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## Prognostic factors affecting survival after surgical resection of gastrointestinal stromal tumours: a two-unit experience over 10 years

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### Abstract

**Background:** Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal neoplasm of the gastrointestinal (GI) tract which has only been recently described based on their specific immunohistochemistry and the presence of particular KIT-related mutations which potentially make them targets for tyrosine kinase inhibition.

**Methods:** Sixty-one patients (29 M; 32 F, median age 60 years; range: 23–86 years) between June 1994 and March 2005, were analyzed from two allied institutions. Patient, tumour, and treatment variables were analyzed to identify factors affecting survival.

**Results:** Of the 61 patients, 55 (90%) underwent complete surgical resection of macroscopic disease. The 5-year overall survival (OS) rate in the 61 patients was 88% and the 5-year disease-free survival (DFS) in the 55 cases completely resected was 75%. Univariate analysis revealed that R0 resection was strongly associated with a better OS rate ( $p < 0.0001$ ). Likewise, univariate analysis also showed high mitotic count of  $> 10$  mitoses/per 50 HPF was a significant variable in worse prognosis for OS ( $\leq 10$  mitoses/per 50 HPF 95% 5-year OS vs.  $> 10$  mitoses/per 50 HPF 74% 5-year OS, respectively;  $p = 0.013$ ). On subsequent multivariate analysis, only high mitotic count remained as a significant negative prognostic variable for OS ( $p = 0.029$ ). Among patients resected for cure, there were 8 recurrences during follow-up. The mean time to recurrence was  $21 \pm 10$  months (range: 4–36 months). Univariate analysis revealed that mitotic count of  $> 10$  mitoses per 50 high power fields, intratumoural necrosis, and pathological tumour size ( $> 10$  cm in maximal diameter) significantly correlated with DFS ( $p = 0.006, 0.002$  and  $0.02$ , respectively), with tumour necrosis and high mitotic count remaining as independent predictive variables affecting prognosis on subsequent multivariate analysis.

**Conclusion:** Most GISTs are resectable with survival principally dependent upon mitotic count and completeness of resection. Future metabolic and genetic analyses will define the role of and resistance to induction or postoperative adjuvant targeted kinase inhibition therapy.

## Background

Gastrointestinal stromal tumors (GISTs) are uncommon tumours which have relatively recently been separated from conventional leiomyomas, leiomyoblastomas, and leiomyosarcomas, based on their specific immunohistochemistry, presumed aetiopathogenesis, molecular biology and differential outcome [1,2]. There is still controversy over their histogenetic origin with immunohistochemical and ultrastructural resemblance to the interstitial cells of Cajal [3,4] as well as from cells which are smooth muscle cell precursors responsible for generation of the slow-wave pacemaker activity of the gut musculature [5]. The designation of these tumours has largely been based on the immunohistochemical expression of c-KIT (CD 117; stem cell factor [6,7], and CD 34) [8], with a relative lack of desmin and S-100 immunoreactivity, although recently, a subset of KIT-negative GISTs has been recognised with the morphological features of classical stromal tumours but retaining PKC- $\theta$  expression [9]. More recently, cytogenetic and comparative genomic hybridisation (CGH) studies have shown characteristic chromosomal patterns in GISTs which have distinguished them from other gastrointestinal mesenchymal tumours, [10] and where most GISTs demonstrate specific DNA copy number changes which correlate with their clinical behaviour and which differentiate benign from malignant cases [11].

Considerable debate still exists concerning the biological behaviour of GISTs, centering largely around the tumour site, tumour size, the presence of intra-tumoural necrosis, and mitotic count [12-14]. Based on this recent data, our study assesses the surgical outcome of unselected GISTs referred to two allied institutions over a 10 year period and analyses the factors affecting prognosis after resection with curative intent.

