Polyps and Neoplasms of The Colorectum – Rapid Fire Cases and “Cancer in a polyp”

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Disclosure Statement
Dr. Montgomery reports no relevant financial relationships with commercial interests.

Lots of cases quickly
Colon biopsies of colon polyps and neoplasms are common and we will review many such samples rapidly:
Let’s review a number of images of polyps that we see in practice

Comparing Solitary Rectal Ulcer and Peutz Jeghers Polyp

Solitary rectal ulcer syndrome, polyoid phase. Glands are angular and separated by lamina propria, which contains smooth muscle bundles.
Comparing Solitary Rectal Ulcer and Peutz Jeghers Polyp

Mucosal prolapse. These lesions may appear grossly polypoid, as in this example.

Mucosal prolapse. Smooth muscle ingrowth into the lamina propria separates glands into lobules. Some crypts appear distorted and diamond-shaped.

Mucosal prolapse. Smooth muscle ingrowth into the lamina propria separates glands into lobules. The epithelium often shows serrated features, as in this example.
Another Odd One

Cap polyposis (not hereditary – cause unknown)
A type of mucosal prolapse syndrome
Mucoid bloody diarrhea, multiple polyps covered with caps of inflammatory exudate
Female predominance, 5-6th decade of life
Surgery sometimes needed to control symptoms

Cap polyposis. These polyps are characterized by hyperplastic epithelium with abundant surface mucus and exudate.
Tubular adenoma with clear cell change. This change bears no clinical significance.

Adenocarcinoma with areas of clear cell change. Though areas of clear cell change are of no clinical consequence in adenomas, they may inform some of the variation in the appearances of invasive carcinomas.

Tubular adenoma with squamous morules ("microcarcinoids"). Morule formation in a tubular adenoma with prolapse change (pseudoinvasion). Some of the glands show associated morules and there is hemosiderin in the center of the field.

Tubular adenoma with squamous morules. Some observers regard these as "microcarcinoids." They express both CK5/6 and endocrine markers in some cases.
Invasive carcinoma with squamous differentiation. Though squamous morules are of no clinical consequence in adenomas, they may inform some of the variation in the appearances of invasive carcinomas.

Invasive carcinoma with squamous differentiation. Note areas of squamous epithelium "budding" off adenomatous glands.

Tubular adenoma in a patient with hereditary non-polyposis colorectal carcinoma. Note the prominent intraepithelial lymphocytes and paucity of apoptotic bodies.

Colonic adenoma with pseudoinvasion. This adenoma has striking epithelial misplacement (prolapse change) with a large zone of misplaced glands in the submucosa. These glands show associated hemorrhage and lamina propria hemosiderin deposition.

Colonic adenoma with pseudoinvasion. In this example a misplaced gland with associated lamina propria also displays striking mucin dissection into the surrounding submucosa. This is not a feature of invasive carcinoma.
Colonic adenoma with pseudoinvasion. This image shows mucin extrusion into the connective tissue at the upper right and abundant hemosiderin deposition. Note that there is a small amount of residual lamina propria that has accompanied the glands, which is evident at the bottom towards the right of the field.

Colonic adenoma with pseudoinvasion. Large, round adenomatous glands are seen here within the submucosa. Note an area of dissecting mucin on the left side of the field. A small amount of associated lamina propria is evident at this power.

Colonic adenoma, gross image. Cut surface reveals the gross appearance of areas of submucosal pseudoinvasion.

Colonic adenoma with pseudoinvasion. This is the same case depicted above showing areas of submucosal pseudoinvasion. Pools of mucin correlate with the glistening cut surface.

Colonic adenoma with pseudoinvasion. Giant pools of mucin are seen here associated with herniated neoplastic glands within the submucosa.

Colonic adenoma with pseudoinvasion. This higher magnification shows that the epithelium of the herniated glands is cytologically similar to that of the adenoma in the mucosa.
Colonic adenoma with pseudoinvasion and associated high grade dysplasia. This area of pseudoinvasion has rounded contours and is associated with considerable hemorrhage and hemosiderin. An area of high grade dysplasia with cribiforming architecture is evident in the center of the field.

