Original article

Definition and clinical significance of tumour rupture in gastrointestinal stromal tumours of the small intestine

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Background: **Tumour rupture is a risk factor for recurrence of gastrointestinal stromal tumour (GIST). In this study, patterns of recurrence after potential tumour seeding were investigated, and a new definition of tumour rupture, based on major and minor defects of tumour integrity, is proposed.**

Methods: **Patients undergoing surgery for non-metastatic small intestinal GIST from 2000 to 2012 were included in the study. Tumour spillage, tumour fracture or piecemeal resection, bowel perforation at the tumour site, blood-tinged ascites, microscopic tumour infiltration into an adjacent organ, and surgical biopsy were defined as major defects of tumour integrity. Peritoneal tumour penetration, iatrogenic peritoneal laceration and microscopically involved margins were defined as minor defects.**

Results: **Seventy-two patients were identified. Median follow-up was 58 (range 7–122) months. Radical surgery was performed in 71 patients. A major defect was recorded in 20 patients, and a minor defect in 21. The 5-year recurrence rate was 64, 29 and 31 per cent in patients with major, minor and no defect respectively ($P = 0{\cdot}001$). The hazard ratio (HR) for major defect *versus* no defect was 3·55 (95 per cent c.i. 1·51 to 8·35). Peritoneal recurrence rates for major, minor and no defect were 52, 25 and 19 per cent respectively ($P = 0{\cdot}002$), and the HR for major defect *versus* no defect was 4·98 (1·69 to 14·68). On multivariable analysis, mitotic index, major defect of tumour integrity, tumour size and age were independently associated with risk of recurrence.**

Conclusion: **Recurrence rates were increased after major, but not minor tumour ruptures.**

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Introduction

Gastrointestinal stromal tumour (GIST) is the most common mesenchymal neoplasm of the alimentary tract. The stomach and small intestine are affected most frequently, accounting for approximately 60 and 30 per cent respectively of all patients with a GIST[1]. Prognosis depends on tumour size, mitotic index and anatomical site, and these variables are included in the Armed Forces Institute of Pathology (AFIP) classification, the modified National Institutes of Health (NIH) consensus criteria and the International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) TNM classification[1–3]. For carcinomas of the gastrointestinal tract, tumour penetration of the peritoneal surface is a risk factor for worse prognosis, and indicates a T4 tumour with consequences for treatment[3,4]. The TNM classification of GISTs does not include peritoneal penetration. Joensuu[2] introduced the concept of tumour rupture. In an analysis of 1198 patients from a population-based series, tumour rupture was associated with a small, but statistically significant, risk of unfavourable outcome[5]. Including rupture as a factor in the risk stratification increased the sensitivity for predicting recurrence[6].

Peritoneal tumour involvement can be confirmed histologically; 'tumour rupture', on the other hand, is an ambiguous expression based on intraoperative judgement, including a variety of clinical settings ranging from the piecemeal excavation of a spontaneously ruptured mass to tumours resected with microscopically involved margins. Not surprisingly, the reported frequency of rupture in GIST series varies greatly, from 2 to 22 per cent[6,7]. Rupture occurs more frequently in small intestinal than

in gastric GIST[8,9]. In a retrospective assessment of 640 patients with primary resected GISTs, Rutkowski and colleagues[9] recorded tumour rupture in 17 per cent of GISTs of the small intestine *versus* 1·5 per cent in gastric GISTs. In contrast to gastric tumours, which often bulge into the gastric lumen with an unaffected peritoneal, or even muscular, lining, small intestinal tumours exhibit exophytic peritoneal growth whereby an attenuated lining lends them prone to rupture. Small intestinal GISTs are larger than gastric GISTs when detected, but, compared with gastric GISTs of equal size and number of mitoses, patients with small intestinal GISTs fare worse[1]. Compared with GISTs of the stomach, the risk of recurrence after complete surgery for GIST of the small intestine is increased by a factor of two to three[5,10].

