

Morphology of Gastrointestinal Stromal Tumors: Historical Perspectives

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About 2/3 of gastrointestinal stromal tumors occur in the stomach and about 1/5 in the small intestine with few in the rectum, colon, and esophagus. Their cells are related to the interstitial cells of Cajal. They differ by site in terms of cell type and growth pattern. Benign and malignant tumors are separated based on their light microscopic appearances, size as measured by innumerable pathologists and assistants and mitotic counts. *J. Surg. Oncol.* 2011;104:874–881. © 2011 Wiley Periodicals, Inc.

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INTRODUCTION

Mesenchymal tumors, both benign and malignant, occur throughout the gastrointestinal tract. Back in the early years of surgical pathology, they were thought to be smooth muscle tumors [1–11]. This should come as no surprise. After all, most of these tumors were composed of spindle cells, and the walls of the gut were full of spindled smooth muscle cells, mostly in the thick layer of muscularis propria, but also in the thinner muscularis mucosae and in the muscle of the blood vessels. So even if the constituent cells did not look very smooth muscle-ish, there was little reason not to consider these tumors to contain neoplastic smooth muscle cells. There are other types of normal gut spindled mesenchymal cells, including fibroblasts and myofibroblasts wherever there is collagen, endothelial cells of blood vessels and lymphatics and Schwann cells in the submucosal and myenteric nerve plexuses. One additional cell type accompanies the ganglion cells and Schwann cells especially in the myenteric plexus, the interstitial cells of Cajal, which are important in pacemaking and interactions among ganglion cells. As will be seen later in this chapter, these interstitial cells have become the cell darlings of the neoplastic mesenchymal gut.

Now we recognize that mesenchymal neoplasms of the gut fall into two categories. The first and the smaller category includes neoplasms that are identical to those that arise in the somatic soft tissues. In this group, the benign neoplasms contain differentiated mesenchymal cells, such as smooth cells in leiomyomas. Most GI leiomyomas are tiny and are found in the esophagus and less frequently in the rectum. Large, typical totally differentiated leiomyomas are rare in the stomach, small bowel, and colon, which might seem bizarre, considering the amount of smooth muscle in those parts of the gut. Submucosal lipomas composed of mature adipocytes arise all throughout the gastrointestinal tract, but they are found mainly in the colon. Patients with von Recklinghausen's disease may form plexiform neurofibromas anywhere in the gut, although they are most common in the colon. Hemangiomas and lymphangiomas occur throughout the gut, but they are uncommon. The typical malignant counterparts, leiomyosarcomas, malignant Schwannomas, and angiosarcomas also arise in the gut, but they are curiosities. By this time, it is likely that published case reports exist for at least one of every imaginable somatic soft tissue tumor, both benign and malignant, that has arisen in the gastrointestinal tract, including liposarcoma, synovial sarcoma, rhabdomyosarcoma, osteosarcoma, and the malignant fibrous histiocytoma/pleomorphic sarcoma group.

The second and far larger and much more important group of mesenchymal tumors is almost unique to the gut, meaning that they are really, really rare anywhere else, except for a few in the mesentery,

omentum, and retroperitoneum. These common mesenchymal tumors of the gut are not the same as those arising in the somatic soft tissues. They are neoplasms composed of spindled cells or, less commonly, rounded (epithelioid) cells, that do not look like differentiated smooth muscle cells, Schwann cells or, for that matter, any other differentiated cell. As a result, they have been given their own name, "gastrointestinal stromal tumors" or GISTs for short. GISTs are mainly spindle cell tumors, although some, especially in the stomach, are composed of epithelioid cells. They are not homogeneous, but they differ in cell type and growth pattern from one part of the gut to another, both anatomically and behaviorally. GISTs are uncommon enough so that in the early reports, it became clear that no institution had accumulated enough of them for statistically significant data. As a result of the rarity of these tumors, many early studies grouped all tumors from all sites together in order to get enough cases for statistical data analysis [3,10,12]. This approach ignored site differences. Such studies were equivalent to combining adenocarcinomas from esophagus, stomach, small bowel, and colorectum and analyzing them as if they were homogeneous carcinomas. We know that carcinomas from all these sites are not the same. They differ in epidemiologic associations, genetic alterations, behavior, method of spread, and histologic features. Were a pathologist to undertake such a study and attempt to publish the results, he or she would probably lose credibility very quickly. Furthermore, the relative rarity of these tumors has required that single institutional studies include cases seen over many decades, thus covering a range of medical care capabilities from the rather primitive of 50 years ago to the sophistication of today. Thus, the lack of large case series analyzing these tumors separately by site and by different treatments undoubtedly led to the fact that GISTs have been surrounded by a mystique that has confounded pathologists, abdominal surgeons, and oncologists, although things are becoming less mystical as new data emerges on classification, genetic changes, and treatment. This is in large part due to the studies from the Armed Forces Institute of Pathology in Washington, DC which has thousands of GISTs, and some centers that are involved in treatment protocol studies that have hundreds [5,6,13–24].

