Rare Anorectal Neoplasms: Gastrointestinal Stromal Tumor, Carcinoid, and Lymphoma

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ABSTRACT

Several uncommon tumors occur in the anal canal such as gastrointestinal stromal tumors, carcinoids, and lymphoma. Increased clinical experience and advancements in molecular biology have improved the accuracy of pathologic diagnosis and guided treatment recommendations, which the author addresses in this article.

KEYWORDS: Gastrointestinal stromal tumors, carcinoid, lymphoma

Objectives: On completion of this article the reader should be able to summarize the management of uncommon anorectal neoplasms.

The most recent data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) on incidence and survival for anal cancer shows that nonepidermoid/nonmelanoma cancers constitute 2.3% of all cases. Five-year overall survival for this category was 37.3% compared with 64% for all other types.[1] The low numbers and historically poor prognosis for these neoplasms has led in the past to general recommendations for abdominoperineal resection as their definitive treatment. In recent years, widespread endoscopic screening and earlier diagnosis have allowed increased clinical experience with the broader spectrum of these tumors, and these reports are summarized in this review. Molecular biology has enabled both precision in pathologic diagnosis and highly effective adjuvant therapy. Lastly, treatment recommendations and clinical trials for rare tumors are available online to enable physicians encountering a rare tumor to avail their patients of advances in therapy.

GASTROINTESTINAL STROMAL TUMORS

Gastrointestinal stromal tumor (GIST) is a designation for a category of spindle cell or mixed-epithelioid neoplasms of the gastrointestinal tract characterized by immunohistochemical expression of the CD117 antigen.[2] The nomenclature has only recently become standardized, and case series prior to 2000 frequently used the former diagnoses of leiomyoma and leiomyosarcoma.[3] Rather than having a smooth muscle cell of origin, these tumors are postulated to arise from the interstitial cells of Cajal (ICC) or a common precursor cell and are characterized by a gain of function mutation in c-KIT (CD117) or PDGFα (platelet-derived growth factor α).[4] ICC also express CD117 and function as pacemaker cells that regulate peristalsis. GIST tumors arise when activating c-KIT mutations cause dysregulated ICC proliferation.[5,6]

The incidence of all-site GIST in the United States is estimated at 3300 to 4350 annually.[7] The majority of GIST occur in the stomach, but also occur

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in the small intestine, colon, rectum, and rarely, in the anal canal. The anorectal location together accounts for 5 to 10% of all GIST.[8,9] At ~200 to 400 cases per year compared with 4660 cases per year of anal carcinoma, anorectal GIST is a rare tumor and few data exist upon which to base surgical and adjuvant therapy. Nevertheless, the prognosis was historically poor and recent developments in the targeted medical therapies for GIST have greatly raised awareness of GIST in general, as well as the prospects for cure.

CD117 is the immunohistochemical antigen corresponding to KIT, a tyrosine kinase receptor. Upon binding its ligand, stem cell factor, KIT activates a cascade of intracellular growth and differentiation signals that are necessary to maintain hematopoiesis, mast cell development, gametogenesis, melanogenesis, and development of the interstitial cells of Cajal.[10] There is high sequence homology between KIT, PDGFα, and the so-called Philadelphia chromosome BCR-ABL mutation of chronic myelogenous leukemia. The tyrosine kinase inhibitor, imatinib mesylate (Novartis Pharma AG, Basel, Switzerland) binds specifically to the kinase domain of these receptors to cause frequently dramatic regression in CD117-positive or PDGFα-positive GIST or leukemic cell burden. CD117 is expressed on several normal tissues as well as in other tumors, including melanoma, Ewing's sarcoma, angiosarcoma, mastocytoma, and seminoma. These tumors, however, have not been shown to respond to imatinib treatment because they are not driven by pathogenic KIT mutations.[11]

Case reports and series published since the nomenclature became more uniform total just over 100 cases. Using the search terms "leiomyoma (LM)," "leiomyosarcoma (LMS)," "stromal," "rectal," and "anal," but not "GIST," Skandalakis et al have analyzed a collection of published cases from 1881 to 1996 that totals 131 for LM and 160 for LMS.[3] It is now evident that the incidence of GIST is 10-fold that of LMS, and that 90% of cases previously ascribed to LMS represent GIST.[11]