A clear-cut definition of 'rupture' is a prerequisite for an assessment of the clinical significance. As the occurrence of rupture often entails adjuvant treatment, currently recommended for 3 years[11,12], definitions have therapeutic implications. In this study, a new definition of tumour rupture based on major, as opposed to minor, defects of tumour integrity is proposed, and the impact on overall and site-specific recurrences in small intestinal GISTs was investigated.

Methods

The Sarcoma Group of the Norwegian Radium Hospital, Oslo University Hospital, is a referral centre for bone and soft tissue sarcoma in the south-eastern region of Norway, with a population of 2·8 million, and also receives patients from other parts of the country. Demographical, clinical and pathology data are recorded in a sarcoma database. Patients with GIST of the small intestine (duodenum, jejunum or ileum) referred for treatment or follow-up after surgery from 2000 to 2012 were identified in the database. Patients with metastases, diagnosed on thoracic, abdominal and pelvic CT, or at surgery, were excluded from analysis. Information was supplemented by retrospective review of all surgical and pathology reports, and histological slides from all specimens, except those that were removed intralesionally, were re-examined for possible tumour penetration of the peritoneum. Follow-up included clinical examination, abdominal and pelvic CT and chest X-ray every 6 months for 5 years, and then yearly from 5 to 10 years after surgery.

Definitions

Defects of tumour integrity were classified retrospectively. Major defect included: tumour spillage, tumour fracture or piecemeal resection; bowel perforation at tumour site; blood-tinged ascites at laparotomy; microscopic tumour infiltration into adjacent organ; and surgical biopsy. Core needle biopsy (CNB) was not included in the definition of a major defect in tumour integrity. Minor defect included: peritoneal tumour penetration (corresponding to a T4a tumour in gastric and colorectal carcinomas[3]); iatrogenic peritoneal laceration; and microscopically involved intestinal resection margins.

The completeness of tumour removal was recorded according to the TNM residual tumour classification[13]: R0, no detectable residual tumour; R1, microscopic residual tumour; R2, macroscopic residual tumour.

Adjuvant treatment

Between May 2004 and August 2008, patients with high-risk GIST according to the NIH or modified NIH consensus criteria were considered for inclusion in the Scandinavian Sarcoma Group (SSG) XVIII/Arbeitsgemeinschaft Internistische Onkologie (AIO) trial (1 *versus* 3 years of adjuvant imatinib)[14]. From September 2008 to May 2011, high-risk patients received imatinib 400 mg daily for 1 year, and from June 2011 imatinib 400 mg daily for 3 years.

Pathology

The diagnosis of GIST was confirmed by a sarcoma pathologist according to World Health Organization recommendations[15]. The majority of tumours were of the spindle cell type with evidence of CD117 (KIT) positivity on immunohistochemical evaluation. Antibodies against the protein discovered on GIST-1 (DOG1) were included in the panel from 2011, and were positive in all tested tumours. Mutational analyses of *KIT* and platelet-derived growth factor receptor α (*PDGFRA*) genes started in 2003. Risk assessment was based on tumour size, mitotic count and anatomical site[1,16].

Statistical analysis

Relative risk (RR) was calculated according to Altman[17]. Survival was estimated according to the Kaplan–Meier method and compared using the log rank test. Multivariable analysis was conducted using the Cox proportional hazards regression model and presented as hazard ratio (HR) and 95 per cent c.i. Established prognostic variables (tumour size and mitotic index) were included in the model, as well as age, sex and defects of tumour integrity. Recurrence-free survival was estimated from date of surgery until first recurrence, and patients were