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THE GIST CONTROVERSIES

Historically, GISTs have stimulated two areas of investigation and resultant debate: first, what is their *differentiation*, that is, *what types of cells do they contain*; and second, what is their *clinical behavior*, that is, *how can we reliably tell those that are benign from those that are malignant*. Unfortunately in attempts to answer these questions, we were hindered in our understanding because, as mentioned above, too many early studies grouped GISTs from all sites and all treatment modalities together.

The Differentiation Issues

Virtually from the outset, the literature concerning gastrointestinal mesenchymal tumors has been confused by the peculiarly common misconception that the origin of a tumor is synonymous with its differentiation. In general, origin means cell of origin, and such precursor cells are not known for any mesenchymal tumor anywhere in the body. Presumably they are some types of undifferentiated stem cell or cells which differentiate as a result of appropriate stimuli. In contrast, differentiation refers to the expression of adult phenotypic characteristics that exist in recognizable tissues, such as smooth or skeletal muscle, Schwann cells, endothelial cells, and adipocytes. Thus, differentiation has nothing to do with origin. In order not to perpetuate this confusion, in this chapter, the term "origin" will not refer to the cell of origin, but to the tissue in which a tumor develops. Most of the discussion therefore will concentrate on differentiation.

The *differentiation* debate resulted from our inability to find consistent mature smooth muscle or Schwann cell features either by light microscopy, electron microscopy, immunohistochemistry or any combination. Certainly, with all the smooth muscle in the gastrointestinal tract, it would be foolish to avoid designating all of these tumors, especially those composed of spindle cells, as smooth muscle tumors, unless there were compelling reasons to do so. As mentioned in the first part of this chapter, the early students of gut mesenchymal tumors were no fools, because they usually referred to these tumors as leiomyomas or leiomyosarcomas. These designations were based upon the light microscopic suggestions of fibrillar cytoplasm in the cells of many of these tumors, the pericellular reticulin fibers which seemed to indicate smooth muscle differentiation, the blunt-ended nuclei which were considered at one time to be a hallmark of the smooth muscle cell, and the fact that many tumors occurred partly or completely within the muscularis propria.

The fact that some tumors contained epithelioid cells which were rounded or polygonal instead of, or as well as, spindle cells, added confusion to the smooth muscle differentiation issue [25,26]. Clearly, these rounded cells do not look like any normal mesenchymal cells of the gut and certainly not like smooth muscle. Some tumors, especially those in the stomach, were even composed entirely of epithelioid cells, but the smooth muscle aura haunted even these unusual tumors, and they were also given smooth muscle names. In fact, the first detailed publications on these epithelioid cell gastric tumors, one by Martin from France and one by Stout in the United States designated them as smooth muscle tumors. Stout even made up a new smooth muscle name for them, "leiomyoblastoma." Then, as if to confuse pathologists even more, there is a gastric mesenchymal tumor that contains spindle cells arranged in the most spectacular palisades imaginable. Who could blame any sane pathologist for deciding such a tumor was a Schwannoma or a neurilemmoma? Thus, there is a body of literature that refers to such a subset of palisaded spindle cell gastric tumors as nerve sheath lesions of one type or another.

Since light microscopic examination alone was not giving unimpeachable evidence of differentiation, it was hoped that the final decisions concerning differentiation would result from two new technical developments, namely electron microscopy and the

immunohistochemical identification of cytoplasmic proteins, some of which occurred in filaments in the cytoplasm. It was assumed that these highly sophisticated techniques should be ready made to tell us exactly what kind or kinds of differentiated cells were contained within these peculiar tumors. Much to the dismay of the students in this field, neither technique turned in completely satisfactory performances for many years.