## Patients and methods

### Patients

Using our hospital databases, we collected the records of patients with a histopathologic diagnosis of primary leiomyoma, leiomyoblastoma, leiomyosarcoma, gastrointestinal sarcoma, and stromal cell tumour of the GI tract from the period including 1994 to October 2004. Each of the patients had undergone surgical resection of their tumour. We recorded the patients' age, gender, presenting clinical symptoms, tumour site, maximal tumour diameter after resection, duration of surgery, surgical procedure, extent of surgical resection, the presence and date of local recurrence or distant metastasis, and the clinical outcome until last follow-up, including date of death where appropriate. There was no strict follow-up protocol in either institution, although follow-up included physical examination, chest X-ray, thoracoabdominal and pelvic computerised tomography (CT) scan, endoluminal

ultrasonography, and GI endoscopy, where appropriate. The median follow-up of all patients was 35 months (range 2-140 months). Those tumours deemed to have histologically free resection margins were included as cases where surgery was performed with curative intent and were referred to as complete (R0) resections. After the surgical treatment, patients were followed regularly using clinical assessment on a 3 monthly basis with abdominopelvic CT and/or ultrasound annually, where appropriate.

### Immunohistochemistry

The tumour samples from all 61 patients were evaluated for various markers by using immunohistochemistry with commercially available antibodies against CD 117-KIT, (1:50, Santa Cruz Biotech, CA USA) S-100 protein, (1:40, Novocastra Labs, USA) Desmin, (1:50, DAKO, Glostrup, Denmark) and Smooth-muscle Actin (1:200, DAKO, Glostrup, Denmark) with qualitative assessment of immunoreactivity in accordance with the manufacturers' instructions. Cases were classified according to risk and their potential for aggressive clinical behaviour based on the NIH consensus statement of 2001 for GISTs, [15] where tumour size < 2 cm and mitotic count < 5/50 high power fields (HPF) was graded as very low risk, tumour size between 2 and 5 cm and a mitotic count < 5/50 HPF was considered low risk, tumours < 5 cm with a mitotic count between 5/50 HPF and 10/50 HPF or tumours between 5 and 10 cm with a mitotic count less than 5/50 HPF were deemed as intermediate risk and tumours > 10 cm and/or those tumours with a mitotic count > 10/50 HPF and tumours > 5 cm with a mitotic count > 5/50 HPF were classified as high risk.

### Statistics

Statistical analysis was performed with SPSS 12.0 software (Chicago, IL, USA). The Student's t test was used to compare continuous variables with the  $\chi^2$  test being utilized for dichotomous variables. Overall survival was calculated from the day of diagnosis until death or the last day of a patient's visit to the outpatient clinic. The disease-free survival was calculated from the first diagnosis until tumour recurrence or distant metastases were found. Kaplan-Meier analysis with a Mantel-Haenszel log-rank test was used to compare overall and recurrence-free survival [16] with the proportional hazards method being used to evaluate significant prognostic factors [17]. All p values < 0.05 are reported.

### Results

Of the resected cases, there were 29 males and 32 females with an overall median age 60 years (range 23-86 years). All tissue samples were proven to be CD-117 positive on immunohistochemical staining. Tumours were located in the stomach in 41 cases (67%), the small bowel in 14

(23%), the colon in 4 (5%) the rectum in 1 (2%), and the duodenum in 2 cases (3%). Three of the 61 patients (5%) presented with synchronous hepatic metastases. The most frequent presenting symptoms included gastrointestinal tract bleeding and abdominal pain in 11 cases (18%) and abdominal fullness and/or discomfort in 7 patients (11%). Twenty patients (33%) had anaemia on presentation with 15 patients (26%) having a palpable abdominal mass on clinical examination. Six patients (10%) were asymptomatic and were referred for incidental GISTs after routine physical examination and investigation.

The surgeries performed for the patient cohort are shown in Table 1. One patient with a gastric GISTs and a single synchronous hepatic metastasis in segment III underwent a non-anatomical wedge resection of the liver at the same time as their gastric resection. Postoperative complications included gastrointestinal hemorrhage in one case, duodenal leakage in a further patient, and urosepsis in one case. Perioperative 30 day mortality was 0 per cent. Pathological assessment of the resected tumours showed a median tumour size of 5.3 cm (range, 0.6–38 cm). Ten tumours (16%) were < 2 cm in maximal diameter, 19 (31%) between 2–5 cm, 17 (28%) between 5–10 cm and 15 (25%) > 10 cm. The mitotic counts were < 5/50 per HPF in 37 cases (61%), between 5 and 10/50 per HPF in a further 6 (10%) and > 10/50 per HPF in 18 (29%) cases. Ulceration of the tumour was noted in 69% (42/61), haemorrhage in 25% (15/61), and tumour necrosis in 28% (17/61). Six patients (10%) underwent palliative surgery because of tumour bleeding resulting in severe anaemia, 3 patients presented with synchronous resectable hepatic metastases, and a further 3 presented with an unresectable intra-abdominal tumour. According to the NIH Consensus Conference criteria, of all cases there were 10 patients (16%) in the very low risk class, 15 cases (25%) in the low risk class, 7 (11%) in the intermediate risk class, and 29 (48%) in the high risk class. Table 2 shows the clinico-pathological data of patients according to the number of mitoses per HPF (i.e.  $\leq$  or  $>$  10/50).

