

ADVANCES IN ENDOSCOPY

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Endoscopic Approach and New Oncologic Strategies for Early Rectal Neoplasia



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G&H What criteria should be used to assess and describe a newly diagnosed rectal lesion?

MB When evaluating a rectal lesion, it is important to remember that rectal lesions are completely different from colonic lesions. Although the colon and the rectum are in a continuum, they are not the same organ. The risk of invasive disease in the colon is substantially less than in the rectum. We evaluated our own data at Westmead Hospital, based on over 3500 referred large (≥ 20 mm) nonpedunculated colorectal polyps (LNPCPs). We found that in the entire cohort, the overall risk of having submucosal invasive cancer in the colon for any given LNPCP was 6%, but in the rectum, the risk was about 2.5-fold higher at 15%. In the rectum, definite evidence of cancer may not be visible; if 15% of rectal lesions are cancerous, about half of them will have covert cancer. Bearing that background information in mind, when evaluating a rectal lesion, it is essential to describe its size, distance from the anus (because that has important implications for resection, either by endoscopy or surgery), and morphology.

G&H What morphologic characteristics predict the likelihood of submucosal malignant invasive cancer in the rectum?

MB When describing polyp morphology, the Paris classification system is often used. An LNPCP would generally be classified as 0-IIa (flat), and a polyp with a nodular (Is) component would be classified as 0-IIa+Is, or if purely nodular, simply 0-Is. The combination of location in the colorectum, Paris classification system, and surface pattern being granular or nongranular allows for a baseline risk of invasive disease and informs the endoscopist

whether an accurate assessment of the lesion can be done by endoscopy in real time. If the lesion is nongranular, the surface is smooth. A granular lesion has many little bubbles on the surface and looks like a bowl of Rice Krispies, known as Rice Bubbles in Australia.

The assessment of a lesion hinges upon whether it contains cancer. If it contains cancer, it must be removed en bloc and all margins free (R0). Lesions not containing cancer can potentially be removed piecemeal, depending on the endoscopy center, workload efficiencies, and local skill set. When evaluating a flat lesion vs a bulky nodular lesion, I like to use another analogy, which is the pizza vs the calzone. Careful endoscopic examination of a flat lesion (the pizza, however big, whether it is family-size or medium-size) will reveal key features—the consumer always can tell the ingredients of the pizza. Of course, the contents of the nodule (calzone) are hidden within. With a benign flat lesion, the key feature is surface homogeneity. This manifests as a regular pit pattern under narrowband imaging or other enhanced imaging techniques. The regular vascular pattern will be apparent as well. This regular repeating pattern looks like a chicken wire mesh or capillary mesh network, and there is no disruption to that regularity (akin to wallpaper). Loss of homogeneity, a demarcated area where there is a disruption to that regular pattern, is the area where there could be invasive cancer. Key features indicating a focus of invasive cancer generally include pits of different sizes, absence of pits, and disrupted microvascular networks (eg, larger vessels, dilated vessels, irregular vessels, absent vessels, interrupted vessels).

Historically, the sensitivity for detecting cancer in all LNCPs has been regarded as approximately 50% to 60%. However, in a study published in 2021, my colleagues and I assessed 1583 LNCPs for submucosal invasive cancer

and found a significant difference between flat and nodular lesions. In flat lesions, the sensitivity was 91% and the specificity was 96% for diagnosing cancer vs 53% and 94%, respectively, in nodular lesions. The likelihood of missing a cancer in a flat lesion in all sites in the colon and rectum is low, about 6 per 1000 cases. However, in a bulky lesion, the miss rate is 6 in 100; sensitivity is poor because in a bulky lesion, the cancer can be hidden within and its optical features not expressed on the surface.

G&H How is the decision made to utilize endoscopic vs surgical techniques for resection of rectal lesions?

MB The decision depends a lot on local skill set and bias. There are no head-to-head trials of endoscopic submucosal dissection (ESD) vs transanal minimally invasive surgery or transanal endoscopic microsurgery (TEM), or vs other procedures such as endoscopic full thickness resection (EFTR). One Dutch study, TREND, compared TEM with endoscopic mucosal resection (EMR) for large rectal adenomas and found that EMR was safer but had higher recurrence (15% after EMR vs 11% after TEM). However, more complications occurred with TEM (26%) than with EMR (18%) resulting in longer hospital stay and so on. The study showed no clear superior outcome for either.

