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Stromal tumours of the gastrointestinal tract: a clinicopathological and ploidy analysis of 33 cases

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Abstract The clinicopathological and DNA flow cytometric data of 33 patients with stromal tumours of the gastrointestinal tract (STGIT) were analysed to select pathological features of prognostic value. Tumours had been previously classified as benign (21 cases) or malignant (12 cases). Data relating to poor prognosis statistically were local invasion, pathological grade, size greater than 10 cm, mitotic index (MI) and necrosis. Pathological grade was related to local invasion. Aneuploidy did not correlate with poor survival although a common trend was detected between both. DNA content may help to predict prognosis of STGIT, but its real value has not yet been clearly established. Currently, stage (invasion), size, MI and pathological grade remain the most useful prognostic factors.

Key words Stromal tumours · Smooth muscle tumours · Gastrointestinal tract · Ploidy Flow cytometry

Introduction

Stromal tumours of the gastrointestinal tract (STGIT) are relatively rare neoplasms with wide variability in their clinical behaviour and pathological features. Stomach and small bowel are the most frequent locations, whereas oesophagus, rectum and anus are uncommon sites of origin (Akwari et al. 1978). The prognosis of patients with STGIT is related to several pathological factors: intra-abdominal recurrence and liver metastases are the predominant patterns of failure in patients who die of leiomyosarcoma (Ng et al. 1992); there is also a general agreement that mitotic index (MI) is a powerful pathological predictor of malignancy (Cooper et al. 1992; Evans 1985; Hendrickson and Kempson 1989). Tumour size appears to have some prognostic value, whereas cellularity and nuclear pleomorphism are considered less important (Hendrickson and Kempson 1989). Although there is some disagreement (Flint et al. 1989), recent studies have shown that ploidy of STGIT is related to microscopic features (Cooper et al. 1992; Federspiel et al. 1987; Kiyabu et al. 1988; Tsushima et al. 1987) and survival (Cooper et al. 1992; Kiyabu et al. 1988; Tsushima et al. 1987).

This study analyses the prognostic value of several pathological features such as extension of the tumour beyond the organ of origin, size of the tumour, ulceration, histological grade, cellularity, MI, nuclear pleomorphism, necrosis and DNA content related data [ploidy, DNA index (DI) and number of cell populations]. We hoped that integration of the DNA measurements with the conventional pathological features would allow us to establish a more accurate prognosis.

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Materials and methods

Thirty-three cases of STGIT were obtained from the files of the Pathology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain. The tumours had been previously classified into two groups: benign (21 cases) and malignant (12 cases). The criteria used for the pathological diagnosis of malignancy included the following in gastric tumours: five or more mitoses per 10 high power fields (HPF), less than five mitosis per 10 HPF but size greater than 10 cm. For small bowel tumours, the presence of even one mitosis per 10 HPF and/or size greater than 4 cm was considered to be indicative of malignancy. Each case was followed and re-evaluated for tumour location, ulceration and size using the clinical and pathological records; cellularity, pleomorphism, necrosis and MI were assessed on the haematoxylin and eosin stained slides. Pleomorphism and the grade of tumours was evaluated according Coindre et al. (1988). Flow cytometry was performed in tissue sections following a modification of the method of Hedley et al. (1985). Briefly, the 50 μm sections were dewaxed in xylol, rehydrated by sequential immersions in 100%, 95%, 70% and 50% ethanol and treated with 0.5% pepsin; the suspension obtained was filtered through a nylon mesh of 50 μm. The nuclei were then stained with RNase A (Sigma, St. Louis, Mo., USA) and 20 μg/ml propidium iodate (Sigma). Nuclear DNA content was measured using an EPICS V Flow cytometer (Becton Dickinson,

Chicago, Ill., USA). The nuclei of normal lymphocytes were used to calibrate the instrument and as external diploid controls and between 50 000 and 100 000 cells were counted per case. The presence of aneuploidy was determined by the DI and was calculated as the ratio between the G0/G1 tumour peak modal channel and the G0/G1 diploid (normal cells) peak modal channel. Theoretically, the DI of normal cells is 1 ± 0.1. Deviations from this value are considered to be evidence of aneuploidy. Follow-up from 10 to 120 months (average 65 months) was obtained. Statistical analysis was performed using the Wilcoxson rank test.