Of the 61 patients resected, 55 (90%) had their tumour completely resected as an R0 resection as described in the methods section. The 5-year overall survival rate for these patients was 88%, compared with 0% (0/6) for those patients who underwent palliative surgery ( $p < 0.0001$ ). During the follow-up period, 5 patients died of recurrent disease, all of whom were in NIH class 4 on initial presentation. A further 2 patients died of myocardial infarction during the follow-up period but were free of tumour at the time of their deaths. Seven patients who experienced recurrence were treated with Imatinib 400 mg daily and 6 of them are still alive after a median follow-up period of 18 months. Figure 1 shows the overall and disease-free survival of all GISTs in the series undergoing all types of resections. On univariate analysis, histological resection-free margins (i.e., R0 resection margins) were strongly associated with improved overall survival (91% 5-year overall survival for complete resection vs. 0% for incomplete resections,  $p < 0.0001$ ). This effect was preserved in patients presenting with advanced classes of disease, where amongst the NIH class 4 patients completeness of resection correlated with overall survival (83% 5-year overall survival for complete resection vs. 0% 5-year overall survival for incomplete resection,  $p = 0.0031$ ). The other significant factor affecting overall survival on univariate analysis was the number of mitoses ( $>$  10 per 50 HPF) where there was a 95% 5-year overall survival for patients with a mitotic count  $\leq$  10 per 50 HPF vs. 74% 5-year overall survival for patients with a mitotic count  $>$  10 per 50 HPF,  $p = 0.013$ ) (Figure 2). Multivariate analysis of these two significant factors detected on univariate analysis revealed that the number of mitoses ( $>$  10 per 50 HPF) was the only significant independent predictive variable affecting overall survival (HR = 12.350; CI 1.295–117.781;  $p = 0.029$ ).

The 5-year disease-free survival in the 55 patients completely resected was 75% (Figure 2). Among those patients resected for cure, 8 patients developed tumour recurrence after a mean of  $21 \pm 10$  months (range: 4–36 months) follow-up. The liver was the most frequent site of tumour relapse ( $n = 6$ ; 75% of the recurrences) and in the 8

**Table 1: Surgical procedures performed in 61 patients affected by gastrointestinal stromal tumours.**

Surgical procedure	N (%)
Wedge gastric resection*	31 (51)
Small bowel resection	14 (23)
Subtotal gastrectomy	8 (13)
Colonic resection	3 (5)
Total gastrectomy	2 (3)
Duodenum-pancreatectomy	2 (3)
Transanal excision	1 (2)

\*One patient underwent non-anatomical wedge liver resection at the same time as the gastric resection for an isolated liver metastasis in segment III.

**Table 2: Clinico-pathological variables of 61 gastrointestinal stromal tumours patients according to number of mitoses per 50 HPF(≤ or > 10)\***

	Mitoses ≤ 10/50 per HPF	Mitoses > 10/50 per HPF	p
<b>Tumour location</b>			0.09
stomach	28 (68)§	13 (32)	
colon-rectum	1 (25)	3 (75)	
small bowel	12 (86)	2 (14)	
duodenum	2 (100)	0	
<b>Surgical resection type</b>			0.04
R0	42 (74)	15 (26)	
R1+R2	1 (25)	3 (75)	
<b>Tumour diameter</b>			0.71
≤ 10 cm	33 (72)	13 (28)	
> 10 cm	10 (67)	5 (33)	
<b>Tumour necrosis</b>			0.21
absent	33 (75)	11 (25)	
present	10 (59)	7 (41)	

\*HPF, high power field

§Numbers in parentheses are percentages.