Table 1 Demographic, clinical and pathological characteristics

		Defect of tumour integrity		
	Total no. of patients ($n = 72$)	Major ($n = 20$)	Minor ($n = 21$)	None ($n = 31$)
Age (years)*	63 (27–86)	63 (27–79)	62 (40–86)	65 (41–83)
Sex ratio (M : F)	34 : 38	9 : 11	7 : 14	18 : 13
Recurrence-free interval (months)*	58 (7–122)	53 (33–69)	61 (7–122)	57 (23–116)
Tumour site				
Duodenum	11 (15)	3	3	5
Jejunum/ileum	61 (85)	17	19	25
Emergency operation	18 (25)	8	5	5
Elective operation	54 (75)	12	15	27
Extent of surgery				
Simple resection	58 (81)	11	19	28
Multivisceral resection	14 (19)	9	3	2
Tumour size (cm)*	6·0 (0·8–26·0)	7·0 (2·0–19·0)	6·4 (1·3–26·0)	5·1 (0·8–20·0)
NIH consensus criteria				
Very low risk	9 (13)	2	4	3
Low risk	19 (26)	2	4	13
Moderate risk	19 (26)	4	8	7
High risk	24 (33)	11	5	8
Unspecified	1 (1)	1	0	0
AFIP criteria				
1	9 (13)	2	3	4
2	19 (26)	2	5	12
3a	18 (25)	4	8	6
3b	7 (10)	3	2	2
4	0 (0)	0	0	0
5	2 (3)	1	1	0
6a	10 (14)	4	2	4
6b	6 (8)	3	0	3
Unspecified	1 (1)	1	0	0
Mutational analysis				
KIT exon 11	25 (35)	9	6	10
KIT exon 9	2 (3)	0	0	2
KIT/*PDGFRA* wild-type	7 (10)	3	1	3
Material unfit for analysis	2 (3)	1	1	0
Analysis not performed	36 (50)	7	13	16
Completeness of resection				
R0 or R1	71 (99)	19	21	31
R2	1 (1)	1	0	0
Adjuvant treatment				
None	59 (82)	14	17	28
For 1 year	3 (4)	1	1	1
For 3 years	4 (6)	1	2	1
Discontinued	2 (3)	1	0	1
Recurrence while treated	3 (4)	2	1	0
Neoadjuvant	1 (1)	1	0	0
Defect of tumour integrity		–	–	–
Major	20 (28)			
Minor	21 (29)			
None	31 (43)			

Values in parentheses are percentages unless indicated otherwise; *values are median (range). NIH, National Institutes of Health; AFIP, Armed Forces Institute of Pathology; PDGFRA, platelet-derived growth factor receptor α.

censored for death from any cause. For peritoneal recurrence, patients were censored at the time of an isolated systemic recurrence. Data analyses were performed using SPSS® version 21·0 (IBM, Armonk, New York, USA). $P < 0·050$ was considered statistically significant.

Results

For the years 2000–2012, the sarcoma database included 350 patients with GIST, of whom 101 had tumours of the small intestine. Among these patients, 28 were diagnosed

Table 2 Defects of tumour integrity related to site of first recurrence

	Total no. of patients ($n = 71$)	Recurrence-free ($n = 44$)	Site of first recurrence			Recurrence at any site ($n = 27$)
			Peritoneal ($n = 12$)	Peritoneal and organ metastasis ($n = 7$)	Organ metastasis ($n = 8$)	
Major defect	19	6	7	3	3	13
Spillage, fracture or piecemeal resection*	8	2	4	1	1	6
Bowel perforation at tumour site	6	3	1	1	1	3
Blood-tinged ascites	2	0	1	0	1	2
Microscopic infiltration of adjacent organ	2	0	1	1	0	2
Surgical biopsy	1	1	0	0	0	0
Minor defect	21	16	3	1	1	5
Peritoneal tumour penetration	14	10	2	1	1	4
Iatrogenic peritoneal laceration	5	4	1	0	0	1
Involved resection margin	2	2	0	0	0	0
No defect	31	22	2	3	4	9

*One patient from this group with residual tumour after resection was excluded.