One question therefore is whether a separate entity of benign leiomyoma needs to be considered in the differential diagnosis of spindle cell tumors of the anorectum. Even when that term was applied to what are now known to be GIST, it was noted that histologically, tumor cells did not resemble well-differentiated smooth muscle cells, but rather had characteristics of both smooth muscle and cells of neural origin.[11] In contrast are the well-described, benignly behaving submucosal tumors of the esophagus that are clearly arising from smooth muscle. Of note, the colon is the second most common site of origin of true intestinal leiomyomas that, considered as a separate entity, outnumber the incidence of GIST in that site. Miettenen et al reviewed 21 rectal LM in a series of 88 colorectal LM.[12] All 88 specimens, ranging in size from 0.1 to 2.2 cm, were completely resected by snare polypectomy. Histologically, LM in this series were located in the submucosa, immediately underlying the epithelium and merging with the smooth muscle cells of the muscularis mucosa. All the specimens were positive for smooth muscle actin (SMA) and desmin. Twenty specimens that were tested for CD117 and CD34 were all negative. They noted that CD117-positive ICC cells could be seen in the myenteric plexus, deeper than the muscularis mucosa. They noted no recurrences with a median follow-up of 46 months. In the authors' separate series of 100 anorectal GISTs subjected to the same immunohistochemical studies, 100% were CD117 positive, 94% were positive for CD34, 8% were positive for SMA, and 7% coexpressed SMA and CD34, and 1% expressed desmin[9] (Table 1).[12–14]

Given the smaller size, cure by snare polypectomy, and negative CD117 staining, it is more appropriate to consider colorectal LM as a completely separate clinical entity to be considered only for the purposes of differential diagnosis. The remainder of this review is applicable to anorectal GIST, even when the literature cited uses the LM or LMS nomenclature.

Anorectal GIST presents with nonspecific symptoms of bleeding, pain, mass sensation, constipation, and anemia.[9] The majority of rectal GIST is located within 10 cm of the anal verge.[13,15] Some tumors are incidentally noted during endoscopic examination for screening or other purposes. Due to the submucosal location of these tumors, pinch biopsies are usually nondiagnostic.

The peak incidence occurs in ages 50 to 59 years, with a slight male predominance.[3] There are no risk factors associated with exposures, but there are genetic predispositions, namely neurofibromatosis type 1, Carney triad, and familial GIST that together account for ~5% of GIST.[7] Very small GIST may be more common than previously known, with multiple tumors less than 5 mm seen in 25% in certain autopsy series.[16] Historically, 20% of GIST patients present with metastatic disease, with the most common sites being liver, peritoneum, lung, and bone.

The diagnostic workup is premised on the recognition of the potential for GIST when a solid, mural

Table 1 Anorectal Leiomyoma Compared with Gastrointestinal Stromal Tumors

Feature	LM[12]	GIST[9]
CD117	0	95%
CD34	0	70%
SMA	100%	25%
Desmin	100%	5%
Size (Mean cm)	0.1–2.2 (0.4)	1.0–>10 (6.0)[13]
Recurrence	0	40–80%[14]

LM, leiomyoma; GIST, gastrointestinal stromal tumor; SMA, smooth muscle actin.

Table 2 Anorectal Gastrointestinal Stromal Tumor Recurrence by Size and Mitotic Rate

Series	*N*	1	2	3	4	5	6
Haque and Dean[19]	19		10			9	
Miettinen et al[9]	105	20	12	7	11	29	26
Tworek et al[14]	22	4	2	1	2	7	6
	Total	24	24	8	13	45	32
	Local Recurrence (%)	1 (4)	4 (17)	6 (75)	6 (46)	28 (62)	23 (72)
	Metastases (%)	0	2 (8)	3 (38)	3 (23)	20 (44)	24 (75)

Group 1, ≤2 cm, mitoses <5/50 high power field (hpf); group 2, 2 to <5 cm, mitoses <5/50 hpf; group 3, ≥5 cm, mitoses <5/50 hpf; group 4, ≤2 cm, mitoses ≥5/50 hpf; group 5, 2 to <5 cm, mitoses ≥5/50 hpf; group 6, ≥5 cm, mitoses ≥5/50 hpf.

mass is noted on digital rectal examination. In addition to a history, physical examination, and endoscopy, pelvic imaging such as endorectal ultrasound or magnetic resonance imaging (MRI), and a staging computed tomography (CT) scan of the chest, abdomen, and pelvis should be performed. These studies provide information on the size of the mass, invasiveness, and evidence of metastatic disease. The radiologic appearance of anorectal GIST is described as a well-circumscribed mass, which may be large but without adenopathy. Evidence of central hemorrhage is a distinguishing feature of GIST compared with carcinoma, and appears as cystic or low-attenuation areas by CT or central hyperintensity on T2-weighted imaging by MRI.[17]

