaging data (see below).

Determine Depth of Invasion

Nodal metastasis from a carcinoma in which the invasion extends into the submucosa of the head of a pedunculated polyp or at any level into the stalk is *extremely* rare, certainly less than 1%.^{9,24} The probability of nodal metastasis becomes significant only with invasion into the submucosa of the bowel wall proper (Table 4), as occurs in sessile lesions or in pedunculated lesions with invasion beyond the stalk.^{9,24} The data shown in Table 4 suggest that the overall risk of nodal metastasis is approximately 5% when invasion is limited to the submucosa of the bowel wall itself (i.e., the average of 11%, 0% and 6.5%) and the lesion has been completely excised.^{8,13,15}

TABLE 4: DEPTH OF INVASION AND PREVALENCE OF POSITIVE LYMPH NODES

| <i>Author No.</i> | Morson ¹⁵ (2084) | Minsky ¹³ (168) | Grigg ⁸ (268) |
|--------------------------|--------------------------------|-------------------------------|-----------------------------|
| <i>Depth of Invasion</i> | <i>% Positive Lymph Nodes</i> | | |
| Submucosa | 11 | 0 | 6.5 |
| M. propria | 12 | 28 | --- |
| Through m.p. | 58 | 39 | --- |

All rectal cancers; all resected by LAR or APR

Determine Histologic Grade & Angiolymphatic Invasion

High-grade or poorly differentiated tumors are more likely to have lymph node metastases than well or moderately differentiated lesions.^{2,7,24} The exact percentage with nodal metastases is difficult to determine because of the small numbers of endoscopically

resectable cases that are poorly differentiated and because of frequent confounding factors such as synchronous angiolymphatic invasion or invasion into the submucosa of the bowel wall. If invasion of vessels or lymphatic channels is present, there is also a higher probability of positive nodes,¹⁴ but likewise the confounding presence of a poorly-differentiated tumor makes this difficult to assess independently.^{2,9,14,24} Nonetheless, based on limited data in endoscopic polypectomy specimens, both factors appear to increase the risk of nodal metastasis and are indicators for colectomy in the absence of mitigating clinical circumstances. The degree to which they increase the risk remains unknown due to limited case numbers.

Endoscopic Completeness of Resection

The status of the polypectomy margin, as an index of prognosis, is controversial. Morson found that if the polypectomy margin was free of the tumor, *regardless of the distance from the neoplasm to the electrocautery margin, the prognosis was uniformly favorable. When the carcinoma extended to the electrocautery margin, but when the endoscopist thought that the lesion was completely resected, the prognosis was again favorable.*¹⁶ This probably reflects the destruction of an additional zone of 0.2-0.3 cm of tissue by electrocautery within the patient beyond what is resected and processed by the pathologist. In contrast, when the endoscopist thought that the excision was incomplete or questionable, the prognosis was less favorable.¹⁶

In addition to the extension of the margin by cautery tissue destruction, the endoscopist also sees the lesion in 3-dimensions, both before and after polypectomy, so that the endoscopist knows if gross lesion remains behind. Furthermore, this information is virtually never disclosed to the pathologist! Thus, the pathologist may state that a lesion is resected based on the histologic appearance of the sample received, when in fact the sample was only a small portion of the lesion and the endoscopist is fully aware that a larger lesion remains in the patient. In marked contrast to the endoscopist's macroscopic 3-dimensional view, the pathologist sees only a tiny fraction of the lesion's margin, and essentially in only 2-dimensions via relatively few 5 µm thick microscopic slices through the margin which in reality is many millimeters or even centimeters in thickness. Thus, based on the enormous sampling limitations of the histologic view, it can virtually *never* be stated with histologic certainty that the lesion has been completely resected. It is the endoscopist's opinion on this matter that should determine this favorable or unfavorable status of the margin, not the pathologist's.

Unfortunately, few studies of endoscopically resected adenomas with adenocarcinomas even comment on the *endoscopist's* assessment of the completeness of excision. Instead, some have suggested that histologic extension of the carcinoma to within 0.1 or 0.2 cm or less of the margin is an unfavorable prognostic sign.^{2,24} Utilization of this criterion as an indication for colectomy of course produces a favorable outcome because the probability of nodal metastasis is distinctly low in this subset of individuals. As has already been discussed, the risk of nodal metastasis is only <1% to ~5% for these lesions without angiolymphatic invasion or poor differentiation (see above). If one uses extension of the tumor to within 0.2 cm or less of the margin (or actually to within any arbitrary distance) as a criterion for resection, one increases the resection rate to an unacceptably high level,

in the opinion of this author. Thus, careful communication with the endoscopist concerning the status of the margin is mandatory in planning the optimal management for a patient with carcinoma arising in an adenoma. If the endoscopist thinks the lesion is completely resected, this is almost always the case. If there is any concern that an endoscopically respectable lesion may not have been completely resected, then additional endoscopic resection or biopsies at the site and/or endoscopic ultrasound may prove helpful.