Adenoma with high grade dysplasia. This focus is found in the lamina propria. There is cribiform architecture and a syncytial arrangement of the glands. Even if there is microscopic invasion into the lamina propria, such invasion in the colon is believed to lack lymphatic access and therefore is biologically regarded as an in situ lesion.

Colonic mucosa, CK7 immunostain. Reactive, non-neoplastic colonic mucosa is often immunoreactive with CK7. Colorectal carcinomas are typically CK7 negative. This case is from a patient with prostatic cancer with extension into the rectum. Single CK7 positive cells seen on the left part of the field are the prostate cancer cells.

Colonic carcinoma with a medullary growth pattern. This syncytial growth pattern with pushing borders is one of the histopathologic features suggesting microsatellite instability in colorectal tumors.
Colonic adenocarcinoma with abundant mucin. This is one of the histologic features suggestive of microsatellite instability. This particular case occurred in a patient with Muir-Torre syndrome, a variant of Lynch syndrome.

Sebaceous carcinoma in a patient with Muir-Torre syndrome. These patients manifest sebaceous neoplasms and microsatellite unstable colorectal cancers.

### Muir-Torre Syndrome

- AD
- Sebaceous neoplasms and keratoacanthomas
- GI (61%) and GU (22%) adenocarcinoma
- Multiple adenomas of GI tract
- Mutations of MSH2 or MLH1 genes (DNA mismatch repair genes)
Rectal well differentiated neuroendocrine (carcinoid) tumor (WDNET). The tumor grows in cords, similar to neuroendocrine neoplasms in other organs.

Rectal well differentiated neuroendocrine tumor (WDNET). A chromogranin immunostain highlights the neoplastic cells in this WDNET.

Rectal well differentiated neuroendocrine tumor (WDNET). These tumors may be positive with prostatic acid phosphatase (PAP), as was this example.
Rectal well differentiated neuroendocrine tumor (WDNET). This particular example was immunoreactive with prostatic acid phosphatase (PAP), a potential pitfall when rectal invasion from known prostatic carcinoma is a consideration.

Rectal well differentiated neuroendocrine tumor (WDNET) showing immunoreactivity with synaptophysin.

This low power image shows lymphoid cells mimicking a well differentiated neuroendocrine tumor (WDNET).

CD45/LCA
Well differentiated neuroendocrine tumor (WDNET) (right) arising in association with a tubular adenoma (left) - = SUPER RARE.

Neuroendocrine carcinoma, G3, large cell type. Note areas of prominent lumen formation, a common occurrence in large cell neuroendocrine carcinomas.

Neuroendocrine carcinoma, G3, large cell type. Note vesicular chromatin pattern, evident nucleoli, abundant cytoplasm, lumen formation, and mitotic activity.

Neuroendocrine carcinoma, G3, small cell type. Small cell neuroendocrine carcinoma tends to grow in sheets, as in this case. Large cell neuroendocrine carcinoma commonly shows a nesting pattern.

Neuroendocrine carcinoma, G3, large cell type. Note lumen formation, prominent nucleoli, and mitotic activity. Note also the adenomatous precursor.

Low-grade colitis-associated dysplasia. This area resembles a tubular adenoma.
Low-grade colitis-associated dysplasia. This is a p53 stain, showing labeling in most of the lesional cells of the dysplastic focus.

High-grade colitis-associated dysplasia. Although this focus displays prominent inflammation, the degree of nuclear hyperchromasia and the loss of polarity is in excess of that attributable to a reparative process.

Low-grade colitis-associated dysplasia. The process extends onto the surface and is unassociated with inflammation.

Low-grade colitis-associated dysplasia. This is a p53 stain.

Low-grade colitis-associated dysplasia. This area shows cribriform glands, loss of nuclear polarity, and abnormal mitotic activity (top of field).

Low-grade colitis-associated dysplasia. This lesion is adenoma-like. When adenoma-like lesions are polypoid, they can be managed as per sporadic adenomas if the patient’s flat mucosa lacks dysplasia.
High-grade colitis-associated dysplasia. The nuclear features trump the architectural ones in evaluating dysplasia.