Although there is no specific staging system for GIST, clinicopathologic studies of GIST from all sites have identified several prognostic factors, the most important being size and number of mitoses.[16,18] These series contain only a small percentage of anorectal cases, but have determined that site of origin of the GIST tumor has prognostic impact as well: gastric having a better outcome than small intestinal GIST of similar size and mitotic activity.[7] Only a few series of anorectal GIST show outcomes stratified by these criteria[9,14,19]; these data are summarized in Table 2. A local recurrence rate of 75% in tumors over 5 cm in size regardless of mitotic rate, and of 62% in tumors under 5 cm, but with five or more mitoses per 50 high power fields supports the general view that anorectal GIST is a site with a poor prognosis.

Surgical Treatment

Complete surgical resection is the primary treatment in most gastrointestinal stromal tumors. The objectives of sphincter preservation and optimal quality of life must be weighed against the risks associated with the highly variable recurrence behavior of anorectal GISTs. Data on recurrence after complete surgical resection from prospective trials is scant with respect to this tumor site. The American College of Surgeons Oncology Group (ACOSOG) Z9000 and Z9001 studies of adjuvant imatinib for completely resected GIST enrolled 750 evaluable patients; extrapolating 5% as involving the anorectum, ~35 cases are embedded in those studies, for which long-term follow-up is still pending.[20,21]

There has been a gradual accumulation of reported experience with treatment outcomes from retrospective case series (Table 3).[13,15,22–26] The criteria cited by the surgeon for local excision versus radical excision were size and location. Transanal full-thickness excision was favored for small lesions in the lower rectum, whereas abdominoperineal resection and low anterior resection with coloanal anastomosis were the most common procedures for radical resections. Transvaginal and pararectal approaches were included among local excision, and associated with 100% recurrence in the series of Vorobyov et al.[15] The interval from surgery to local recurrence ranged from 3 months to more than 7 years.[15] Series reporting a high rate of local recurrence have longer follow-up, for example, 77% LR in Chang-

Table 3 Recurrence of Anorectal Gastrointestinal Stromal Tumor by Type of Resection

	Local Excision				Radical Resection			
	N	LR	Met	DOD	*N*	LR	Met	DOD
Vorobyov et al[15]	29	9	5	5	7	0	0	0
Walsh and Mann[22]	10	6	3	5	8	0	4	4
Changchien et al[23]	13	10	5	7	29	9	13	16
Hassan et al[13]	5	0	2	2	9	1	4	3
Li et al[24]	1	0	1	1	5	1	2	1
Baik et al[25]	1	0	0	0	6	2	0	0
Chen et al[26]	3	0	0	0	7	0	3	NS
Totals (%)	62	25 (40)	16 (26)	20 (32)	71	13 (18)	26 (37)	24 (37)

LR, local recurrence; Met, metastasis; DOD, died of disease; NS, not stated.

chien et al with a median follow-up of 48 months, compared with 0% LR in Chen et al[26] with follow-up ranging from 6 to 24 months. Nevertheless, repeat resection, local or radical, yielded remissions lasting 9 to 100 months.[22] Based on these observations, Walsh and Mann[22] recommend periodic follow-up of ostensibly benign lesions for possible distant or local recurrence for longer than 4 years.

With the observed high rates of local recurrence, the circumstances under which local excision is appropriate are controversial. A collective surgical series of GISTs from all sites, of which 16% were rectal, showed no effect of margins on overall survival, reflecting the equally dismal 55% distant metastasis rate in cases resected with negative margins.[8] For rectal GIST, similar proportions are found; Hassan et al[13] observed that two of five locally resected, and four of nine radically resected patients died of metastatic disease. One third of recurrences are both local and distant and occur within 2 years, implying a higher rate of local recurrence in high-risk tumors, and that local excision is relatively safe in low-risk tumors, that is $\leq$3 cm diameter and $\leq$5 mitoses/high power field (hpf) (Table 2). In cases where an excisional biopsy has been performed, experienced pathologic analysis is crucial to determining the prognostic category for the resected specimen. A multidisciplinary review of these cases should be performed to complete the staging, consider whether more radical surgery is required, determine if adjuvant therapy is needed, and to ensure long-term follow-up.