Electron microscopic studies, beginning in the late 1960s and continuing through the mid-1980s, found that most tumor cells were undifferentiated, although some had a few imperfect smooth muscle or Schwann cell features. In these studies, it appeared that most of the cells of most stromal tumors, regardless of site of origin, lacked cytoplasmic sophistication [27–32]. There were mitochondria, occasional profiles of endoplasmic reticulum of smooth and granular type, scattered ribosomes, an occasional filament or two, but nothing that was characteristic of a differentiated mesenchymal cell type. An occasional cell had some minor features which suggested smooth muscle differentiation such as a few pinocytotic vesicles, or an increase in the number of cytoplasmic microfilaments, with occasional aggregation into dense bodies. A rare cell contained a subplasmalemmal linear density, also a smooth muscle feature. However, none of these cells were even close to normal smooth muscle cells in terms of cytoplasmic differentiation.

In a few cells of other tumors, there were minor suggestions of Schwann cell differentiation including elongated processes which seemed to be tightly applied to each other and occasionally even bits of pericellular basement membrane. In occasional tumors, the cells contained structures that suggested nerve differentiation, including synaptic vesicles, and such tumors were even given their own special designation, namely, "gastrointestinal autonomic nerve tumors" or "GANTs" [33–35]. However, in order to determine if a tumor belongs in this class, electron microscopic examination was necessary, because by light microscopy, the tumors designated as autonomic nerve tumors were identical to other common stromal tumors in the specific sites in which they arose. Therefore, no distinctions are now made between the autonomic nerve tumors and the other typical tumors that look the same.

Electron microscopic examination is expensive and time-consuming, and in spite of its ability to show exquisite cellular and matrix detail, it still was no help in clarifying the type of cell or cells in these peculiar, uniquely gastrointestinal stromal tumors. In spite of these occasional flirtations with differentiation by electron microscopic examination, the overwhelming cellular constituents of almost all tumors were found to be neither differentiated Schwann cells nor differentiated smooth muscle nor differentiated anything else. In fact, they were not even differentiated fibroblasts. This was the case for all the common stromal tumors arising throughout the gut.

The generic "stromal tumor" name was first used in a 1983 article on gastric tumors by Mazur and Clark [30]. They used electron microscopy to attempt to define the constituent cells, and as in previous studies, they found that the tumor cells were neither smooth muscle nor Schwann cells, but they made the prophetic suggestion that the cells may have something to do with cells of the myenteric nerves. This would prove to be true in another article almost two decades later. Now these tumors are all referred to as "gastrointestinal stromal tumors," or "GISTs" for short. It took a while for this terminology to gradually gain acceptance, and is now the standard in the literature, regardless of the medical specialty. Malignant stromal tumors may be referred to simply as "sarcomas," but that has not gained much acceptance, so they are called malignant GISTs. Specific smooth muscle or neural designations are now reserved for tumors that are composed entirely of unquestionably differentiated smooth muscle cells or Schwann cells.

Immunohistochemical studies began to appear in the mid-80s using early generation antibodies and detection systems [12,34–37]. The only consistently positive marker was *vimentin*, a cell protein that does not occur in mature smooth muscle cells of the gut muscularis,

although it does occur in endothelium and in fibroblasts. It is amazing that among these early immunohistochemical studies, cells of histologically identical tumors were reported to express smooth muscle markers such as an actin, Schwann cell markers such as S-100, *both* or *neither*. There had to be differences in antibodies, techniques, fixatives, and interpretations to explain these differences. As newer antigens were identified and antibodies to them produced, they were thrown at GISTs with variable success in defining differentiation of the cells. It is only following the discovery by Hirota et al., published in 1998 [38], that most GISTs had mutations in the c-kit gene, that we began to use antibodies to the c-kit protein and discover that GISTs contain that protein. In fact, about 95% of all GISTs are c-kit positive, or if they are not, then they usually have the c-kit mutation or a mutation in a related kinase gene, the platelet-derived growth factor receptor alpha (PDGFR- α) gene [13–16,39,40]. The antibody currently used widely is CD117. The indigenous GI tract cell that also contains that protein is the interstitial cell of Cajal (ICC), a neural cell in the myenteric plexus that is said to have a pacemaker function. Presumably these are the cells that led to the concept of a GANT. Once the ICC connection was discovered, the concept of the GANT has disappeared. GISTs also contain heavy molecular weight caldesmon, a protein found in smooth muscle, but also in some ICCs. Thus, after 40 years of trying to determine the cell type in these tumors, the last dedicated to immunohistochemistry, we have come to the conclusion that GISTs are tumors that are composed of either interstitial cells of Cajal, closely related cells or their precursors. As a result, there is no longer any debate on differentiation.

