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Gastric Smooth Muscle Tumors: Diagnostic Dilemmas and Factors Affecting Outcome

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Abstract. We reviewed the 46 gastric stromal tumors that were treated at our institution between 1958 and 1992. The most common presenting symptoms were gastrointestinal bleeding, pain, and fatigue or malaise. The tumors ranged from 4 to 150 mm, with surgery most often being a wedge excision or partial gastrectomy. Abdominal computed tomography was the most specific diagnostic test obtained preoperatively. Factors associated with decreased survival included size ≥ 8 cm ($p = 0.02$), more than 0–3 mitoses per 10 HPF ($p < 0.001$), positive margins or unresectability ($p = 0.008$), and tumor pathologic grade II or more ($p = 0.004$). These tumors have an unpredictable behavior. Surgical resection with negative margins remains the best therapy, but resection for palliation is sometimes indicated as it can be associated with prolonged survival.

Gastric smooth muscle tumors often present a management problem to the surgeon. They are so uncommon that even large series have relatively few patients [1–8]. Furthermore, the criteria for malignancy are so unreliable that sometimes only in retrospect can the tumor be called benign or malignant based on its behavior years subsequent to resection [9–11]. We reviewed the Lahey Clinic experience with these tumors from 1958 to 1992 in an attempt to define the spectrum of disease and to evaluate factors that affect outcome after surgery.

Materials and Methods

The hospital and outpatient records of 46 patients treated surgically for smooth muscle tumors of the stomach were reviewed for the years 1958 to 1992. For clarity of analysis, tumors arising elsewhere in the gastrointestinal (GI) tract were not included. The original pathology slides were reviewed by one pathologist for nuclear grade and mitotic count. The operative notes and the pathologic gross description, if any, were used to assign tumor size. Follow-up was obtained by chart review and telephone. Adjusted and disease-free survival distributions were calculated by the product-limit method of Kaplan and Meier using BMDP1L statistical software. Statistical significance of differences between distributions was analyzed by the Tarone-Ware method. Probability values are two-tailed with $p < 0.05$ regarded as statistically significant.

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Results

There were 46 patients (19 women, 27 men) with a median age of 62 years (41–93 years). The most common presenting symptoms were anemia or GI bleeding (39%), followed by pain (26%), fatigue or malaise (22%), early satiety (13%), and abdominal distension (9%). Ten patients were asymptomatic, their tumors being found at laparotomy. The median size of the tumors of the asymptomatic patients was 20 mm (4–120 mm) and that of the patients with symptoms 35 mm (4–150 mm). The duration of symptoms in those who had them ranged from less than 1 month to 6 years (median 6 months).

The preoperative evaluation suggested the diagnosis of "smooth muscle tumor" in 18 patients (39%); in 6 others the less specific diagnosis of "stomach tumor" was made (total 52%). Of the tests performed, computed tomography (CT) was the most accurate, suggesting the diagnosis of smooth muscle or stomach tumor in 10 of 10 cases in which it was obtained (Fig. 1). A barium upper GI series suggested this diagnosis in 23 of 31 cases (74%) and endoscopy in only 13 of 22 cases (59%). In all cases, when a lesion was seen endoscopically it was biopsied; however, only 3 of these 13 cases revealed the diagnosis of smooth muscle tumor. One case was biopsied endoscopically, and the lesion was called a benign stromal tumor; 2 years later bleeding led to resection of a malignant leiomyosarcoma with a high mitotic rate.

The operative procedure varied with the size of the tumor and with the date the surgery was performed. Smaller tumors were sometimes "shelled out" (three cases, median size 20 mm). This procedure has become much more infrequent in recent years, done once each during 1959, 1963, and 1988.