Adjuvant and Neoadjuvant Therapy

Surgery alone is clearly not curative for the majority of patients with GIST. Before the advent of targeted therapy with tyrosine kinase inhibitors, there was no effective chemotherapy. The agent most effective in other soft-tissue sarcomas, doxorubicin, showed a response rate in GIST of 5%.[16] Radiation therapy was also of no known benefit.[27] The median survival for metastatic or unresectable GIST in the era before imatinib was 12 months.[28]

In 2001, a multicenter phase II trial of imatinib mesylate (Gleevec, formerly STI571; Novartis) in 147 patients with metastatic or unresectable recurrent GIST showed an 86% response rate (53.7% had a partial response ranging from 50 to 96% reduction in tumor bulk, 27.9% had stable disease).[27] Mild (grade I to II) adverse effects of periorbital or peripheral edema, nausea, diarrhea, and fatigue were reported in 98%, but grade III to IV occurred in 21%. Tumor or gastrointestinal hemorrhage of severity ranging from grade I to IV occurred in 11%. The response was durable beyond 46 weeks, and 90% of patients were alive at 64 weeks. The most recent SEER data for median survival with metastatic GIST is now 33 months, reflecting the impact of imatinib on disease course.[28]

Favorable results in unresectable GIST were quickly followed by adjuvant trials. ACOSOG Z9000 phase II trial of adjuvant imatinib for GIST enrolled 107 evaluable patients from 2001 to 2003 of which 92% were located in the stomach or small intestine and possibly 6% were located in the colon or rectum. Eligible patients had high-risk CD117-positive tumors: >10 cm (84%), tumors that had ruptured (17%), or those with no more than four peritoneal metastases present at surgery (13%). Therapy (imatinib 400 mg once daily) was initiated within 84 days of surgery and continued for one year. The results showed an overall survival (OS) of 99%, 97%, and 97% at 1, 2, and 3 years respectively.[20] Recurrence-free survival (RFS) at one year (the year of therapy) was 94%, one year after completion of imatinib RFS was 73% and 61% at 2 years after cessation of imatinib. The risk of relapse differed by the type of KIT mutation: the majority (exon 11 mutation) showed 62% RFS at 3 years, whereas exon 9 mutations were unfavorable, showing earlier relapse (RFS 0% at 3 years). More favorable genotypes were PDGFα and no detectable mutation (90% and 77% RFS at 3 years). The ACSOG intergroup Z9001 trial opened in 2002 as a phase III randomized, double-blinded trial of imatinib 400 mg or 800 mg versus placebo, administered for one year following complete resection of a primary GIST. Patients were stratified by tumor size (3 to 6, 6 to 10, or >10 cm). The primary endpoint was RFS. A planned interim analysis of 644 evaluable patients found that participants taking imatinib had a significant RFS benefit (97% 1-year RFS versus 83%, HR 0.325, $p = 0.0000014$).[21] In April 2007 enrollment in the study was halted, the participants unblinded, and all those on placebo were offered imatinib, whereas those who had progressed on the 400 mg dose were allowed to crossover to the 800 mg dose. At the time of study closing, the 1-year RFS in the group for patients with tumors 3 to 6 cm in size was 100% for the imatinib group and 95% for the placebo group ($p =$ N.S.). The groups were not stratified by mitotic rate. Therefore, this study cannot describe a subset that is so low risk as to not benefit from adjuvant imatinib. However, given the costs and toxicities of potentially lifelong treatment with imatinib, and the effectiveness of imatinib when started at the time of diagnosed metastatic or recurrent disease, it remains to be proven whether upfront adjuvant imatinib is superior to salvage therapy with respect to overall survival. The European Organization for Research and Treatment of Cancer (EORTC) 62024 study addresses this question and has completed its accrual goal of 750 patients. Interim results may become available in 2010.[29]

Neoadjuvant imatinib as a cytoreduction effort to spare adjacent organs or vital structures has been reported in a large case series[30] and a phase II clinical trial

(Radiation Therapy Oncology Group [RTOG] 0132/ American College of Radiology Imaging Network [ACRIN] 6665).[31] In this trial, 52 analyzable patients were enrolled, 30 with advanced primary GIST (defined as ≥5 cm) and 22 with recurrent or metastatic disease. The treatment was 8 to 12 weeks of imatinib 600 mg daily until surgery. There was one patient with rectal GIST and two perirectal GIST in the primary group. There is no description of whether the rectal cases were able to undergo a sphincter-sparing operation because of tumor shrinkage. Relapse-free survival was comparable to that achieved with adjuvant imatinib. The authors conclude that rendering metastatic or recurrent GIST resectable is likely to result in an improved OS compared with imatinib therapy alone due to the tendency for imatinib resistance to develop in residual tumor after 2 years of therapy.