Results

The number of cases, male to female ratio, age, location, size, evidence of ulceration and status of margins are recorded in Table 1. Other pathological data, such as tumour differentiation, necrosis, MI, pathological grade, ploidy, DI and number of cell populations per case, are shown in Table 2. In this series (Table 1) STGIT, particularly those with previous pathological diagnosis of malignancy, were more common in females (1:2). The mean age at diagnosis was 57.2 years, with a range between 17 and 84 years. Twenty-six tumours were located in the gastric wall whereas seven appeared in the small bowel; no cases were located in oesophagus and large bowel. The mean diameter of the tumours was 7.3 cm, with a range between 0.8 and 27 cm. Ulceration was a common finding, being present in 18 cases (59%). Invasion of adjacent bowel or peritoneum was found in 6 cases (19%) and lymph node metastases were found in 1 of these. To emphasize the importance of invasion, all data of these 6 patients are collected in Table 3. Size was also related to invasion (the mean diameter of non-invasive tumours was 5 cm vs 19 cm for invasive tumours). Microscopically (Table 2), STGIT were composed of spindle cells grouped in fascicles (Fig. 1), although 6 tumours contained mainly epithelioid cells with round, usually clear cytoplasm and central nuclei (Fig. 2). Two cases were hypocellular with marked hyalinization, 15 were normocellular and 16 were hypercellular. Pleomorphism was mild in 11 cases and marked in 5 (Fig. 3). Necrosis was found in 8 tumours: focally (<30% of the tumour area) in 6 and extensive (>30% of tumour area) in 2. Mitoses per 10 HPF were zero in 16 cases, one in 6 tumours, between two and four in 3 tumours, between five and nine in 3, and ten or more in 5. No clear vascular invasion was found. A pathological grade was obtained after scoring pleomorphism, necrosis and mitoses. Twenty-six STGIT were grade I, 6 grade II, and 1 grade III. DNA analysis showed diploidy in 20 and aneuploidy in 13 (39.5%). The relationship between ploidy and survival is shown in Fig. 4. Seven of the aneuploid tumours had only one hypodiploid cell line; the other 6 contained more than one cell clone, one diploid and the remainder aneuploid.

Statistical analysis revealed the following significant correlations: size of the tumour greater than 10 cm, local invasion, high pathological grade, more than five mitoses per 10 HPF and tumour necrosis all correlated with short survival. Aneuploidy was only statistically significant in tumours greater than 10 cm. Pathological grade appears to be a more accurate prognostic parameter than ploidy: it correlated with survival and local invasion (Table 4).

Table 1 Stromal tumours of the gastrointestinal tract: clinicopathological findings

Number of patients	33
Sex (male: female)	1:2
Age (years; mean and range)	57.2 (17–84)
Site: stomach	26
small bowel	7
Size (cm; mean and range)	7.3 (0.8–27)
Mucosal ulceration	18
Invasion	6

Table 2 Stromal tumours of the gastrointestinal tract: pathologic results

A. Tumour differentiation:	
resembling normal tissue (1 point)	17 (51.5%)
mild pleomorphism (2 points)	11 (33.3%)
marked pleomorphism (3 points)	5 (15.2%)
B. Necrosis (unrelated to ulceration):	
none (1 point)	25 (75.7%)
<30% (2 points)	6 (18.2%)
>30% (3 points)	2 (6.0%)
C. Mitoses:	
<5 (1 point)	25 (75.7%)
5–9 (1 point)	3 (9.0%)
10–19 (2 points)	2 (6.0%)
>20 (3 points)	3 (9.0%)
D. Grade (sum of A+B+C):	
I (3–4 points)	26 (78.8%)
II (5–6 points)	6 (18.2%)
III (7–9 points)	1 (3.0%)
E. Ploidy:	
diploidy	20 (60.5%)
aneuploidy	13 (39.5%)
F. DNA Index:	
<1.20	31 (94.0%)
≥1.20	2 (6.0%)
G. Cell populations:	
1	27 (81.8%)
>1	6 (18.2%)

Table 3 Stromal tumours of the gastrointestinal tract with local invasion; (*A* aneuploidy; *DOD* died of disease)

Age/sex	Location	Size	Grade	Ploidy	Mitoses per 10 high power fields	Necrosis	Lymph node involvement	Follow up
50/f	Stomach	–	II	A	28	No	No	DOD 9 months
78/f	Stomach	>20	II	A	13	Yes	No	DOD 10 months
38/f	Small bowel	>20	II	A	4	Yes	No	DOD 12 months
65/f	Small bowel	27	I	A	8	No	No	DOD 24 months
61/f	Small bowel	30	I	A	5	No	Yes	DOD 18 months
69/f	Small bowel	18	II	A	4	Yes	No	DOD 18 months