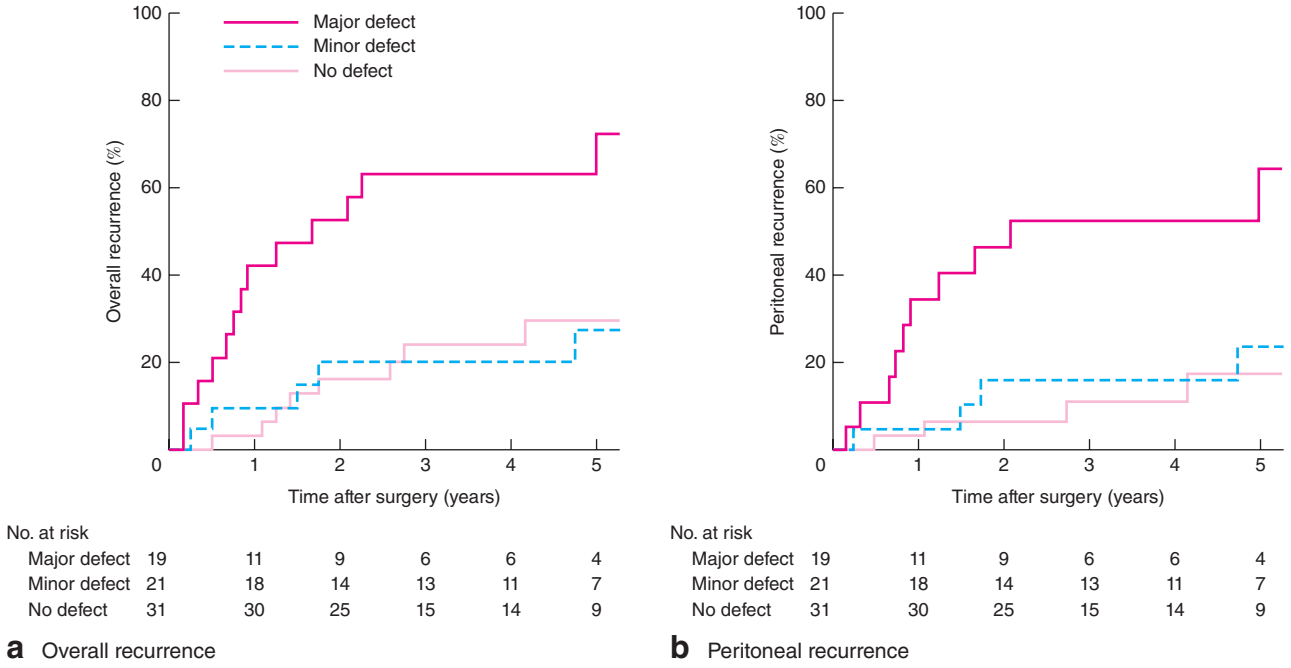

Fig. 1 Kaplan–Meier curves of estimated recurrence after surgery for non-metastatic gastrointestinal stromal tumours of the small intestine: **a** overall and **b** peritoneal recurrence. **a** $P = 0{\cdot}001$, **b** $P = 0{\cdot}002$ (log rank test)

with synchronous metastases and were excluded from the study. Of the remaining 73 patients with non-metastatic GIST, 11 had duodenal GIST and 62 had a tumour of the jejunum or ileum. Demographic, clinical and pathological characteristics are presented in *Table 1*. One patient with a 1·5-cm GIST discovered as an incidental finding during a gynaecological procedure was discharged without follow-up, and was not included in the present analysis. Surgical mortality included one patient with an incompletely resected (R2) high-risk GIST of the duodenum, who died from complications after a Whipple procedure. This patient was excluded from analyses of recurrence, which therefore included 71 patients.

Tumour integrity

Defects of tumour integrity were documented in 41 patients. A major defect was diagnosed in 20 patients and a minor defect in 21. The types of defect and the relationship between tumour integrity and the NIH consensus[16] and AFIP[1] criteria are outlined in *Table 1*.