Imatinib resistance is associated with the outgrowth of resistant secondary mutations in the KIT or PDGFRα genes. A multitargeted tyrosine kinase inhibitor, sunitinib, can induce objective responses and slow the progression of disease (27.3 versus 6.4 weeks) and is Food Drug Administration (FDA) approved for this indication.[32] Repeat resection after response to sunitinib is investigational.

In summary, the preponderance of clinical experience with GIST has been with gastric and small intestinal sites. Anorectal GIST has a higher risk behavior than tumors arising in the stomach, but tumors <3 cm diameter and with <5 mitoses/hpf have a low recurrence risk and appear to be safely treated by full-thickness transanal excision. Larger tumors or tumors with ≥5 mitoses/hpf should be resected by low anterior resection with coloanal anastomosis or abdominoperineal resection and should also be considered for adjuvant therapy with imatinib. Follow-up with both physical examination and abdominopelvic CT scan should be performed every 3 to 6 months for 3 to 5 years, then annually.[16] Salvage therapy with a second-line tyrosine kinase inhibitor and possible reexcision can significantly prolong overall survival.

CARCINOID AND NEUROENDOCRINE TUMORS OF THE ANORECTUM

Carcinoid tumors of the anorectum are uncommon, constituting 1.3% of rectal tumors, an incidence corresponding to one for every 2,500 proctoscopies.[33] Nevertheless, the rectum is the second most common site of origin of gastrointestinal carcinoids.[34] Tumors originating in the rectum are typically small (median diameter 0.6 cm) submucosal nodular or polypoid lesions.[34,35] Over 90% of rectal carcinoids are located within 4 to 13 cm above the dentate line. Microscopic features include organoid clusters of benign-appearing cells containing granules representing chromogranin A as well as various neuroendocrine hormones.[36] Unlike carcinoid tumors arising in the midgut, rectal carcinoids do not express serotonin and almost never manifest the carcinoid syndrome, even when metastatic to the liver.[37,38]

These small, submucosal nodules may be asymptomatic or incidental findings during proctoscopic examination, but can also cause nonspecific symptoms of rectal bleeding, constipation, pain, tenesmus, or pruritus ani.[39] Median age at diagnosis is 56, with no predilection by gender.[36]

Rectal carcinoids are notable for a size-dependent risk of distant mestastasis, which is extremely low for tumors <1 cm, >70% in tumors over 2 cm, and intermediate (4 to 30%) for tumors 1 to 2 cm in size.[36,40] Other prognostic features from large retrospective studies include invasion into the muscularis mucosa, ≥2 mitoses per high powered field, and lymphovascular invasion. Using a scoring system of 0 or 1 for the absence or presence of any of these features, and a score of 2 for size ≥2 cm, found a 5-year RFS of 100% for tumors with a score of 0, but a recurrence rate of 70 to 100% at 5 years for tumors scoring 1 to 2 (intermediate risk) or ≥3 (high risk).[41] A proposed staging system using similar criteria applied retrospectively to 4701 rectal carcinoid cases contained within the National Cancer Institute's SEER database from 1973 to 2004 classified 83% of patients into stage I, 6.5% into stage II, 2.8% into stage III, and 7.4% into stage IV. Five-year survival rates were 97%, 84%, 27%, and 20% for stages I through IV, respectively.[35]

Surgical Management

Reported surgical series show that up to 90% of rectal carcinoids are initially removed endoscopically.[42,43] These excisional biopsies can leave involved margin rates of 30 to 90%. In a retrospective study of 85 rectal carcinoids,[42] 68 (80%) were diagnosed by endoscopic excision. Forty-six of these had only subsequent endoscopic reexcision or surveillance. Margins on the initial biopsy were positive in 38 of 46 (83%). Although 7 of 46 patients had residual carcinoid removed on subsequent endoscopy, there was no progression to regional or distant disease in a median follow-up of 2 years (range 0 to 16 year). Twenty-two endoscopically excised carcinoids plus one case referred without prior biopsy went on to surgery, 19 by transanal excision and four patients by transanal endoscopic microsurgery (TEM). Surgical excision left a positive margin in three of 24 (13%) patients. Eight patients in the series had radical excision, six by low anterior resection and two by APR. All of these cases obtained negative margins and five of six had positive lymph nodes. There was one pelvic recurrence at 1 year (13%). Three of the eight had hepatic metastases at presentation and one more developed hepatic metastases at one year. The remaining four patients were free of