Low-grade colitis-associated dysplasia. This lesion shows goblet cell arranged in a disorganized jumbled fashion at the surface.

Some observers refer to this disorganized pattern of upside down and sideways oriented goblet cells as “dysplastic goblet cells.”

Serrated colitis-associated low-grade dysplasia. There are sufficient nuclear changes that this lesion differs from colitis-associated serrated change that resembles a hyperplastic polyp and it can be reported as serrated colitis-associated low-grade dysplasia.

Serrated colitis-associated high-grade dysplasia. This lesion shows serrated features and cribriform architecture.
Serrated colitis-associated high-grade dysplasia. This lesion shows serrated features and cribriform architecture.

There were 187 patients with confirmed IBD and 1 or more histologic findings of SEC without prior dysplasia. Mean IBD duration was 16 years, and median follow-up time was 28 months. The rate of high-grade dysplasia or CRC was 17 per 1000 patient-years. Thirty-nine of 187 patients (21%) had synchronous or metachronous dysplasia or CRC. Location concordance was 68%. Multivariable analysis found SEC on follow-up examinations, older age at IBD diagnosis, male gender, and a first-degree relative with CRC were associated with dysplasia in IBD patients with SEC.

Dysplasia-associated lesion or mass/DALM. This is an endoscopic image of a poorly defined lesion that showed dysplasia on biopsies.
Dysplasia-associated lesion or mass (DALM). This lesion is histologically like a tubular adenoma (with low-grade dysplasia) but was derived from a flat ill-defined lesion that was not amenable to endoscopic removal.

Unfortunately p53 labeling is not consistently helpful in confirming an impression that a lesion is colitis-associated rather than a sporadic adenoma.

Sporadic adenoma arising in a patient with Crohn’s disease. This lesion arose outside the field of colitis and has a “top-down” growth pattern.
Beta catenin pattern in tubular adenoma. The nuclei of the lesional cells show labeling (but not the nonneoplastic nuclei).

Adenocarcinoma arising in a patient with colitis. Single cells invade the lamina propria. Note that the surrounding glands show only low-grade dysplasia.

Adenocarcinoma arising in a patient with colitis. Single cells invade the lamina propria. Note that the surrounding glands show only low-grade dysplasia.

High-grade neuroendocrine carcinoma, small cell type, arising in association with colitis. Ki-67 staining shows striking nuclear expression in almost every tumor cell.
Gastric carcinoma metastatic to the colon. The atypical cells are very subtle and almost blend into the lamina propria.

Mesothelioma extending into the colonic mucosa. The cells are more bland than those of most adenocarcinomas and the lesion infiltrates between colon glands.

Mesothelioma extending into the colonic mucosa. This is a calretinin stain.

Mesothelioma extending into the colonic mucosa. This is a CK7 stain.
Malignant Polyps- Background

When carcinomas arise in adenomas of the colon, invasion of the lamina propria is considered biologically equivalent to high-grade dysplasia (since the lamina propria of the colon is believed to lack lymphatic access). Intramucosal carcinoma in the colon is thus staged as Tis rather than T1). So some observers do not report this invasion either. We report intramucosal carcinoma in adenomas as such and always include a note stating that it is biologically equivalent to high-grade dysplasia (Tis) and that complete polypectomy should be adequate management. We report our findings this way in case additional sampling discloses deeper invasion.

Background

Polyps containing invasive carcinoma comprise about 5% of all adenomas. The chance that any given adenoma contains invasive carcinoma increases with polyp size, and the incidence of invasive carcinoma in adenomas >2 cm ranges from 35% to 53%. Therefore, any polyp >2 cm in diameter should be approached with the suspicion that it might harbor an invasive cancer.

Background, Reporting Cont

Although we have no validation, we generally reserve a diagnosis of high-grade dysplasia in colorectal adenomas for lesion that have cribriform architecture and/or loss of nuclear polarity rather than only cytologic atypia or stratification of nuclei to the surface. The reasoning is that if we miss a bit of intramucosal carcinoma in the colon, it is not of any consequence, whereas we use a lower threshold in the esophagus and stomach.