The Behavior Issue

Our ability to predict behavior was hampered by the fact that these are rare tumors, and any series included cases seen over many decades during which medical and surgical care has evolved dramatically. Then there is the annoying fact that both benign and malignant GISTs are composed of similar cells, so telling benign from malignant based upon cellular differentiation has been tough. GISTs can be separated into three behavioral categories: (1) obviously benign; (2) obviously malignant; and (3) of indeterminate behavior. Some indeterminate tumors have a mix of benign and malignant features, so they present mixed histologic messages. Others are indeterminate because they are unique, and we have no experience with them. The number of cases that are put into the indeterminate category is inversely related to the experience of the pathologist who makes the diagnosis. In general, the malignant tumors are obviously malignant. It is the benign tumors that cause the problems, since many or even most pathologists are uncomfortable diagnosing any GIST as benign, probably because of limited experience with them. Furthermore, patients with tumors that are diagnosed as benign are not as likely to have follow-up as those with tumors diagnosed as malignant. Cancer registries follow patients with malignant, not benign tumors. Many malignant GISTs contain benign areas, and some benign GISTs contain tiny foci that look malignant. These facts suggest that malignant GISTs arise in pre-existing benign tumors. There is no data to indicate how large a malignant component in an otherwise benign tumor makes the whole tumor malignant.

Behavioral predictions, in most studies, have been based upon the morphologic features of cellularity, mitoses, size, ischemic necrosis, and pleomorphism [14–16,40]. The results of numerous studies have been inconsistent in regard to specific features, but all agree that the malignant GISTs are more cellular, more mitotically active, and bigger than are their benign counterparts, although what is cellular, mitotically active and big varies from study to study and from one primary site to another. The evaluation of cellularity is difficult unless the pathologist has a lot of experience with these tumors. Thus, cellularity has not been a satisfactory criterion to teach or to analyze, although it is really very important. Nevertheless, we have been able to train our house officers and fellows to recognize the difference between benign and malignant

cellularity. Mitotic counts are quantitative data, but counts are not reproducible from one observer to another. If size is considered to be an independent determinant of malignancy, then there will be no such thing as a large benign tumor, and we know for a fact that large benign tumors occur, especially on the greater curvature of the stomach. Furthermore, size is also not a reproducible measurement, and in the studies in which size has been thought to be an important prognostic feature, the tumors were measured by many different individuals with different interests in precise measurements, and they were measured during various degrees of fixation. However, size is probably a *stage* indicator for the malignant GISTs, since size and metastases and/or death from tumor are related, much as they are for many other cancers throughout the body. Nuclear and cellular pleomorphism is uncommon in GISTs, except that it is common in benign epithelioid cell tumors of the stomach. Many tumors, even benign ones, if they grow large enough, have central necrosis. Mucosal invasion is a superb marker of malignancy, whereas invasion of deeper layers is not, except in the abdominal colon. However, in extensively ulcerated tumors, mucosal invasion may not be found because the ulcer obliterates the invaded mucosa. Also we have seen small foci of mucosal invasion in otherwise completely benign tumors, and we do not know if this indicates different behavior. Tumor rupture was reported to be an adverse prognosticator in one study from Finland. DNA content and proliferative indices may help to separate benign from malignant, but the data are not conclusive, so these parameters have not been useful in individual cases.

A consensus conference at the National Cancer Institute was convened in April 2001 to discuss GISTs, their differentiation, their response to treatment and how to tell benign from malignant tumors. The result was a set of recommendations for determining risk of aggressive behavior based on a combination of mitoses and size, in spite of the limitations involving reproducibility of both measurements as outlined above in Table I. [41]

Table I does not recognize any differences in site of origin, but lumps tumors in all sites together. It also does not recognize the existence of benign tumors, and certainly not large benign tumors.

For the inexperienced pathologist, this is a way of deciding what is malignant and how bad it is likely to be based only on numbers, in other words, an escape from needing experience. From my standpoint, however, the best way to tell if a GIST is malignant is to study its microscopic features carefully and use *multiple parameters*, including those mentioned above. No one feature, by itself is a perfect indicator of malignancy. Also all available data has resulted from *retrospective* studies, and there are no studies that have applied specific criteria *prospectively* in order to prove if they work.