Formal resections (gastrectomy or hemigastrectomy) were performed in 21 cases, tending to be the procedure chosen for larger tumors with a median size of 50 mm (10–140 mm). Wedge resections were done 19 times for tumors with a median size of 22 mm (4–120 mm). Three tumors were thought to be unresectable because of local extent ($n = 2$) and widespread metastatic disease

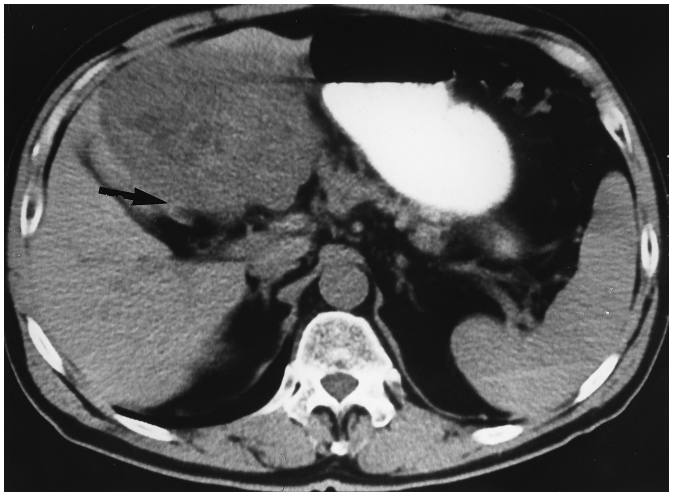


Fig. 1. Abdominal computed tomograph of a large gastric leiomyosarcoma (arrow).

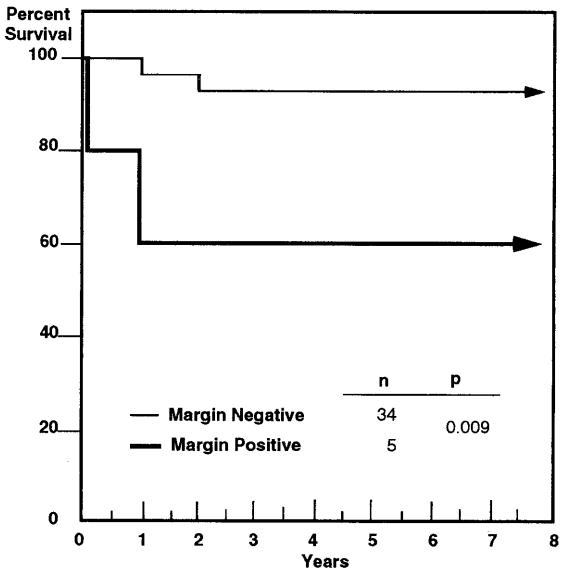


Fig. 2. Survival curves for negative and positive margins.

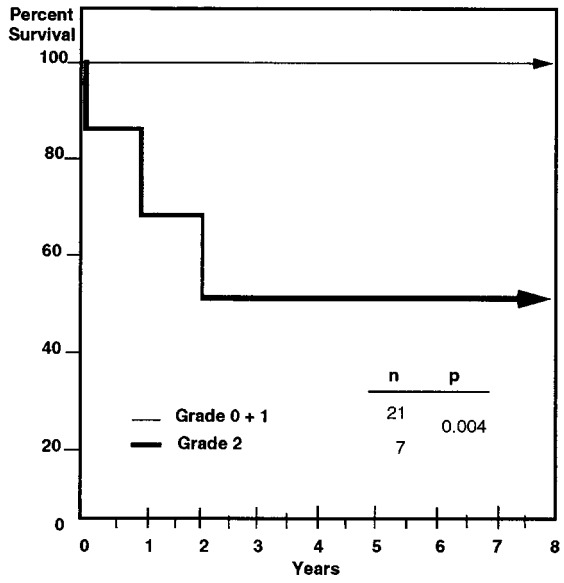


Fig. 3. Survival curves for tumor grade.

($n = 1$) and so were biopsied only. Three of the other cases were classified as incomplete resections due to positive margins, leaving a total of 40 of 46 that were completely resected.

The median size of the tumors was 55 mm (4–180 mm). Of the 41 slides available for review, the number of mitoses ranged from 0 to 20 per 10 high-power fields (HPFs). There was some variation within the individual tumors, with some ranging from 0 to 3 per 10 HPFs.