disease for up to 10 years of follow-up. The authors conclude that endoscopic excision alone is prone to leave positive margins and requires either close endoscopic surveillance or a wider surgical excision. Tumors 1.0 to 1.9 cm with high-risk features such as muscular or lymphovascular invasion should be treated by radical resection because of the high rate of involved lymph nodes and the absence of effective adjuvant therapy. Larger or metastatic tumors are radically resected as the best chance of local control.

Imaging for Staging and Surveillance

Endoscopic ultrasound is useful for preoperative assessment of invasion and lymph nodes and in combination with endoscopy for surveillance. Tumors 2 cm or larger or with high risk features should be staged with CT scan and ^{111}In-labeled octreotide (somatostatin receptor scintigraphy, or Octreoscan; Covidien AG, Mansfield, MA) to evaluate for metastatic disease preoperatively and annually for 3 years. Any symptoms that may subsequently develop should prompt an evaluation for late distant recurrence.

LYMPHOMA OF THE ANORECTUM

Anorectal lymphoma is rare, representing 0.2% of rectal malignancies and 9% of non-Hodgkin's lymphomas (NHL).[44] Like other primary gastrointestinal lymphomas, they are characterized by a normal chest x-ray, no hepatosplenomegaly or superficial adenopathy, and a predominant mass or chronic ulceration in the anus or rectum with only local lymphadenopathy. The mean age at diagnosis for cases not related to AIDS, versus those that are is 65 versus 34 years. There is a significant male predominance due to the association with AIDS. Risk factors in non-HIV patients include longstanding ulcerative colitis and immunodeficiencies from other causes. In HIV carriers, a CD4 count below 100 per mm^3 is the major additional risk factor.

Anorectal lymphoma in patients who are not HIV carriers represent only ~10% of the incidence. In the early years of the AIDS epidemic, both NHL and the anorectal site of origin increased significantly; with a latency of 4 to 6 years, AIDS patients taking zidovudine faced a probability of contracting NHL of 46.4% after 36 months of treatment.[45] Lymphomas associated with AIDS are usually extranodal and the anorectal site is involved in this setting in 26%. The development of highly active antiretroviral therapy (HAART) created a trend of decreased deaths from opportunistic infections, but increased death from malignancy. Fortunately, at the same time there has been a lower rate of progression from HIV-carrier status to AIDS. The net effect is that the surge in anorectal lymphomas may be over; in San Diego County, the incidence of AIDS-related NHL fell from 26 per 1000 person-years to 6.5 per 1000 person-years in the period 1988 to 1995 compared with 1996 to 2000.[46]

The treatment of anorectal lymphoma is drastically different depending on the HIV status and grade of the lymphoma. Surgical excision is necessary to obtain adequate tissue for histologic diagnosis. AIDS-related B cell lymphomas are classified as highly aggressive, but recently have been shown to benefit from combined HAART, chemotherapy, and granulocyte colony stimulation factor (GCSF). Non-AIDS related anorectal lymphomas are typically indolent lymphomas of the mucosal-associated lymphatic tissue (MALT) type. A retrospective series of 45 primary colorectal lymphomas treated prior to 1987 at St. Mark's and St. Bartholomew's hospitals (London, UK) reported that the majority of localized rectal lymphomas were treated by radical resection, those receiving adjuvant radiation seemed to have improved survival.[44] Current National Comprehensive Cancer Network (NCCN) guidelines recommend observation if excision yields negative margins; locoregional radiation is used if margins are positive. Local recurrence can be treated with radiation, whereas stage III-IV disease or systemic recurrence is treated like follicular lymphoma.[47]