Table 3 Multivariable Cox regression analysis of risk of recurrence

	Recurrence at any site		Peritoneal recurrence	
	Hazard ratio	*P*	Hazard ratio	*P*
Age (years)*	1·05 (1·01, 1·09)	0·008	1·05 (1·00, 1·10)	0·039
Sex				
F	1·00 (reference)		1·00 (reference)	
M	1·67 (0·66, 4·24)	0·280	3·94 (1·20, 12·94)	0·024
Tumour size (cm)*	1·09 (1·02, 1·16)	0·008	1·12 (1·05, 1·21)	0·001
Mitotic index (per 50 HPF)				
≤ 5	1·00 (reference)		1·00 (reference)	
> 5	7·27 (2·80, 18·90)	< 0·001	8·98 (2·49, 32·43)	0·001
Defect of integrity				
None	1·00 (reference)		1·00 (reference)	
Minor	1·67 (0·49, 5·71)	0·413	3·51 (0·74, 16·74)	0·115
Major	3·85 (1·36, 10·90)	0·011	8·57 (2·16, 33·98)	0·002

Values in parentheses are 95 per cent c.i. *Continuous variable. HPF, high-power fields.

There were 18 emergency and 54 elective operations (*Table 1*). The RR of any defect of tumour integrity in emergency compared with elective operations was 1·39 (95 per cent c.i. 0·95 to 2·05; $P = 0·092$), and the RR of major defect was 2·00 (0·98 to 4·10; $P = 0·059$). Multivisceral resections were performed in 14 patients (*Table 1*). The RR of any defect of tumour integrity in multivisceral *versus* simple resections was 1·71 (1·23 to 2·40; $P = 0·002$), and the RR of major defect was 3·39 (1·75 to 6·56; $P < 0·001$).

Recurrence

Recurrences were recorded in 27 of 71 patients (*Table 2*). The abdominal cavity was the site of first recurrence in 12 patients, abdominal cavity and liver concomitantly in seven, liver alone in seven, and liver and lungs in one patient. The median time to recurrence for patients who developed peritoneal metastases was 15 (range 2–71) months, and for organ metastases 17 (2–71) months.

For all patients, the estimated 5-year recurrence rate was 39 per cent, and the peritoneal recurrence rate was 29 per cent. Patients with major defect of tumour integrity had a significantly higher overall recurrence rate than those with minor or no defect ($P = 0·001$) (*Fig. 1a*). The estimated 5-year recurrence rate was 64, 29 and 31 per cent for major, minor and no defect respectively. The HR for recurrence for major defect *versus* no defect was 3·55 (95 per cent c.i. 1·51 to 8·35).

Major defect increased the risk of peritoneal recurrence, whereas minor defect did not ($P = 0·002$) (*Fig. 1b*). Estimated 5-year peritoneal recurrence rates were 52, 25 and 19 per cent for major, minor and no defect respectively. The HR for major defect *versus* no defect for peritoneal recurrence was 4·98 (95 per cent c.i. 1·69 to 14·68).

In multivariable analyses including age, sex, tumour size, mitotic index (more than 5 per 50 high-power fields) and defects of tumour integrity as variables for worse outcome, a major defect of tumour integrity was associated with recurrence at any site (HR 3·85, 95 per cent c.i. 1·36 to 10·90) and with peritoneal recurrence (HR 8·57, 2·16 to 33·98) (*Table 3*). The established risk factors (mitotic index, tumour size and age) were also confirmed, with an increased HR (*Table 3*). A minor defect was not associated with recurrence at any site, or with peritoneal recurrence.

Adjuvant treatment

Twelve patients received adjuvant treatment with imatinib (*Table 1*). Treatment was discontinued in two patients after 2 and 4 months because of intolerable side-effects. Both patients later had tumour recurrence in the liver. In three patients, tumour recurrence occurred during adjuvant treatment, at 3, 9 and 10 months. Of the remaining seven patients, three were treated for 1 year; one of these patients had recurrence in the peritoneum and liver at 50 months. Four patients were treated for 3 years, of whom one had recurrence in the peritoneum at 57 months after surgery.