A more recent modification separates the two major primary sites, stomach and small intestine to reflect the fact that proportionately more small intestinal tumors are malignant compared to stomach tumors [42].

TABLE I. Proposed Approach for Defining Risk of Aggressive Behavior in GISTs (From the NCI Consensus Conference of April 2001)

	Size in cm	Mitoses/50 HPF
Very low risk	<2	<5
Low risk	2–5	<5
Intermediate risk	<5	6–10
	5–10	<5
High risk	>5	>5
	>10	Any count
	Any size	>10

The risk refers to adverse outcome, such as metastases.

TABLE II. Modified Approach for Defining Risk of Aggressive Behavior in GISTs, Separating Stomach from Small Bowel (2007) [42]

Mitotic index	Tumor feature	Risk of tumor progression	
	Size (cm)	Stomach	Small bowel
<5 per 50 HPF	≤2	Very low	Very low
	>2 ≤ 5	Very low	Low
	>5 ≤ 10	Low	Moderate
≥5 per 50 HPF	>10	Moderate	High
	≤2	Very low	Moderate
	>2 ≤ 5	Moderate	High
	>5 ≤ 10	High	High
	>10	High	High

At the end of Table II, the authors suggest that GISTs arising in other sites should probably be stratified in a similar fashion as small bowel tumors. In truth, there is little data to support that.

A major problem with the tumor designations based on site, size, and mitoses is that no tumor is recognized as benign. Every tumor is given a risk or progression, no matter how small and no matter how bland they appear histologically. We know that some tumors, even large ones, never progress and are potentially definable as benign. Perhaps these charts will 1 day be further modified to reflect this.

Drugs aimed at the kinases on the membranes of the malignant GIST cells have altered the behavior of many advanced tumors. As a result, the natural history of these tumors has already changed dramatically, and is likely to change even further as more tumors are treated with specific drugs and fewer tumors are allowed to run their natural courses.

Now that we have some criteria, no matter how imperfect, from separating benign from malignant, and we now know the differentiation of the constituent cells, we can analyze the morphologic characteristics more specifically, with emphasis on site differences. First, the gross characteristics.

GROSS FEATURES

GISTs, both benign and malignant, are almost always circumscribed rather than infiltrative, although some of the largest malignant tumors grow as a confluence of multiple nodules. The smallest tumors are confined to the submucosa, muscularis propria, or both in combination, while the large ones also protrude into the subserosa. The smallest tumors are solid. The cut surfaces are pale and finely granular with scattered dark vascular spots. Larger ones, especially those that have ulcerated are likely to be cystic with central liquefaction and hemorrhage. Some of the largest tumors, both benign and malignant, have huge central cysts with only thin rims of viable tumor.

SITE SPECIFICITY

GISTs arise predominantly in the stomach and small intestine. Colonic GISTs are rare, whereas, rectal GISTs are more common. A few appendiceal GISTs have been reported, but there are too few for significant data analysis. Hardly any GISTs arise in the esophagus, yet the esophagus is the major site for totally differentiated leiomyomas. Specific GISTs, both benign and malignant, as well as mesenchymal tumors that are not GISTs, generally arise in specific sites. Thus, the stromal tumors are not the same in all areas of the gastrointestinal tract. Furthermore, a particular type of tumor in one site may be predictably benign, whereas a histologically similar, although not necessarily identical, tumor arising in a second site may be predictably malignant. This type of local variability has been well known and totally accepted for mesenchymal tumors arising in extra-gastrointestinal sites.

For instance, we appreciate the fact that certain bone tumors arise commonly in certain bones and rarely or never in other bones. We know that rhabdomyosarcomas of the head and neck are likely to be of the embryonal subtype, whereas those of the peripheral soft tissues more commonly have the alveolar pattern. Similarly, the esophageal mesenchyme seems capable of producing a cast of tumors different from that produced by the mesenchyme in its immediately distal neighbor, the stomach.

Actually, there is one stromal tumor that is common to all sites. That is a small tumor located in the muscularis propria of any part of the gut, often straddling the myenteric plexus, which sometimes seems to blend with the tumor cells [43]. These tiny tumors are often sclerotic and periodically have calcific foci. Most of the reported tumors have been in the stomach, since that is where they are most common. They are usually found by abdominal surgeons who come across these tiny bumps during procedures for other reasons, such as cancer resections. Because of their location in the muscularis, they tend to look like subserosal nodules and resemble nodules of metastatic cancer. As a result, they are often sent for frozen section. For this reason, they have been known colloquially as “incidentalomas.” A recent publication referred them as “tumorlets,” a remarkably creative designation [43].