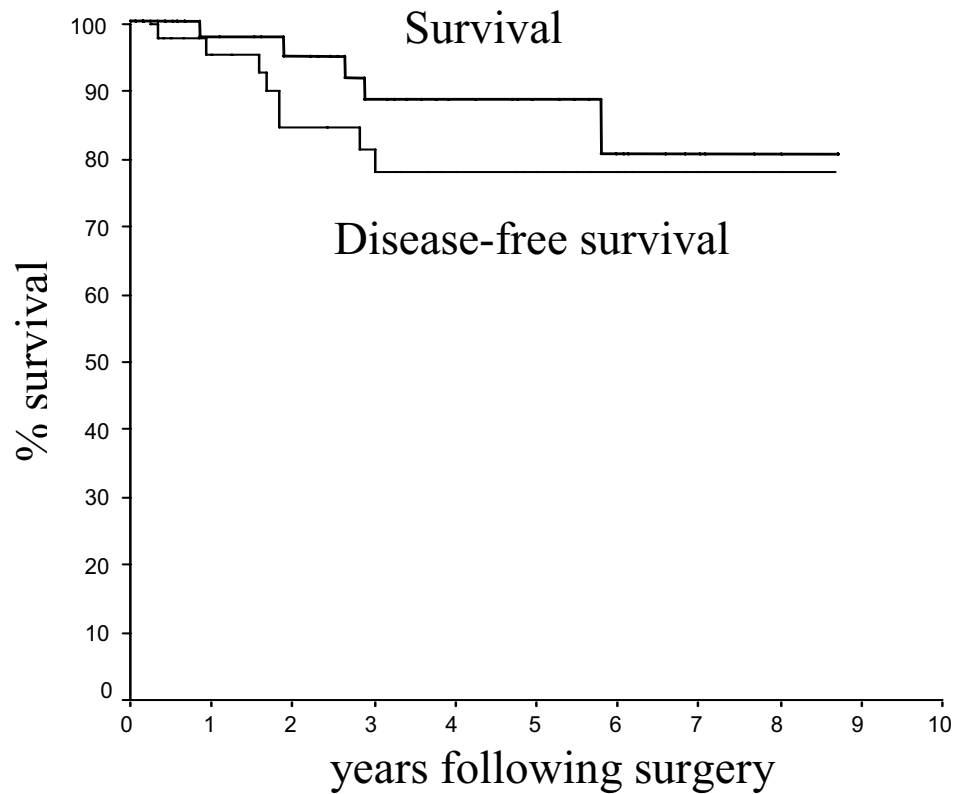
patients, survival after recurrence was 30% at 3 years. Patients designated as NIH class 4 had a 5-year disease-free survival rate of 65% compared with 94% for all other groups combined ( $p = 0.03$ ). On univariate analysis, a higher number of mitoses (i.e. > 10 per 50 HPF) correlated with worse disease free-survival in those resected for cure (87% for < 10 mitoses/per 50 HPF vs. 57% for > 10 mitoses/per 50 HPF respectively,  $p = 0.006$ ), as did tumour size (tumours < 10 cm in maximal diameter had an 86% disease-free survival at 5 years compared with only 63% for those tumours > 10 cm in size;  $p = 0.02$ ). The presence of tumour necrosis was also significantly associated with a worse disease-free survival on univariate analysis (51% vs. 91% 5-year disease-free survival with or without tumour necrosis respectively;  $p = 0.002$ ). On multivariate analysis of these three significant factors detected on univariate analysis, only tumour necrosis and the number of mitoses (> 10 mitoses/per 50 HPF) proved to be significant independent predictive variable affecting disease-free survival (HR = 11.226; CI 2.199–57.315;  $p = 0.004$  and HR = 8.054; CI 1.842–35.205;  $p = 0.006$ , respectively).

## Discussion

Analysis of 61 cases of mixed-site GISTs in our study obtained from two tertiary referral centres over a 10-year period reveals that both overall survival and disease-free survival are affected by a high mitotic count in the tumour after resection with curative intent. The primary tumour sites noted in our study are similar to other previous reports [18,19], with a similar demographic of presenting symptoms including gastrointestinal bleeding, abdomi-

nal pain and the presence of an abdominal mass [20-22]. CT and MRI are generally used for the preoperative imaging of GISTs [23-25]. However, there are no well-established, published guidelines to help surgeons determine the optimal manner in which to evaluate this intraabdominal, site-specific class of tumours. Although not reported in the results section of our current report, our limited use of endoluminal ultrasound has been unable to assist in the definition of malignant versus benign cases. Nevertheless, this has been as previously described [26], where tumour margin irregularity and heterogeneity with intra-tumoural degeneration and larger tumour size were more indicative of malignancy. No patient in our series underwent preoperative image-guided biopsy or aspiration cytology as has been advocated by some authors [27]. Lastly, recent data shows a potential value for preoperative positron emission tomography (PET) in the prediction of malignant potential with a correlation between  $^{18}\text{F}$ FDG uptake and mitotic count [28]