Of the 12 patients who started adjuvant treatment, nine had defects of tumour integrity. Three of five patients with a major defect had recurrence, and two of four with a minor defect. Of the three patients with no defect of tumour integrity, and who received adjuvant treatment, two had tumour recurrence.

One patient received neoadjuvant treatment before multivisceral resection with a Whipple procedure for GIST of the duodenum. Adjuvant imatinib was not given, and this patient was free from disease at 33 months' follow-up.

In the 58 patients undergoing complete surgery who did not receive neoadjuvant or adjuvant treatment, the HR for recurrence with a major defect of tumour integrity *versus* no defect was 5·57 (95 per cent c.i. 2·06 to 15·08; $P = 0·001$). There was no difference in recurrence rates between patients with minor defects and those with no defect (HR 0·72; 95 per cent c.i. 0·19 to 2·79; $P = 0·646$).

Discussion

In this study of 71 completely resected GISTs of the small intestine, recurrence rates did not differ between patients with a minor defect of tumour integrity and those with no defect. In contrast, patients with major defect had a higher recurrence rate, both peritoneal and overall. A major defect of tumour integrity remained an independent risk factor in multivariable analysis, together with mitotic index, tumour size and age.

The terms adopted in the present study – major and minor defects of tumour integrity – consider biological and surgical phenomena not accounted for in the established classification systems. Tumour penetration of the peritoneum, a common finding in small intestinal GISTs, is not included in the TNM classification for GIST as it is for carcinomas of the gastrointestinal tract[3]. Iatrogenic peritoneal laceration is not considered an R1 resection according to the TNM residual tumour classification[13]. With microscopically involved resection margins, these two variables are termed 'minor defects of tumour integrity' in the present study. Tumour spillage, fracture or piecemeal resection is not defined as an R1 resection in GIST[13]. In this study, they are termed 'major defects of tumour integrity'. Surgical biopsy, followed by complete excision, is staged piecemeal resection. Blood-tinged ascites and microscopic infiltration into an adjacent organ, also termed 'major defects of tumour integrity' in the present study, reflect longstanding breaches of tumour integrity and are shown here to have a particularly poor prognosis.

'Tumour rupture' is an established concept in GIST[7,18,19]. Rutkowski and co-workers[7] first documented rupture as an independent risk factor for recurrence, and tumour rupture is included as a variable in the modified NIH classification[2]. However, in the pooled analysis of these population-based series[5], tumour rupture was defined inconsistently, including R1 resections in one study[7], only gross tumour spillage in another[8] and even mucosal perforation in a third study[20]. Tumour rupture has so far emerged as a risk factor in multivariable analysis in two series of GIST[6,7]. In one of these studies[7], rupture was widely defined, including R1 resections, and the recurrence rate associated with rupture was 61 per cent. In another series[6], only 2 per cent of tumours were classified as ruptured, indicating a strict definition, and 90 per cent of these patients with tumour rupture relapsed. Hohenberger and colleagues[21] identified 23 patients with tumour rupture in a database that included 554 patients with GIST; in this study no exact definition of rupture was given. Eighteen patients relapsed; among the five who did not, four received adjuvant or ongoing imatinib treatment. In the SSG XVIII/AIO trial[14], comparing 1 *versus* 3 years of adjuvant imatinib in high-risk patients, 20 per cent had tumour rupture. R1 resection was included in the definition of rupture. Among patients in this SSG VIII/AIO trial, the absence of rupture was associated with a favourable prognosis in multivariable analysis, with a HR of 0·56, but was of less importance than mitotic index and anatomical site of the tumour[22]. This trial[14,22] included only high-risk patients who received adjuvant therapy, making comparison with other studies difficult.

Ideally, studies designed to identify prognostic factors should be conducted without adjuvant treatment as a confounding factor. However, 11 years after the introduction of adjuvant imatinib, excluding these patients from clinical series would be a considerable sacrifice for scientific stringency. Accordingly, in the American College of Surgery Oncology Group (ACOSOG) Z9000 and Z9001 trials there was no difference in recurrence rates between those who received adjuvant imatinib after R1 resection and those who did not[23]. In the present study, analysis of patients who did not receive imatinib confirmed major defect of tumour integrity as a significant marker of poor prognosis, as well as the lack of relationship between minor defect and recurrence. However, the numbers were small.