The following is a collection of often little known and possibly minimally important facts about GISTs and other mesenchymal tumors in specific sites in the gut. There are data concerning relative distribution, and likelihood of malignancy at each site.

Esophageal Stromal Tumors (ESTs)

In the esophagus, small, typical, differentiated leiomyomas frequently arise in the two muscle layers, especially the muscularis propria. Granular cell tumors occur here more than anywhere else. There are too few esophageal GISTs for there to be any meaningful conclusions about their morphologic characteristics and behavior. The largest series, that from the AFIP, only has 17 cases [17]. The few reported tumors seem to be identical to those in the stomach. In fact, some arose at the GE junction, so they may actually have been primary in the proximal stomach and not the distal esophagus.

Gastric Stromal Tumors (GASTs)

Since GASTs are the most common GISTs, by far, there is a richer literature about them than about stromal tumors elsewhere [5,6,9,11,18,19,27,44,45]. About 1/5 of the GASTs are malignant. The benign ones come in two varieties, spindle cell and epithelioid cell. Because the stomach floats within the upper peritoneal cavity and because of the size of the viscus itself, even benign stromal tumors can grow to enormous sizes, especially if they arise on the greater curvature and project into the peritoneal cavity or into the omentum. As a result, in the stomach, large benign tumors are more common than they are elsewhere. The benign spindle cell tumors often make spectacular microscopic palisades, and the cells commonly have a single vacuole that compresses the nucleus at one pole. Benign epithelioid cell tumors often contain giant cells, some with single nuclei and many with multiple nuclei, and these nuclei may be pleomorphic. In contrast, malignant epithelioid cell tumors rarely contain pleomorphic cells but are composed of small, tightly packed uniform cells. Malignant GASTs sometimes have an unusual myxoid stroma. Furthermore, although gastric stromal tumors are found mostly in the body of the stomach, some types arise preferentially in the cardia and fundus, while others are rarely found there. Thus, there is site specificity even within this single viscus. Malignant GASTs are aggressive tumors with a 5-year survival of about 40%. The most common metastatic sites are the peritoneal surfaces and liver, followed by the retroperitoneum and nodes in about 15% of cases. The only syndrome that includes gastric stromal tumors is Carney’s triad, which usually occurs in young females who

have multiple small malignant epithelioid cell tumors with a low metastatic risk, functioning mainly extra-adrenal paragangliomas that are also often multiple, and multiple pulmonary cartilaginous tumors or chondromas [46]. The most common combination is gastric and pulmonary tumors. Not every patient has all the three original parts of the syndrome. In a 1999 publication, Carney added three more components, non-functioning adrenal cortical tumors that occur in about 15% and esophageal leiomyomas and duodenal stromal tumors that occur in about 10% each [47].

The stomach is almost the exclusive gastrointestinal site for glomus tumors which can mimic the epithelioid GASTs, but which are composed of smooth muscle cells which stain accordingly. The stomach is also the most common site for a peculiar Schwannoma variant which is also composed of spindle but which makes a lot of collagen, something not found in stromal tumors, and it also tends to be surrounded by a cuff of lymphocytes.

Duodenal Stromal Tumors (DUSTs)

There are only a few publications dealing specifically with DUSTs, separate from other small bowel tumors [20,48]. Five to 10% of GISTs arise in the duodenum, mostly in the second part where they are equally split between benign and malignant. Tumors arising more distally are mostly malignant. DUSTs tend to be on the medial wall and push into or even invade the pancreas. Microscopically, they are almost all spindle cell tumors. There are several patterns of growth, which help to distinguish benign from malignant. Benign DUSTs often have an organoid pattern superficially in the submucosa, in which bundles of tumor cells are separated by fine fibrous septa containing small vessels. Benign tumors also commonly have rounded or elongated big lumps of collagen, known as skeinoid fibers, scattered among the spindle cells, especially deep in the tumors. In contrast, malignant DUSTs usually have neither an organoid pattern or skeinoid fibers. Almost all tumors larger than 4 cm across are malignant. The 5-year survival for malignant DUSTs is about 2½ years. The usual sites of metastases are liver in almost all cases, peritoneal surfaces, retroperitoneal soft tissue, bone, and nodes in about 25% each. Peculiarly, in the duodenum and the rest of the small bowel, predominantly epithelioid cell tumors are almost all malignant, in contrast to the stomach where they are mostly benign.