REFERENCES

1. Madeleine MM, Newcomer LM, eds. Cancer of the anus. National Cancer Institute's's Surveillance, Epidemiology, and End Results Program (SEER). Bethesda, MD: National Cancer Institute; 2007:43
2. Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol 1998; 152(5):1259–1269
3. Hatch KF, Blanchard DK, Hatch GF III, et al. Tumors of the rectum and anal canal. World J Surg 2000;24(4):437–443
4. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol 2002;33(5):459–465
5. Nigri GR, Dente M, Valabrega S, et al. Gastrointestinal stromal tumor of the anal canal: an unusual presentation. World J Surg Oncol 2007;5:20
6. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of C-KIT in human gastrointestinal stromal tumors. Science 1998;279(5350):577–580
7. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med 2006;130(10): 1466–1478
8. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000;231(1):51–58
9. Miettinen M, Furlong M, Sarlomo-Rikala M, Burke A, Sobin LH, Lasota J. Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the rectum and anus: a clinicopathologic, immunohistochemical, and

molecular genetic study of 144 cases. Am J Surg Pathol 2001;25(9):1121–1133
10. Eisenberg BL, Judson I. Surgery and imatinib in the management of GIST: emerging approaches to adjuvant and neoadjuvant therapy. Ann Surg Oncol 2004;11(5):465–475
11. Katz SC, DeMatteo RP. Gastrointestinal stromal tumors and leiomyosarcomas. J Surg Oncol 2008;97(4):350–359
12. Miettinen M, Sarlomo-Rikala M, Sobin LH. Mesenchymal tumors of muscularis mucosae of colon and rectum are benign leiomyomas that should be separated from gastrointestinal stromal tumors—a clinicopathologic and immunohistochemical study of eighty-eight cases. Mod Pathol 2001;14(10): 950–956
13. Hassan I, You YN, Dozois EJ, et al. Clinical, pathologic, and immunohistochemical characteristics of gastrointestinal stromal tumors of the colon and rectum: implications for surgical management and adjuvant therapies. Dis Colon Rectum 2006;49(5):609–615
14. Tworek JA, Goldblum JR, Weiss SW, Greenson JK, Appelman HD. Stromal tumors of the anorectum: a clinicopathologic study of 22 cases. Am J Surg Pathol 1999;23(8):946–954
15. Vorobyov GI, Odaryuk TS, Kapuller LL, Shelygin YA, Kornyak BS. Surgical treatment of benign, myomatous rectal tumors. Dis Colon Rectum 1992;35(4):328–331
16. Demetri GD, Benjamin RS, Blanke CD, et al; NCCN Task Force. NCCN Task Force report: management of patients with gastrointestinal stromal tumor (GIST)—update of the NCCN clinical practice guidelines. J Natl Compr Canc Netw 2007;5(Suppl 2):S1–S29, quiz S30
17. Levy AD, Remotti HE, Thompson WM, Sobin LH, Miettinen M. Anorectal gastrointestinal stromal tumors: CT and MR imaging features with clinical and pathologic correlation. AJR Am J Roentgenol 2003;180(6):1607–1612
18. Dematteo RP, Gold JS, Saran L, et al. Tumor mitotic rate, size, and location independently predict recurrence after resection of primary gastrointestinal stromal tumor (GIST). Cancer 2008;112(3):608–615
19. Haque S, Dean PJ. Stromal neoplasms of the rectum and anal canal. Hum Pathol 1992;23(7):762–767
20. DeMatteo RP, Owzar K, Antonescu CR, et al. Efficacy of adjuvant imatinib mesylate following complete resection of localized, primary gastrointestinal stromal tumor (GIST) at high risk of recurrence: The US. Intergroup Phase II Trial ACOSOG z9000 (Abstract No. 8). Abstract presented at: American Society of Clinical Oncology 2008 Gastrointestinal Cancers Symposium; January 25–27, 2008; Orlando, FL
21. DeMatteo R, Owzar K, Maki R, et al. Adjuvant imatinib mesylate increases recurrence free survival (RFS) in patients with completely resected localized primary gastrointestinal stromal tumor (GIST): North American Intergroup Phase III Trial ACOSOG z9001 (Abstract No. 10079). Abstract presented at: 2007 American Society of Clinical Oncology Annual Meeting; June 1–5, 2007; Chicago, IL
22. Walsh TH, Mann CV. Smooth muscle neoplasms of the rectum and anal canal. Br J Surg 1984;71(8):597–599
23. Changchien CR, Wu MC, Tasi WS, et al. Evaluation of prognosis for malignant rectal gastrointestinal stromal tumor by clinical parameters and immunohistochemical staining. Dis Colon Rectum 2004;47(11):1922–1929
24. Li JC, Ng SS, Lo AW, Lee JF, Yiu RY, Leung KL. Outcome of radical excision of anorectal gastrointestinal stromal tumors in Hong Kong Chinese patients. Indian J Gastroenterol 2007; 26(1):33–35
25. Baik SH, Kim NK, Lee CH, et al. Gastrointestinal stromal tumor of the rectum: an analysis of seven cases. Surg Today 2007;37(6):455–459
26. Chen CW, Wu CC, Hsiao CW, et al. Surgical management and clinical outcome of gastrointestinal stromal tumor of the colon and rectum. Z Gastroenterol 2008;46(8):760–765
27. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347(7):472–480
28. Artinyan A, Kim J, Soriano P, Chow W, Bhatia S, Ellenhorn JD. Metastatic gastrointestinal stromal tumors in the era of imatinib: improved survival and elimination of socioeconomic survival disparities. Cancer Epidemiol Biomarkers Prev 2008; 17(8):2194–2201
29. Hohenberger P. Should adjuvant imatinib be used as primary treatment for gastrointestinal stromal tumors? Nat Clin Pract Oncol 2008;5(5):240–241
30. Rutkowski P, Nowecki Z, Nyckowski P, et al. Surgical treatment of patients with initially inoperable and/or metastatic gastrointestinal stromal tumors (GIST) during therapy with imatinib mesylate. J Surg Oncol 2006;93(4): 304–311
31. Eisenberg BL, Harris J, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. J Surg Oncol 2009;99(1):42–47
32. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006;368(9544):1329–1338
33. Caldarola VT, Jackman RJ, Moertel CG, Dockerty MB. Carcinoid tumors of the rectum. Am J Surg 1964;107:844–849
34. Soga J. Early-stage carcinoids of the gastrointestinal tract: an analysis of 1914 reported cases. Cancer 2005;103(8):1587–1595
35. Landry CS, Brock G, Scoggins CR, McMasters KM, Martin RC II. A proposed staging system for rectal carcinoid tumors based on an analysis of 4701 patients. Surgery 2008;144(3): 460–466
36. Pinchot SN, Holen K, Sippel RS, Chen H. Carcinoid tumors. Oncologist 2008;13(12):1255–1269
37. Orloff MJ. Carcinoid tumors of the rectum. Cancer 1971; 28(1):175–180
38. Oberg K. Carcinoid tumors, the carcinoid syndrome, and related disorders. In: Kronenberg HM, ed. Williams Textbook of Endocrinology. Philadelphia, PA: Saunders Elsevier; 2008:1821
39. Memon MA, Nelson H. Gastrointestinal carcinoid tumors: current management strategies. Dis Colon Rectum 1997;40(9): 1101–1118
40. Jetmore AB, Ray JE, Gathright JB Jr, McMullen KM, Hicks TC, Timmcke AE. Rectal carcinoids: the most frequent carcinoid tumor. Dis Colon Rectum 1992;35(8): 717–725
41. Fahy BN, Tang LH, Klimstra D, et al. Carcinoid of the rectum risk stratification (CaRRS): a strategy for preoperative outcome assessment. Ann Surg Oncol 2007;14(2):396–404
42. Kwaan MR, Goldberg JE, Bleday R. Rectal carcinoid tumors: review of results after endoscopic and surgical therapy. Arch Surg 2008;143(5):471–475