Others have shown that one of the principal prognostic factors determining cancer-specific outcome is tumour size, where tumours > 10 cm in maximal diameter have a relatively worse survival following surgical resection [2,12,18]. Our study was unable to substantiate an effect of tumour size except on univariate analysis of overall survival. This effect was not maintained on multivariate analysis, although larger patient numbers are probably required to determine a true effect of tumour size on cancer-specific outcomes. In this respect, GISTs, which exceed 5 cm in maximal diameter, have been previously shown to correlate with a worse prognosis independent of their

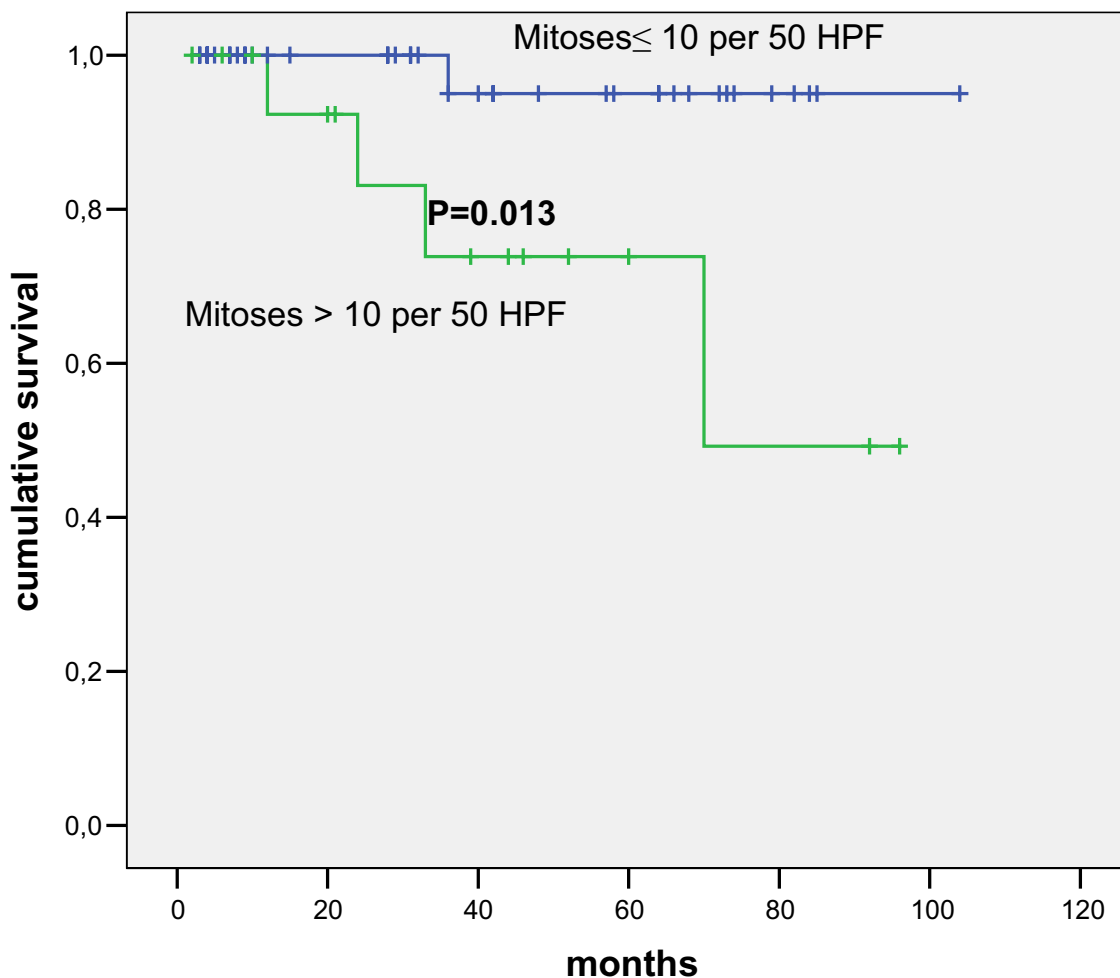


Patients at risk:	61	39	35	26	19	15	9	4	1	0	0
	55	37	31	24	16	13	9	4	1	0	0

**Figure 1**  
Overall survival and disease-free survival in 61 patients with GIST tumours.

primary location, [19,29] where tumour diameter is part of most prognostic indices designed to govern treatment algorithms for patients deemed at high risk [2,15,30]. Equally, as in our study, most reports have shown high mitotic count to equate with a worse tumour-specific outcome [12,31], although some recent studies have excluded this factor along with that of intratumoural necrosis from model analyses since they have not been proven to be independent prognostic markers of survival [12,32]. Our study showed an effect of intratumoural necrosis on disease-free but not overall survival. Other studies have confirmed more objective immunohistochemical evaluation of cellular proliferation as correlating with an overall worse outcome using Ki 67 analysis, [2] proliferating cell nuclear antigen labelling index, cellular apoptotic marker (Bcl-2 and Bax) expression and overall tumour cellularity estimates [12,33,34].

The clinicopathologic evaluation of GISTs is particularly difficult, since these tumours have only recently been characterized and since some previous studies have still grouped these tumours with spindle-cell and epithelial neoplasms, which may share similar histopathology, but which possess divergent outcomes. Attempts have been made to categorize these tumours by the establishment of an individualized immunophenotype based on neural and smooth muscle immunodifferentiation although up to one-quarter of these neoplasms cannot adequately be categorized on this basis [35]. No patient in our series was treated primarily with the tyrosine kinase inhibitor Imatinib, which has been shown to be valuable in metastatic kit-positive GISTs [36,37]. We have used this in our units only after proven disease recurrence. This issue is complex, since although most GISTs acquire a gain-of-function c-KIT mutation, many tumours ultimately