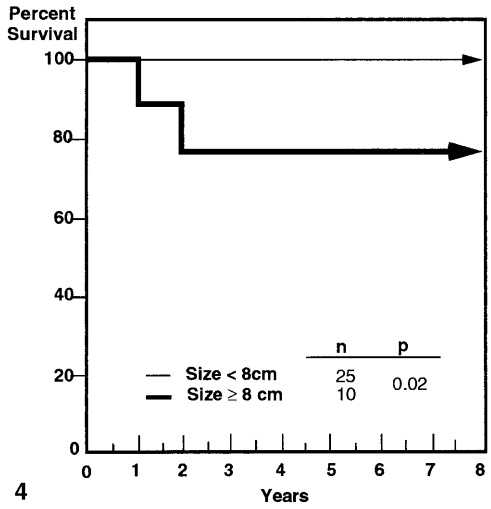
Assignment was made to a nuclear grade based on nuclear size, shape, and hyperchromicity. All leiomyoblastomas, or epithelioid leiomyomas of borderline malignancy, were called grade I by convention. There were 16 tumors graded 0 (benign), 15 grade I/III, and 10 grade II/III. The descriptive terms assigned to the tumors in their original pathologic descriptions included 18 leiomyomas (one of which was hyalinized); one of these lesions was thought on re-review to be a low grade leiomyosarcoma and two to be of borderline potential. There were eight "atypical" or "cellular" leiomyomas, two of which were thought at this review to be leiomyosarcomas. There were five leiomyoblastomas (this did not change on review), nine leiomyosarcomas, and one schwannoma. In those cases where the diagnosis was revised, it was done in light of the cellularity and nuclear features (not knowledge of adverse outcome).

The factors associated with a poor prognosis were a size of 80 mm or above, grade of II or III or greater, incomplete resection, and more than 0 to 3 mitoses per 10 HPFs.

Positive margins were significant for both survival and disease-free survival ($p = 0.008$) (Fig. 2); it included three patients with unresectable lesions who had biopsies only, all of whom were dead of disease at 1 to 12 months. Three with positive margins were long-term survivors. One patient had invasion of the pancreas, had an incomplete resection, but survived 67 months to die of a myocardial infarction. The second patient had a wedge resection with positive margins but is alive with no evidence of disease 133 months later. The third patient had positive margins where the tumor had invaded the transverse colon and pancreas but survived disease-free until lost to follow-up after moving to Florida 59 months after surgery. All of these lesions would have been classified as "malignant" because of the number of mitoses per high-power field and grade of atypia.

The most significant determinant of survival was tumor pathologic grade. Grade 0 or I compared with grade II predicted both survival ($p = 0.004$) and disease-free survival ($p = 0.005$), with no patient developing recurrent disease who had a tumor grade of 0 or I. Of those with grade II lesions, however, 60% were dead at 5 years. The life-table analysis for tumor grade is shown in Figure 3.

The size of the tumor also predicted survival (both total and disease-free), with no patient whose tumor was <80 mm having recurrence or death due to tumor ($p = 0.02$) (Fig. 4). Mitotic rate tended to predict prognosis, with both of the patients who had 20 or more mitoses per 10 HPFs dying of disease at 1 and 25 months.



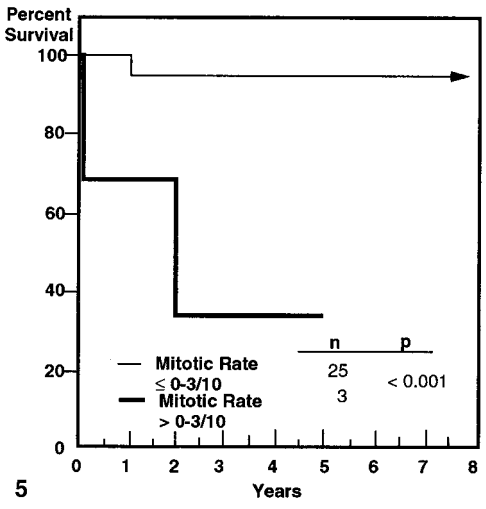


Fig. 4. Survival curves for tumor size.