Small Intestinal Stromal Tumors (SISTs)

The small intestine is the second most common site for GISTs, so the literature is substantial [7,8,21,49–51]. About 1/5 of all SISTs arise in the jejunum and ileum. There have been a few reports of tumors arising within Meckel's diverticula, but most of these are probably tumors that have become centrally necrotic and cystic and therefore looked like diverticula. The findings of an organoid pattern and skeinoid fibers are as helpful in identifying benign tumors in the jejunoileum as in the duodenum. From various published reports, it seems that about 40–50% of all SISTs are malignant, although the number varies from study to study, and in many studies, the criteria for malignancy are not even stated.

The 5-year survival for all malignant SISTs is about 25%. Thus, most malignant SISTs are aggressive lesions. The usual sites of metastases are the liver and peritoneal surfaces in about 70%, the lung in only about 10% and the lymph nodes hardly ever.

There are two published studies in which specific morphologic features were correlated with known metastases. The results are comparable by univariate analysis with cellularity, mitotic count, size, epithelioid cell morphology, and mucosal invasion all of which correlated with metastases, but in the study that evaluated the parameters by multivariate analysis, only cellularity and mitoses were independent, significant markers of metastasis.

Colonic Stromal Tumors (COSTs)

There is little data on stromal tumors of the abdominal colon, because they are so uncommon [21,52]. Most of the published data lumps colonic with anorectal tumor, but they are separate entities and have to be analyzed separately. The largest published series only has 37 cases. They are perhaps only half as common as those in the rectum. As best as we can tell, stromal tumors of the abdominal colon are mostly malignant, are histologically composed of spindle cells, but are nevertheless histologically heterogeneous and behave aggressively. In fact, in the largest series, nearly all tumors over 1 cm across with more than five mitoses in 50 high power microscopic fields were fatal. In the only studies comparing colonic with rectal sarcomas, the 5-year survival for colonic tumors was close to 20%, while it was nearly 60% for rectal tumors. A few GISTs have been found in the appendix, but there are too few for meaningful data. The largest series only has four cases [23].

Rectal Stromal Tumors (RESTs)

The rectum, and, to a lesser extent, the sigmoid colon, contain two different mesenchymal neoplasms. One is a small nodular expansion of the muscularis mucosae, the leiomyomatous polyp. The second is a deep intramural highly cellular spindle cell stromal tumor which superficially resembles the benign spindle cell lesion in the stomach, but which is likely to be malignant [24,53–57]. RESTs tend to arise in the distal rectum, so they may appear to involve the anus as well, and some of the publications refer to the rectum and anus as being a single primary site. Most of them are composed of long, large spindle cells. In contrast to spindle cell tumors in other sites where the malignant tumors are composed of small, more crowded cells; in the rectum even the malignant ones have large cells. Histologically, the malignant RESTs are often deceptively benign appearing. Possibly because of their location in the muscularis propria which puts them deep in the pelvis, coupled with the difficulty in removing them completely short of an abdominal-perineal resection, these tumors tend to recur, occasionally several times before they metastasize. Furthermore, they are often slow growing, so recurrences may not appear until 5 or more years after resection, and several recurrences may occur before metastases appear. This has led to a problem analyzing survival, because too many reported cases of supposedly benign tumors have not been followed long enough to determine if they truly are benign. Ten years minimum follow-up may be necessary before a deep intramural rectal tumor can be thought of as benign, and in some cases even 10 years is not long enough. It is conceivable that almost every deep intramural spindle cell stromal tumor of the anorectum that involves the muscularis propria is malignant, maybe not at first, but subsequently after one or more recurrences. Those tumors completely confined to the submucosa seem to behave as if they are benign, although some of them are histologically bizarre.

HOW TO DEAL WITH GISTs IN THE MANAGED CARE ENVIRONMENT?

Managed care stresses fiscal responsibility, often coupled with profit for the provider, at the same time not always emphasizing excellence in quality. The following are the important GIST issues with which pathologists must deal, in order to accomplish efficient, satisfactory diagnosis, recognizing economic constraints, yet without sacrificing quality.

The Use of Needle Biopsies

These days, many GISTs are first encountered by pathologists as needle biopsies of large intra-abdominal masses. Because of current drug therapy for malignant GISTs that require not just the GIST

diagnosis but demonstration of *c-kit* positivity, pathologists dealing with these small samples are faced with several potential problems.