In carcinomas of the gastrointestinal tract, peritoneal tumour penetration, iatrogenic tumour perforation and positive resection margins all increase the risk of recurrence[24,25]. In the present study, none of these variables was associated with an adverse prognosis, in either the total population or in those who did not receive adjuvant treatment, although the patients were few. In the analysis of the 72 patients who had R1 resection in the ACOSOG Z9000 and Z9001 trials, recurrence-free survival did not differ from that in patients who had an R0 resection[23]. In the present study, a distinction was made between tumour penetration of the peritoneum and iatrogenic peritoneal laceration, the former being a biological phenomenon and the latter a surgical event. In this retrospective classification the distinction appears somewhat arbitrary. A peritoneal breach seen on the histological slide may as well be an iatrogenic defect unrecorded in the surgical report as a penetrating tumour. However, as both were categorized

as minor defects of tumour integrity, misclassification would not have influenced the results.

CNB was not included in the definition of minor defect. The question was not addressed, as only one patient in the present series was submitted to CNB. This patient had a simple resection with iatrogenic peritoneal laceration for a jejunal tumour and was disease-free at 69 months with no adjuvant therapy. In the SSG XVIII/AIO trial, CNB was not considered rupture, and recurrences were not increased in patients who were submitted to it[26]. A growing body of evidence indicates that CNB can be performed without risk in abdominal and retroperitoneal sarcomas[27]. Nevertheless, CNB is both semantically and biologically a breach of tumour integrity, and the present authors suggest that CNB be included in the definition of minor defect in future studies.

This study has indicated that a major defect of tumour integrity is an independent risk factor for both peritoneal and overall recurrence after complete surgery for GIST of the small intestine. Minor defects do not seem to be associated with such a risk, and should therefore not be considered as tumour rupture.

Disclosure

The authors declare no conflict of interest.

References

1 Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Arch Pathol Lab Med* 2006; **130**: 1466–1478.

2 Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. *Hum Pathol* 2008; **39**: 1411–1419.

3 Sobin LH, Gospodarowicz MK, Wittekind C (eds). *TNM Classification of Malignant Tumors (UICC)* (7th edn). Wiley-Blackwell: New York, 2009.

4 Ludeman L, Sheperd NA. Serosal involvement in gastrointestinal cancer: its assessment and significance. *Histopathology* 2005; **47**: 123–131.

5 Joensuu H, Vehtari A, Riihimäki J, Nishida T, Steigen SE, Brabec P *et al.* Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. *Lancet Oncol* 2011; **13**: 265–274.

6 Yanagimoto Y, Takahashi T, Muguruma K, Toyokawa T, Kusanagi H, Omori T *et al.* Re-appraisal of risk classifications for primary gastrointestinal stromal tumors (GISTs) after complete resection: indications for adjuvant therapy. *Gastric Cancer* 2015; **18**: 426–433.

7 Rutkowski P, Nowecki ZI, Michej W, Debiec-Rychter M, Woźniak A, Limon J *et al*. Risk criteria and prognostic factors for predicting recurrences after resection of primary gastrointestinal stromal tumor. *Ann Surg Oncol* 2007; **14**: 2018–2027.

8 Takahashi T, Nakajima K, Nishitani A, Souma Y, Hirota S, Sawa Y *et al.* An enhanced risk-group stratification system for more practical prognostication of clinically malignant gastrointestinal stromal tumors. *Int J Clin Oncol* 2007; **12**: 369–374.

9 Rutkowski P, Bylina E, Wozniak A, Nowecki ZI, Osuch C, Matlok M *et al.* Validation of the Joensuu risk criteria for primary resectable gastrointestinal stromal tumour – the impact of tumour rupture on patient outcomes. *Eur J Surg Oncol* 2011; **37**: 890–896.