If there is any suspicion for submucosal invasive cancer, then the patient should have pelvic magnetic resonance imaging (MRI) to establish lymph node status. The treating team may need to refer to the MRI later, and often there is nonspecific, minor lymph node enlargement or prominence in the pelvis. MRI is not so helpful for T staging, and we generally consider it unreliable. At Westmead, we have had many cases staged as T3 or T2 that were just mucosal lesions, or benign polyps. However, the N stage is important, so any suspicion for invasive cancer is enough to warrant a pelvic MRI. Once I examine the lesion endoscopically, if I suspect that it could contain—or is at risk of—invasive cancer, then the lesion must be removed by an en bloc strategy, particularly in the rectum, because there is the potential to save the patient from morbid surgery. This strategy is important in the rectum because the outcomes of surgery are not nearly as favorable as they are in the right colon. In addition, there is a risk of stoma as well as many other risks associated with rectal surgery, including anastomosis leak (which is 10% to 20%), urinary and bowel dysfunction, and sexual dysfunction. If there is the potential to cure the patient with suspected cancer by a minimally invasive procedure, whether ESD or TEM, then en bloc resection should be considered.

The morphology of the lesion also determines the risk. For a flat granular lesion in the rectum (like a flat bowl of Rice Bubbles), the risk of cancer is very low. Such

a lesion may be removed by EMR if evaluated carefully. However, any large nodular lesion of more than 10 mm needs to be removed by an en bloc strategy. This was the conclusion of a paper published in *The American Journal of Gastroenterology* by our team that evaluated a prospective observational cohort of LNPCPs that underwent EMR up until 2017. In 2017, we switched to using a selective resection algorithm. If cancer was suspected based on morphology, then ESD was performed. About two-thirds of the lesions were managed by ESD, and every cancer that was eligible for cure by en bloc resection was cured; as a result, patients were spared surgery. Many centers may opt to perform TEM; however, ESD is much more precise. The margin can be visualized very clearly. The submucosal muscle fibers can be cut one at a time and—at least when the lesion is below the peritoneal reflection—an endoscopic intermuscular dissection (EID) can be performed, so the inner circular layer of the rectal muscle can be removed if necessary. There are emerging data on EID as a means of curing early disease as well.

G&H What is the latest consensus on choosing EMR, ESD, or EFTR for managing rectal lesions?

MB I do not think there is a consensus. A good medical analogy is the management of breast cancer, which for the longest time was managed by mastectomy and is now mostly managed by local excision followed by sentinel lymph node biopsy and sometimes lymphadenectomy. Mastectomy currently comprises a much smaller percentage of all breast cancer surgery. The same thing is happening with cancer of the esophagus and rectum because these are vital organs that are conduits to the stomach and to the outside. Disturbing a vital organ has a huge impact on quality of life. Researchers are working hard to develop algorithms that allow us to preserve the primary organ whilst curing the cancer.

Ultimately, for the rectum and the esophagus, many more patients will undergo local R0 (clear margin) excision. Once the tumor is out, the definitive T stage can be determined and that then allows for risk stratification of lymph node or distant metastasis. Many patients with rectal or esophageal cancer could be managed by local excision followed by close surveillance, adjuvant radiotherapy, or other therapy depending on patient preference. Rectal cancer patients generally have strong preferences regarding postprocedure care and do not want a stoma. For some patients, that is not an option. For patients who have a T1B tumor, deep submucosal invasion, the tumor can still be excised, and they can be offered follow-up radiotherapy. However, the field is in a state of flux, and there are no firm data or, in my opinion, consensus on the optimal treatment algorithm.