Fig. 5. Survival curves by mitotic rate.

When we divided the patients into those with more than 0 to 3 mitoses per 10 HPFs and those with fewer, there was a significant difference in total and disease-free survival ($p < 0.001$) (Fig. 5).

None of these factors—size > 80 mm, positive margins, mitotic rate, or pathologic grade—was a consistent predictor of recurrence or death.

Discussion

This study of our institution's experience with gastric smooth muscle tumors was prompted by the frustration of uncertain diagnosis in many cases of smooth muscle tumors of the stomach. There is a well known difficulty with these lesions distinguishing benign from malignant [4, 5, 8, 12] both by frozen section at the time of surgery and on permanent section. This confusion occasionally creates a difficult surgical dilemma but is of more importance for predicting prognosis and advising the patient who may wish to know if the disease was benign or malignant and be skeptical of equivocation. This problem is made even more difficult by the long survivals of patients with unresectable disease or the possibility of disease recurrence after a long interval. Our data reaffirm what is becoming recognized as the lack of a clear border between benign and malignant lesions [13].

The difficulty of assigning a useful descriptive term to these tumors, especially leiomyosarcoma versus leiomyoma, has been frequently described [4, 8, 12]; of our cases, on reexamination of the pathology slides, five of the cases were redefined in the direction of more malignant potential. For this reason, we agree with Cooper et al. [4] that these lesions may be more properly referred to as "stromal neoplasms," as this term does not imply a greater certainty in diagnosis than is really meant. Both unexpectedly benign [9–11] and malignant [5, 8] behavior has been reported.

Other studies have differed in their conclusions about the importance of certain variables. Unfortunately, studies of GI smooth muscle tumors from individual institutions are limited by the rarity of the disease, especially when the site is confined to the stomach.

Size has been found to be a factor in prognosis in some studies [1, 4, 6, 12, 14, 15] and not in others [2, 10]. In our group of patients, size tended to predict survival, with the breakpoint for which a statistically significant survival difference was found being at 8 cm.

Mitotic count has been reported to differentiate reliably between good and bad prognoses in some studies [2, 5, 12, 14] but not in others [6, 11]. We found a significant difference in the behavior of tumors with more versus fewer than 0 to 3 mitoses per 10 HPFs. Cooper et al. pointed out that mitotic count as a predictor of malignant behavior has the disadvantage of being both subjective and poorly reliable; and indeed in our group there were patients with significant variation in mitotic rate even within the same tumor.

Our study found that resectability was a critical determinant of prognosis, but even with a high grade (II) and positive margins we had one long-term survivor. This finding suggests that an aggressive surgical strategy should be recommended for all these tumors, as a good result can sometimes occur even with multiple factors that suggest a bleak outlook. There are some other reports of long-term survivors with gross unresected or metastatic disease [9–11].

Grade in our series reliably predicted the prognosis of these patients, although here it reflected multiple factors including the comparably favorable prognosis of leiomyoblastomas [15].

The diagnosis of these tumors can be elusive because the mucosa is preserved even in large tumors. Endoscopy is becoming increasingly popular for evaluating the kind of symptoms with which these tumors often present, such as anemia and GI bleeding and pain; to some degree, it has supplanted barium studies. Smooth muscle tumors, though not a common cause of upper GI symptoms, are more likely to be missed by the endoscope. Fortunately (for diagnosis if not for cost containment) CT scans are also becoming more popular; and in our experience it was the most accurate test when it was obtained. Endiscopy and biopsy are highly unreliable for detecting these lesions and for diagnosing malignancy. The physician should be wary of obtaining false reassurance from these tests.

Although the tumor should be completely resected with a negative margin if possible, our series reflected no difference in

survival between wedge resections and more formal gastrectomies or partial gastrectomies. This result has been reported by others as well [1, 5]. If the tumor can be removed by wedge resection with a negative margin, preferably at least 2 cm, there is no need for a formal resection or for a lymph node dissection [16].