Some colleagues do not even report high-grade dysplasia in colorectal adenomas to forestall overtreatment by surgical colleagues who harbor the erroneous notion that high-grade dysplasia should prompt a colectomy.

What most US colleagues report in a malignant polyp

Whether there is a poorly differentiated component
Whether there is vascular space invasion
Whether the polyp is out (usually we want to see a clearance of 2mm or more.)

In the less lazy parts of the world (UK suggestions below)

Polyp configuration (as if the endoscopist did not know)
Haggitt or Kikuchi level of invasion
Depth and width of invasion
Histologic grade
Vascular invasion
Tumor budding
Status of excision margins (1 mm suggested as the “cutoff point”)

Now let's take a polyp out
Carcinoma arising in an adenoma. This lesion has extended into the superficial submucosa, thereby attaining the possibility for lymphatic access. Were it not for a small focus of vascular space invasion that was identified in this lesion, it would be amenable to polypectomy given the long stalk seen in the lower right portion of the field.

Invasion into the lamia propria is Tis?

What about poorly differentiated carcinoma with invasion restricted to lamina propria
Rarely encountered presumably because such lesions quickly invade into the submucosa
Poorly differentiated carcinoma in a tubular adenoma. Invasion is only into the lamina propria.

Can lamina propria invasion of poorly differentiated carcinoma be managed conservatively?


ANSWER – CASE BY CASE BASIS

Substaging pT1

Haggitt's Classification | Number of Cases | Nodal Involvement |
---|---|---|
Level 1 | 42 | 0 |
Level 2 | 24 | 6 (25%) |
Level 3 | 185 | 27 (15%) |

Haggitt's substaging is recommended for pedunculated lesions (42-85%).[1]


Back to the basics of malignant polyps

Haggitt 1
Hagitt 2

Substaging pT1

Kikuchi substaging is recommended for non-polypoid lesions (15-58%)! But you only know where the bottom is in a resection!!!!!

Lymphatic Invasion

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<th>Sub</th>
<th>LN Metastasis</th>
<th>No Metastasis</th>
<th>P-Value</th>
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<tbody>
<tr>
<td>L1 (33%)</td>
<td>45</td>
<td>32 (71%)</td>
<td>0.001</td>
</tr>
<tr>
<td>L0 (67%)</td>
<td>91</td>
<td>86 (95%)</td>
<td>0.001</td>
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<tr>
<td>V1 (25%)</td>
<td>34</td>
<td>31 (91%)</td>
<td>0.38</td>
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<tr>
<td>V0 (75%)</td>
<td>102</td>
<td>87 (85%)</td>
<td>0.01</td>
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Multivariate Analysis: L1 OR 7.12 (p=0.001)
V1 no predictor (uni-/multivariat

<table>
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<th>Sub</th>
<th>LN Metastasis</th>
<th>No Metastasis</th>
<th>P-Value</th>
</tr>
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<tbody>
<tr>
<td>L1 (24%)</td>
<td>76</td>
<td>51 (67%)</td>
<td>&lt;0.01</td>
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<tr>
<td>L0 (76%)</td>
<td>246</td>
<td>225 (91%)</td>
<td>0.01</td>
</tr>
<tr>
<td>V1 (14%)</td>
<td>45</td>
<td>32 (71%)</td>
<td>&lt;0.01</td>
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<tr>
<td>V0 (86%)</td>
<td>277</td>
<td>244 (88%)</td>
<td>&lt;0.01</td>
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Multivariate Analysis: L1 OR 3.19 (p<0.01)
V1 no independent predictor

As of now, there are a few issues that go beyond the less detailed approach to polyps in the US. These boil down to measuring things:

Do we need to measure the depth of invasion and the width of the invasive front of early colorectal carcinomas?
Do we need to report tumor budding? Do we need to count lots of fields to do so? Do we need to do stains for keratins to do so? What is the difference between budding poorly differentiated carcinoma?
Should we stain for vascular invasion?

Poorly differentiated carcinoma with signet ring cell features arising in an adenoma (the adenoma is absent in this field).
Do we need to measure depth on invasion?