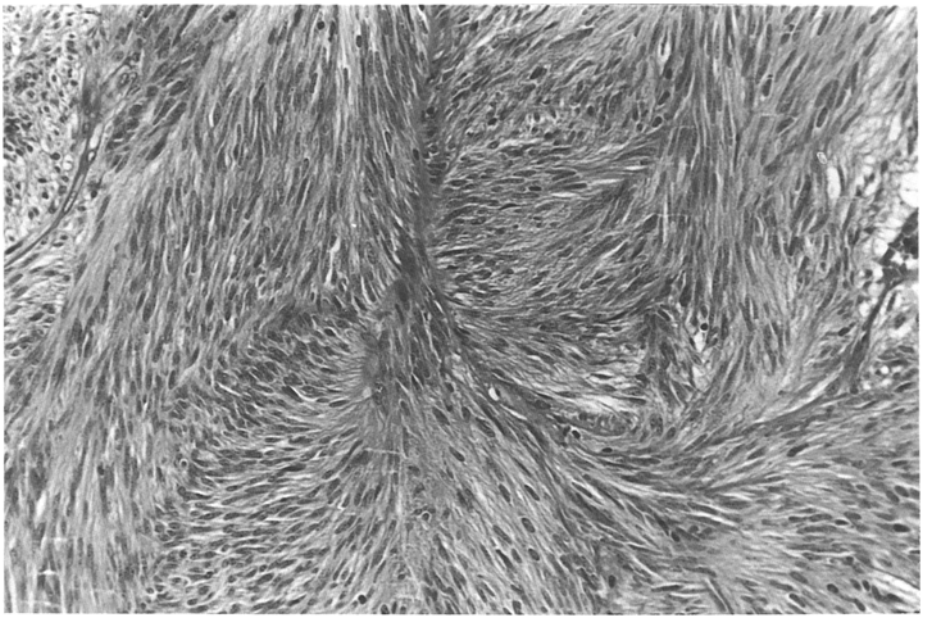

Fig. 1 Stromal tumour of the gastrointestinal tract with bundles of spindle cells containing regular elongated nuclei

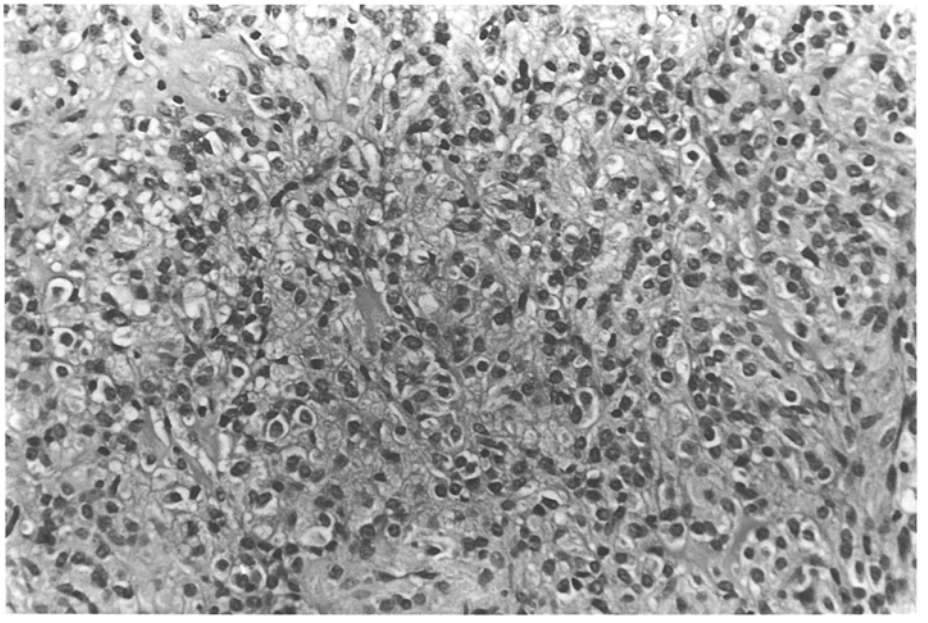

Fig. 2 Stromal tumour of the gastrointestial tract showing round-polygonal cells with clear cytoplasm and central nuclei