These tumors can present technical challenges to the surgeon by virtue of their size or location. A large smooth muscle tumor near the gastroesophageal junction may not be easily resectable with the desirable 2 cm margin without performing a total gastrectomy. As an alternative, if the tumor is high on the lesser curve, a tailored hemigastrectomy of the Madlener type (resecting a tongue high onto the lesser curve) may be possible. If the tumor has invaded adjacent organs, they should be resected en bloc. In the case of a smooth muscle tumor on the greater curvature, splenectomy may be necessary to obtain clean margins, and the chance of cure is worth the small additional risk of morbidity.

Formal lymph node dissections were not done in our patients, and other series have not shown them to affect survival [16]. As with other sarcomas, lymphatic spread is not the primary route of metastasis [17].

Interpretation of the histology of these tumors remains in some ways the most challenging part of their care. Cooper et al., using DNA flow cytometry, found that DNA aneuploidy correlated with poor prognosis and was especially helpful in patients with intermediate other criteria, such as mitotic counts. This technique, already accepted for breast cancer, may prove to be clinically useful for smooth muscle tumors as well.

Gastric smooth muscle tumors are an uncommon surgical problem, further complicated by the extremely nebulous border between benign and malignant behavior. Size, mitotic rate, grade, and even positive margins or the presence of metastases do not infallibly predict the long-term postoperative course; and persistent disease is occasionally compatible with long survival. An aggressive initial surgical approach, aiming for resection with a negative margin, remains the best initial treatment for these lesions, whether the frozen or final pathology report is "benign" or "malignant." Afterward, these patients need long-term follow-up because of these tumors' heterogeneous nature and unpredictable behavior.

Résumé

Nous avons analysé 46 tumeurs stromales traitées dans notre institution entre 1958 et 1992. Les symptômes révélateurs les plus fréquents ont été l'hémorragie gastro-intestinale, la douleur, la fatigue ou le malaise. Les tumeurs mesuraient entre 4 et 150 mm et le geste chirurgical le plus souvent pratiqué a été soit la résection à minima («wedge resection») soit la gastrectomie partielle. La tomodensitométrie abdominale a été l'examen diagnostique le plus spécifique en préopératoire. Les facteurs associés à un pronostic défavorable (survie diminuée) étaient la taille tumorale supérieure ou égale à 8 cm ($p = 0.02$), la présence de plus de trois mitoses par 10 champs à fort grossissement ($p < 0.001$), l'envahissement des marges ou la non-résecabilité ($p = 0.008$) et une tumeur classée grade II ou plus ($p = 0.004$). Ces tumeurs, cependant, ont un comportement imprévisible. La résection chirurgicale ayant assuré des marges de résection indemnes reste la thérapeutique de choix. La résection à visée palliative peut être indiquée si elle procure une survie prolongée.

Resumen

Hicimos la revisión de 46 tumores estromales del estómago tratados en nuestra institución entre 1958 y 1992. Los síntomas de presentación más frecuentes fueron sangrado gastrointestinal, dolor y fatiga o malestar. El tamaño de los tumores osciló entre 4 y 150 mm; los tipos más frecuentes de cirugía fueron la resección en cuña y la gastrectomía parcial. La tomografía computadorizada representó el examen diagnóstico preoperatorio más específico. Los factores asociados con disminución de la supervivencia incluyeron: tamaño de 8 mm o mayor (p3D0.02), más de 0-3 mitosis por 10 campos de mayor aumento ($p < 0.001$), márgenes de resección positivos o irresecabilidad (p3D0.008) y grado histológico tumoral II o mayor (p3D0.004). Sin embargo, estos tumores exhiben un comportamiento impredecible. La resección quirúrgica con márgenes negativos sigue siendo la mejor modalidad terapéutica, pero las resecciones paliativas están indicadas, por cuanto pueden lograr supervivencias prolongadas.

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