- (1) First, we have to determine if the biopsy came from a GIST or some other tumor type. We have seen such biopsies that we cannot classify with confidence.
- (2) Sometimes it may not be possible, based solely on imaging studies, to determine if a huge abdominal tumor has arisen in the gut or in some other site such as the omentum, mesentery, or retroperitoneum.
- (3) Furthermore, it may not be possible to tell in what part of the gut a huge tumor arose. Right now, we do not know how important site of origin is in determining the efficacy of the new therapies.
- (4) Once we determine that the tumor is a GIST, then we need to determine if it is malignant. Most malignant GISTs are easy to diagnose as malignant based on cellularity and mitoses. There are large benign tumors that may be needled, and it may be difficult to determine with confidence if that tumor is malignant, based upon the small sample size. In many sarcomas, there are areas that look benign. Ancillary findings, including mucosal invasion will not be present in needle biopsies.
- (5) If the tumor is a GIST and it is malignant, how should a negative c-kit stain be interpreted? A small set of GISTs are kit negative. In addition, we have seen GISTs with variable c-kit staining from one area to another, and the needle may only capture a negative focus.
- (6) Furthermore, how should we interpret a tumor that does not look like a GIST, but which is c-kit positive? As we examine more and more mesenchymal tumors with better antibodies, we may find that there are non-GISTs that are c-kit positive. About a quarter of angiosarcomas are kit positive as are most mesenteric fibromatoses, although neither of these look anything like a GIST. Melanomas which can resemble malignant GISTs are also often positive.

At the moment, these issues have not been resolved, but they will have to be resolved, if needle biopsies are to be considered as diagnostically definitive and if they direct therapy.

The Use of Frozen Section and Gross Intra-Operative Consultation

Many GISTs are discovered incidentally during laparotomies for other reasons, so they are surprises to the surgeon, who may want to know immediately what type of tumor it is. Since GISTs are expansile intramural tumors with variable extramural components, the *gross* differential diagnosis is GIST, metastatic tumor, and much less likely, lymphoma. Primary GI carcinomas do not have such gross appearances. If the size guidelines are used to help determine if a tumor is malignant, the careful size measurement should be undertaken. Perhaps measuring it three or four times by different pathologists may help to alleviate measurement inconsistency.

On a frozen section, often the best a pathologist can often do is to identify the tumor as mesenchymal, but even that can be difficult, especially with the epithelioid cell gastric tumors that mimic carcinoma on frozen section. The determination of whether it is benign or malignant usually can only be made later when the permanent sections are available. Even in proven malignant tumors, the mitotic rate can be very low, no more than one or two mitotic figures in 50 high power microscopic fields, an impossible determination to make on frozen section. Furthermore, almost every benign tumor looks highly cellular on frozen sections that are usually much thicker than permanent sections. In rare tumors the cellularity and numbers of mitotic figures are so great that the diagnosis of malignancy is easy, even on frozen section. If a tumor is malignant, then, as mentioned above, size

correlates with metastatic risk. If the surgeon asks us to evaluate the margins of resection, that usually can be done grossly, since these are not very infiltrative tumors.

The Best Use of the Pathologist's Time

Careful evaluation of the H&E stained sections is most important, looking for the features described above. Mitotic counts are not reproducible from one pathologist to another, but if a pathologist adheres to the current diagnostic and staging guidelines such as are part of the first ever AJCC GIST staging in 2010, then counting mitoses is necessary. If the tumor has mitoses that are easily found when scanning several high power fields, that is good, although not unequivocal, evidence of malignancy. There are no rules based on proven facts as to how many blocks of a tumors are necessary to evaluate, but in my undocumented experience, no more than 4–5 blocks, even from the largest tumors, will probably be sufficient to tell if it is malignant. If the tumor is ulcerated, a couple of blocks from the ulcer edges in order to detect mucosal invasion are suggested.

The Need for Special Studies

This is dealt with in Chapter 1. Actually there is not a single immuno stain or combination of stains that will improve diagnosis over simple H&E, but staining for c-kit protein seems to be the standard for diagnosis. Therefore, if a bowel wall tumor is suspected as being a GIST, then the only stain that needs to be done is the c-kit. If that is negative, then other antibodies can be used. A c-kit negative tumor is unlikely to be a GIST, since few GISTs are kit negative, but remember that a few of them are.

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