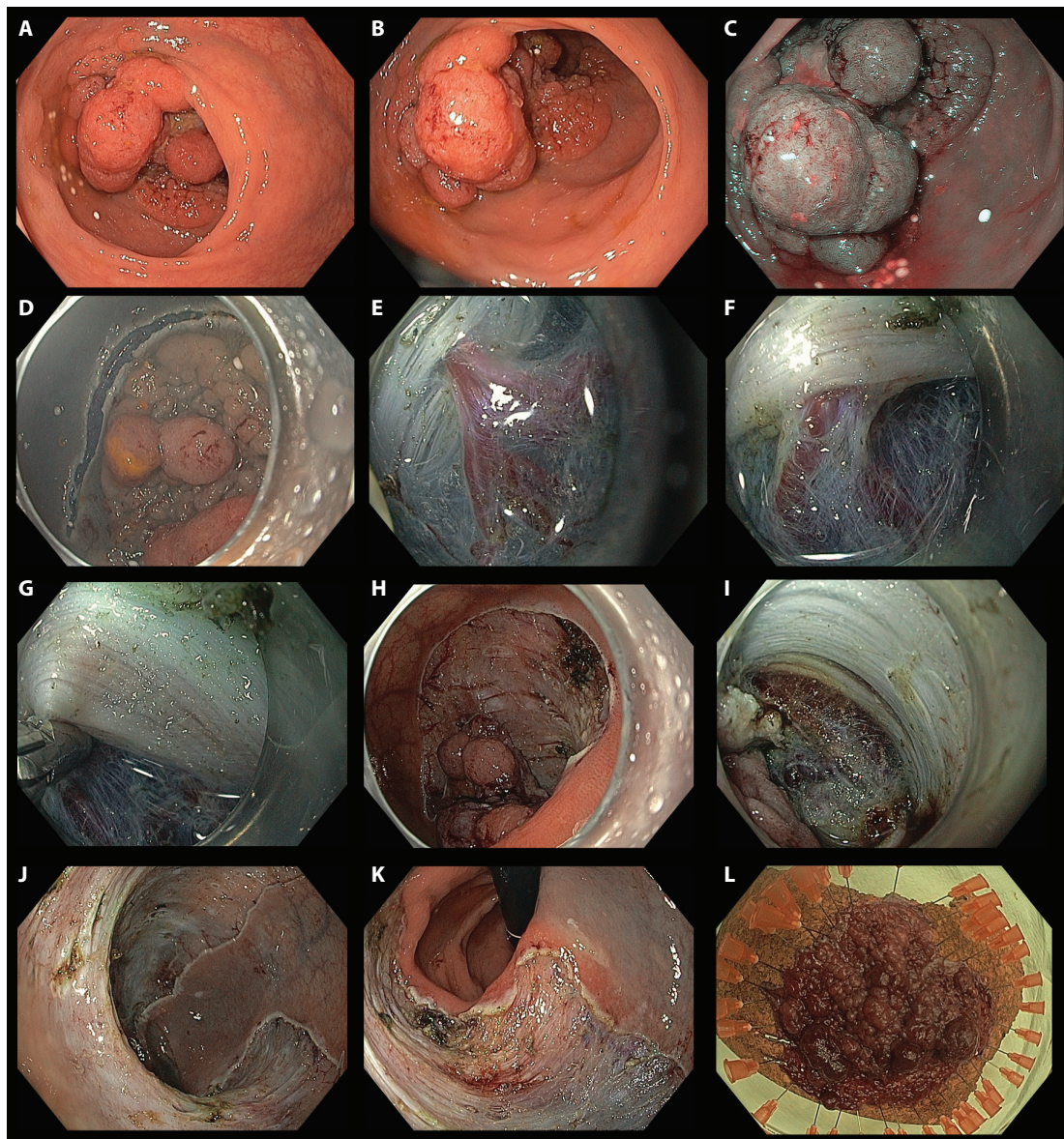


Figure. (A-L) A 5-cm, 75% circumferential, proximal rectal, mixed nodular LNCP excised en bloc by tunneling ESD. Histology revealed a tubulovillous adenoma with focal low-risk submucosal invasive cancer. (J-K) All margins free. Considered cured by ESD. ESD, endoscopic submucosal dissection; LNCP, large nonpedunculated colorectal polyp.