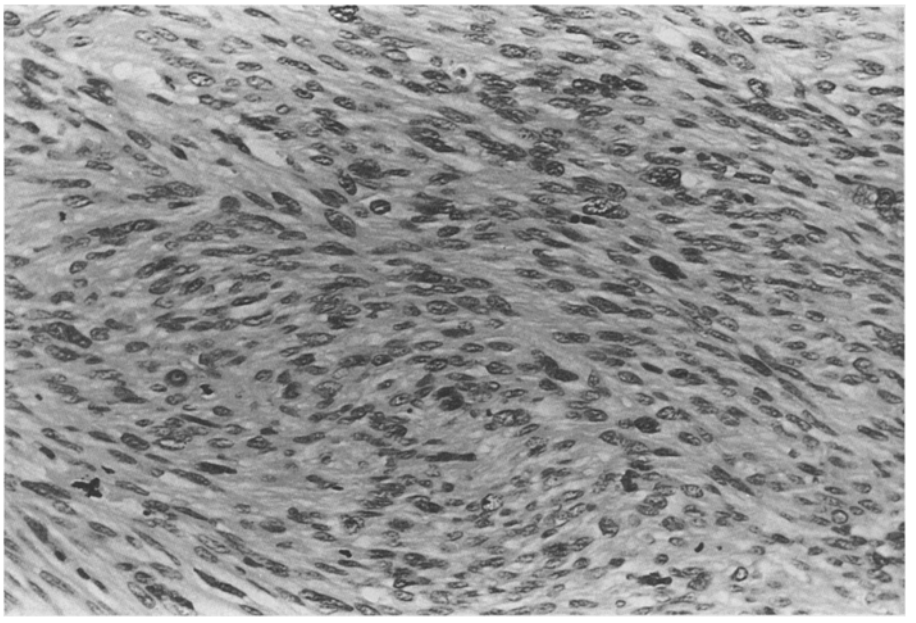

Fig. 3 Stromal tumour of the gastrointestinal tract with spindle cells, pleomorphism and occasional mitoses

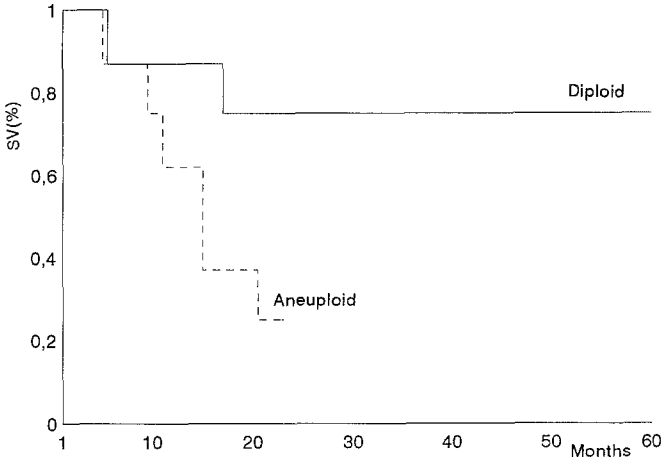

Fig. 4 Stromal tumours of the gastrointestinal tract: life table of ploidy

Table 4 Stromal tumours of the gastrointestinal tract: statistical results

Survival related to:	
size >10 cm	$P<0.01$
local invasion (Yes/No)	$P<0.01$
grade (I versus II and III)	$P<0.01$
mitoses (5 per 10 high power fields)	$P<0.02$
necrosis (yes/no)	$P<0.02$
Ploidy related to:	
size >10 cm	$P<0.03$
Grade related to:	
survival	$P<0.01$
local invasion	$P<0.009$

Discussion

Excluding gastric schwannomas, most STGIT have smooth muscle differentiation, with positivity for HHF–35 (a muscle specific actin) in 92% of cases (Ueyama et al. 1992). Since we only had conventional morphological data without immunohistochemistry or electron microscopy studies to confirm the histogenesis of neoplasm, we will use that terminology. Although these tumours are very rare in the osophagus and anus and uncommon in the rectum, they are occasionally found in the stomach and small bowel (Akwari et al. 1978; Cooper et al. 1992; Hendrickson and Kempson 1989). These authors did not find significant differences between the behaviour of tumours in various locations but other investigators have stated that most gastric tumours are benign, whereas 80% of those located in small bowel are malignant (Nemer et al. 1977). Our results support the latter statement. In our series, the patient's age at presentation was similar to that referred to in the literature (Appelman 1984; Cooper et al. 1992; Evans 1985). Malignant tumours were more common in females than in males, raising the global male to female ratio of our series to 1:2. The average ratio reported in the literature is close to 1 (Cooper et al. 1992; Evans 1985; Uezama et al. 1992).