Patients at risk:

≤10 per 50 HPF	43	20	17	12	4	1	0
>10 per 50 HPF	18	11	7	3	2	0	0

**Figure 2**  
Overall survival according to number of mitoses for the 61 patients with GIST tumours.

demonstrate some resistance to targeted molecular therapy during treatment [38]. It appears that c-KIT gene mutations are pivotal molecular events in the life of these tumours, adversely affecting their overall prognosis after surgery [39]. Equally, there is controversy regarding the mechanisms of Imatinib resistance which are dependent upon missense mutations of the kinase domains of KIT and PDGFRA and there is no clear evidence at the present time that routine molecular analysis of GISTs to assess exon mutations alters management [40]. Moreover, the

follow-up protocol for resected GISTs has not been established although there are relatively specific changes detectable in tumours treated primarily with Imatinib on CT and MR imaging, including changes in tumour size, attenuation, enhancement, and vascularity [41,42]

**Conclusion**

Our and other studies suggest that complete surgical resection (R0 resection) of GISTs as well as their initial size, mitotic activity, and the presence of intratumoural necro-

sis are potentially important variables associated with overall outcome, with the principal factor affecting overall survival being the mitotic count. These findings have been suggested in another very recently published report [43]. In the era of Imatinib effectiveness, it is unclear what is the role of preoperative induction or postoperative adjuvant targeted therapy, as well as the place of surgery in partial Imatinib responsiveness or in isolated metastatic disease [44]. In this light, at the present time, it may be that a clinico-pathological interpretation of the risk status of the tumour, as used in our study, is the most practical approach for such decision where complete surgical resection (R0 resection) is the key prognostic factor [45] and where high-risk GISTs surgery is supported by a selective approach towards induction or postoperative adjuvant molecular therapy [46,47].

### Competing interests

The author(s) declare that they have no competing interests.

### Authors' contributions

AC, study conception and design and drafting of manuscript; APZ, critical revision, drafting of manuscript; MI acquisition of data; SG, performed immunohistochemistry; EB, analysis and interpretation of data; RB, acquisition of data; GP, performed immunohistochemistry; FL performed immunohistochemistry; PDV, acquisition of data; CT, acquisition of data; BA, critical revision.

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