As a practical matter, this author never provides measurements concerning the resection margin in an endoscopically resected adenoma with adenocarcinoma, but rather only provides one of two comments on this issue: either that the lesion *appears completely resected*, or that the *completeness of resection cannot be assessed histologically*. The latter commentary is used if carcinoma is either at the cauterized resection margin, or for polyps resected in a piecemeal fashion such that the true margin cannot be known histologically. *In either case, a statement is also provided that the endoscopist's opinion on the completeness of resection is more important than the pathologist's.*

SUMMARY OF FACTORS THAT APPEAR TO INCREASE THE PROBABILITY OF NODAL METASTASES

Unless there is invasion into the submucosa of the underlying bowel wall, incomplete excision, poor differentiation or angiolymphatic invasion, surgery is not indicated because of the low risk of nodal metastasis (<1%) that could potentially be cured by a resection.^{9-11,24,27} Authorities are in uniform agreement that pedunculated lesions of this type are adequately treated by endoscopic resection alone.

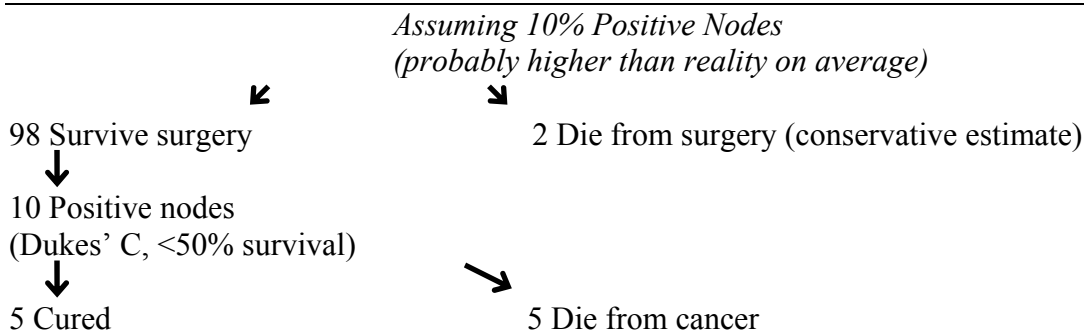
In fact, the risk of nodal metastasis is low enough (~5%), that even with invasion into the submucosa of the underlying bowel wall (in sessile lesions mostly), an argument can also be made for not pursuing surgical resection if the tumor has been completely removed endoscopically (see Tables 5 and 6). Thus, the risk of nodal metastasis must be weighed against the risk of operative morbidity and mortality from a segmental colectomy with nodal dissection. The mortality risk is not unappreciable and averages between 2% to almost 7%.^{3,21,25} The mortality risk of colorectal cancer surgery rises significantly with increasing patient age, as determined from the Nationwide Inpatient Sample for all patients undergoing colorectal cancer surgery during 1997 (N=20,862).³ In this database, age-stratified mortality was: age <50, 0.8%; age 50-65, 1.3%; age 66-80, 2.9%, and age >80, 6.9%.³ Surgical mortality is also greater with low-volume surgical centers or surgeons relative to high-volume centers or surgeons.^{3,21}

The final factor to be considered in the overall risk assessment and management plan, in addition to microstaging data and operative mortality, is that patients who are discovered to have positive lymph nodes, namely those with Dukes' C adenocarcinoma, have a cure rate of 50% or less even with surgery (see Tables 5 and 6).

If surgery is pursued for a completely endoscopically resected adenocarcinoma that is well to moderately differentiated and without angiolymphatic invasion, then all parties

must be aware of the high probability (95-99%) that nothing will be found in the resection specimen.

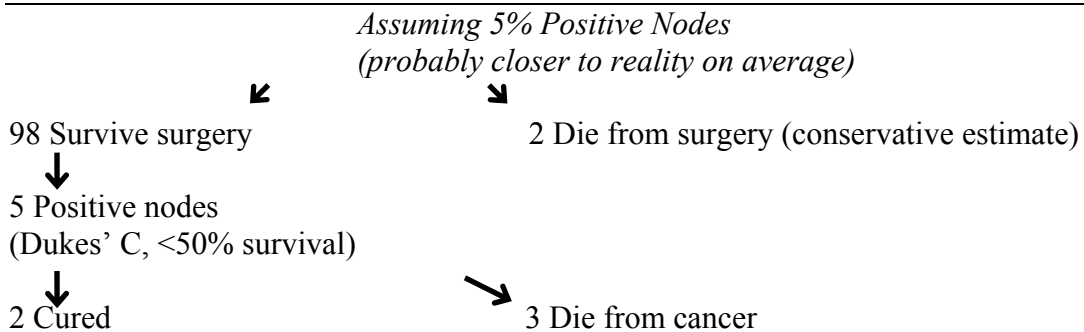
**TABLE 5: SESSILE CARCINOMA WITH SUBMUCOSAL WALL INVASION
100 PATIENTS -- SURGICAL RESECTION**



THUS

100 operations, 5 patients cured
7 Dead - 2 from surgery, 5 from cancer
10 would have died if no operations done

**TABLE 6: SESSILE CARCINOMA WITH SUBMUCOSAL WALL INVASION
100 PATIENTS-- SURGICAL RESECTION**



THUS

100 operations, 2 patients cured
5 Dead - 2 from surgery, 3 from cancer
5 would have died if no operations done

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