Our colleagues in Europe have mentioned this method in their guidelines but fallen short of formally endorsing it.

What is not clear in these studies is how often the polyps that would be considered ones requiring subsequent resection after measuring would be the same ones that would require follow-up resection using the easier old fashioned method of reporting.


Risk factors for an adverse outcome in early invasive colorectal carcinoma

Ueno et al. Gastroenterology 127: 385-394, 2004

<table>
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<th>Depth of submucosal invasion (µm)</th>
<th>Number of Cases</th>
<th>Nodal involvement</th>
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<td>&lt; 500</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>500-1000</td>
<td>35</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>1000-2000</td>
<td>36</td>
<td>2 (5.6%)</td>
</tr>
<tr>
<td>2000-3000</td>
<td>61</td>
<td>11 (18%)</td>
</tr>
<tr>
<td>3000-4000</td>
<td>45</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>4000-5000</td>
<td>31</td>
<td>6 (19%)</td>
</tr>
<tr>
<td>&gt;5000</td>
<td>38</td>
<td>8 (21%)</td>
</tr>
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The odds ratio of nodal involvement with minimum p-value was 5.0 (range 1.5-17.0) at the threshold of 2000µm for tumour depth.

Problems in measuring depth

The tumor obscures the muscularis mucosae.

Carcinoma arising in an adenoma. Note invasion of the malignant glands into the submucosa.
Tumor budding ("sprouting")

Tumor budding can be defined as the presence of isolated tumor cells, singly or in clusters of <5 cells at the advancing tumor front.

It is essentially the crux of epithelial-mesenchymal interaction!

This phenomenon can be spotted at 4x and may be some observers' view of a poorly differentiated component.

Tumor budding ("sprouting")

Was even significant in the early papers concerning measuring depth of invasion (eg Kitajima J Gastroenterol 2004; 39:534)

All studies note that it is a marker for aggressive lesions.

Many very detailed studies with lots of ways to count it.

Tumour cell dissociation (TCD) / budding

| TCD criteria for budding = if they could see it at 4x and confirm it at 10, it was budding |

Even an American can do this.

Their results were terrific.

This easy budding method correlated with vascular invasion, bad response to neoadjuvant tx, LN metastases.

Tumor budding that lazy US pathologists can handle

A nice Irish one (Rogers et al – Kieran Sheahan last author – Mod Pathol 2014: 27: 156)

SIMPLE criteria for budding = if they could see it at 4x and confirm it at 10, it was budding

Even an American can do this.

Their results were terrific.

This easy budding method correlated with vascular invasion, bad response to neoadjuvant tx, LN metastases.
Does it help to do keratin stains for budding?

Not really.
There are many ways to assess it but consistent reproducibility has been obtained by Puppa et al. whether or not keratin stains were used.

Keratin staining detected more budding, but the impact of adding keratin stains on predicting outcome is unknown.


Budding

Since budding is an adverse prognosticator and easy to recognize, it might be important to report it. We have begun to do so in our lazy US hospital.

Budding correlates with poor tumor differentiation (no surprise), lymphatic invasion, level of invasion, local and distant metastases, shortened disease-free and overall survival.

Measuring depth in CRC

Not sure. Deeper is worse but in US, criteria for clearance of deep margin are more generous – 2 mm is considered the adequate margin, whereas margin less emphasized in European and Japanese studies/criteria.

A lesion that lacks 2 mm deep clearance is more likely to be a thick one so likely to be further treated.

Relationship between the rate of lymph node metastasis and SM depth in early colorectal cancer

![Table Image]

Do we need to stain for endothelial markers to search for vascular invasion?

The vintage Cooper studies noted that patients whose lesions were even “suspicious for vascular invasion” tended to behave as though vascular invasion.

We do not stain but there is nothing wrong with this practice. BUT we report “suspicious for vascular invasion”.

![Diagram Image]
What we do at our place

The old fashioned 3 things (is there vascular invasion, is there a poorly differentiated component, is the lesion out and a measurement is made.
Budding variable but some report it as "poorly differentiated component"
No staining for keratins or endothelial cells
The patients somehow do just fine