43. Koura AN, Giacco GG, Curley SA, Skibber JM, Feig BW, Ellis LM. Carcinoid tumors of the rectum: effect of size, histopathology, and surgical treatment on metastasis free survival. Cancer 1997;79(7):1294–1298
44. Shepherd NA, Hall PA, Coates PJ, Levison DA. Primary malignant lymphoma of the colon and rectum. A histopathological and immunohistochemical analysis of 45 cases with clinicopathological correlations. Histopathology 1988;12(3): 235–252
45. Ioachim HL, Antonescu C, Giancotti F, Dorsett B, Weinstein MA. EBV-associated anorectal lymphomas in patients with acquired immune deficiency syndrome. Am J Surg Pathol 1997;21(9):997–1006
46. Diamond C, Taylor TH, Aboumrad T, Anton-Culver H. Changes in acquired immunodeficiency syndrome-related non-Hodgkin lymphoma in the era of highly active antiretroviral therapy: incidence, presentation, treatment, and survival. Cancer 2006;106(1):128–135
47. The NCCN. Clinical Practice Guidelines in Oncology™ Non-Hodgkin Lymphoma (Version I. 2009). Fort Washington, PA: National Comprehensive Cancer Network, Inc.; Available at: http://www.nccn.org. Accessed February 15, 2009