As prognostic factors, local invasion or metastases appear more important than site of origin (Cooper et al. 1992) and are more frequently associated with poor prognosis (Cunningham et al. 1993; Ng et al. 1992). In our experience, this is the most significant predictor of short survival; it occurs most commonly in small bowel tumours and correlates with their characteristic aggressive behaviour (Akwari et al. 1978; Nemer et al. 1977).

We found a significant correlation between tumour size over 10 cm and tumour-related death. According to

the literature, gastric tumours less than 5.5 cm never metastasize, tumours between 5.5 and 10 cm do so in 30% of cases and tumours larger than 10 cm metastasize in over 60% of cases (Appelman 1984; Evans 1985; Hendrickson and Kempson 1989). In the small bowel, however, tumours over 4 cm in diameter are considered to be potentially malignant (Appelman 1984). In contrast, other investigators have pointed out that regardless of location, tumour size over 6 cm is usually associated with malignant behaviour (Cooper et al. 1992).

The large average size of our cases might explain the frequency of mucosal ulceration: 59% versus 35% in other series (Cooper et al. 1992), in which the mean size of the tumours was smaller than in ours. However, ulceration has not been proved to be an independent prognostic factor (Cooper et al. 1992).

MI is another significant feature related to prognosis (Akwari et al. 1978; Appelman 1984; Cooper et al. 1992; Evans 1985; Hendrickson and Kempson 1989; Ranchod and Kempson 1977). Over ten mitoses per 10 HPF is a clear sign of malignancy (Cooper et al. 1992; Evans 1985). In those cases having between five (or even 3) and nine mitoses per 10 HPF, survival is difficult to predict (Cooper et al. 1992; Hendrickson and Kempson 1989) but patients with tumours containing one to five mitoses per 10 HPF should have a good prognosis (Evans 1985). In the small bowel, even one mitosis per 20 HPF is suggestive of malignancy (Appelman 1984). The size of the tumour modifies the previously stated criteria; gastric tumours larger than 5 cm and containing over five mitoses per 10 HPF are considered to be likely to show malignant behaviour, whereas those with fewer than five mitoses per 10 HPF are thought to be of uncertain malignant potential (Cooper et al. 1992). Our data also support these observations.

The presence or absence of necrosis was as good a prognostic factor as the MI; pleomorphism, however, proved to be of no prognostic value. In previous studies the pathological grading of leiomyosarcomas was based exclusively on the MI (Cooper et al. 1992; Evans 1985). In our series, we have applied the criteria that have been used for grading spindle cell sarcomas of soft tissues (Coindre et al. 1988), namely a combination of mitoses, necrosis and nuclear pleomorphism. By doing this we encountered a better correlation between grade and survival than that obtained by comparing single variables, MI included. The pathological grade also correlated well with invasion of adjacent structures.

In STGIT, tumour ploidy has been analysed by flow cytometry (Cooper et al. 1992; Cunningham et al. 1993; Kiyabu et al. 1988; Tsushima et al. 1987) and cytophotometry (Cunningham et al. 1993; Federspiel et al. 1987; Flint et al. 1989). The frequency of aneuploidy varies from 25% (Cooper et al. 1992) to 41% (Kiyabu et al. 1988) rising to 54% in sarcomas (47% in low-grade and 71% in high-grade sarcomas; Kiyabu et al. 1988). In our series, aneuploidy was found in 39.5% of all STGIT and in 54.5% of the tumours that killed the patients. Aneuploidy of the G0/G1 peak has been related to short survival in some univariate statistical analysis (Cooper et al. 1992; Cunningham et al. 1993; Kiyabu et al. 1988; Tsushima et al. 1987) but its significance is lost in the multivariate analysis (Cunningham et al. 1993). Abnormal nuclear DNA content was also related to pathological grade (Kiyabu et al. 1988; Tsushima et al. 1987) and size (Tsushima et al. 1987). However, other investigators have not found a relationship between ploidy and histological diagnosis (Flint et al. 1989). Although we have detected a trend, we have not found a statistically significant correlation between ploidy and either survival, pathological grade, MI or tumour necrosis. However, aneuploidy was found in five of six borderline tumours (MI between three and nine per 10 HPF) and four of these patients died. In summary, although DNA studies may help to predict the behaviour of STGIT (mainly in cases where adequate staging cannot be performed) their real value has not yet been established. Stage (invasion), size, MI and pathological grade remain the most useful prognostic factors.

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