G&H How should multidisciplinary care of rectal cancer patients be organized at a tertiary center?

MB Every rectal tumor needs to be discussed by a team of informed, presumably like-minded individuals, who put the patient's best interests at the center of the discussion based on the best available clinical science. This team may include colorectal surgeons, advanced endoscopists (who are generally gastroenterologists but not necessarily, as they

could be surgeons as well), radiation oncologists, medical oncologists, and nursing team members. They should hold a multidisciplinary team (MDT) meeting to decide what is the best treatment for each patient in terms of, for example, the patient's comorbidities, expectations, quality of life, and longevity. The team members should not argue for their own therapy (that is an example of a dysfunctional MDT); rather, they should be deciding what is best for the patient.

Management of rectal cancer by surgery has been the traditional paradigm, which is increasingly changing. A few years ago, we formed a working MDT at Westmead Hospital. Prior to that time, there was a significant proportion of patients who were having surgery for tumors that could have been managed by endoscopic resection. Since that time, the practice of recommending surgery has virtually stopped. In Australia, this has saved a significant amount of money, maybe between \$20,000 and \$30,000 per patient treated, and morbidity associated with inpatient care. The average hospital stay after surgery is probably 10 days to 2 weeks vs 1 day after endoscopic management. In the United States, the savings could be even higher.

G&H Do these new approaches affect decisions about when to utilize endoscopic resection techniques and which specific technique to use?

MB Yes, because if cancer is suspected, the lesion must be removed en bloc. We perform 2 or 3 rectal ESD procedures every week. Approximately 20% of resected lesions will contain early cancer, half of them covert. A substantial proportion of cancerous lesions will be low-risk R0 resections and cured by ESD (Figure). We perform a large number of ESDs in the upper gastrointestinal tract for suspected or proven early cancer, particularly in the esophagus. With the tumor out, the clinician has the full T stage. Patients are potentially cured. If not, then they can have adjuvant therapy, or they can still undergo surgery. ESD does not compromise the possibility of surgery.

G&H What is the level of recurrence for resected rectal lesions, and how should scarred or incompletely resected lesions be treated?

MB With ESD, the recurrence rate should be less than 1%. Recurrence, if it occurs, might be a small amount of adenoma at the margin. Usually, the rectal lesion removed by ESD is an LNPCP, a large laterally spreading adenoma that developed a focus of cancer within it. This is typical of an early lesion. If there is something left at the margin, it is usually an adenoma. However, currently with ESD, the risk of recurrence should be very low, or less than 1%. Most flat lesions in the colon, particularly lesions in the right colon, are removed by EMR, and the risk of recurrence is only 2% to 3%.

The rate of recurrence after endoscopic procedures has been shown to have declined in randomized trials, not just our own but others, and in large prospective series because of the advent of the snare tip of the margin technique. Recurrence, which was historically between 15% and 20%, is now reduced to 1% to 4% in expert centers.

Also, if the adenoma recurs, the lesion is diminutive and can be removed relatively easily. We use the cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST) technique. Basically, we excise as much of the tumor as possible with the snare, then there is usually some recalcitrant scarred tissue that will not lift. Any remaining tissue, because it has been freed up on all edges, can be removed with biopsy forceps, followed by ablation of the surface area with a snare. The use of CAST and its excellent results have been presented in several papers from our center.

G&H Are there any new strategies for managing rectal neoplasia on the horizon?

MB Early disease will probably be managed by local excision plus or minus adjuvant therapy, based on staging after local excision of the tumor. In addition, there is the prospect in the future that locally advanced disease could be downstaged and then managed by local excision. The goal would be to preserve the rectum in the long term. However, being able to manage advanced disease in this way would depend on the location of the tumor in the rectum; for example, advanced disease in the upper rectum is likely best managed by a low anterior section. When considering all factors, rectal neoplasia is a heterogeneous group of disorders influenced by tumor biology, location of the tumor, and the patient's age and comorbidities. We are in the era of personalized medicine, in which treatment decisions must be individualized based on patients' needs and wishes and the most high-quality and current science we have.

Disclosures

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Suggested Reading

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