10 DeMatteo RP, Gold JS, Saran L, Gönen M, Liau KH, Maki RG *et al.* Tumor mitotic rate, size, and location independently predict recurrence after resection of primary gastrointestinal stromal tumor (GIST). *Cancer* 2008; **112**: 608–615.

11 ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012; **23**(Suppl 7): vii49–vii55.

12 National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology: Soft Tissue Sarcoma*. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp [accessed 9 November 2013].

13 Wittekind C, Compton CC, Greene FL, Sobin LH. TNM residual tumor classification revisited. *Cancer* 2002; **94**: 2511–2516.

14 Joensuu H, Erikson M, Sundby Hall K, Hartmann JT, Pink D, Schütte J *et al.* One *vs* three years of adjuvant imatinib for operable gastrointestinal stromal tumor. *JAMA* 2012; **307**: 1265–1272.

15 Fletcher CD, Bridge JA, Hogendoorn PCW, Mertens F (eds). *WHO Classification of Tumours of Soft Tissue and Bone*. International Agency for Research on Cancer: Lyons, 2013.

16 Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ *et al*. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol* 2002; **33**: 459–465.

17 Altman DG. *Practical Statistics for Medical Research*. Chapman and Hall: London, 1991.

18 Kitabayashi K, Seki T, Kishimoto K, Saitoh H, Ueno K, Kita I *et al*. A spontaneously ruptured gastric stromal tumor presenting as generalized peritonitis: report of a case. *Surg Today* 2001; **31**: 350–354.

19 Cegarra-Navarro MF, de la Calle MA, Girela-Baena E, Garcia-Santos JM, Lloret-Estan F, de Andres EP. Ruptured gastrointestinal stromal tumors: radiologic findings in six cases. *Abdom Imaging* 2005; **30**: 535–542.

20 Tryggvason G, Gislason H, Magnusson MK, Jonasson JG. Gastrointestinal stromal tumors in Iceland, 1990–2003: the Icelandic GIST study, a population based incidence and pathologic risk stratification study. *Int J Cancer* 2005; **117**: 289–293.

21 Hohenberger P, Ronellentfitsch U, Oladeji O, Pink D, Ströbel P, Wardelmann E *et al*. Pattern of recurrence in

patients with ruptured primary gastrointestinal stromal tumour *Br J Surg* 2010; **97**: 1854–1859.
22 Joensuu H, Eriksson M, Sundby Hall K, Hartmann JT, Daniel Pink D, Schütte J *et al.* Risk factors for gastrointestinal stromal tumor recurrence in patients treated with adjuvant imatinib. *Cancer* 2014; **120**: 2325–2333.
23 McCarter MD, Antonescu CR, Ballman KV, Maki RG, Pisters PW, Demetri GD *et al*. Microscopically positive margins for primary gastrointestinal stromal tumors: analysis of risk factors and tumor recurrence. *J Am Coll Surg* 2012; **215**: 53–59.
24 Eriksen MT, Wibe A, Syse A, Haffner J, Wiig JN. Inadvertent perforation during rectal cancer resection in Norway. *Br J Surg* 2004; **91**: 210–216.
25 Wibe A, Rendedal PR, Svensson E, Norstein J, Eide TJ, Myrvold HE *et al.* Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. *Br J Surg* 2002; **89**: 327–334.
26 Eriksson M, Reichardt P, Sundby Hall K, Schütte J, Ramadori G, Hohenberger P *et al.* Needle biopsy through the abdominal wall for the diagnosis of GIST – does it pose any risk for tumor cell seeding and recurrence? *Connective Tissue Oncology Society (CTOS), 17th Annual Meeting*, November 2012 (Abstract).
27 Wilkinson MJ, Martin JL, Khan AA, Hayes AJ, Thomas JM, Strauss DC. Percutaneous core needle biopsy in retroperitoneal sarcomas does not influence local recurrence or overall survival. *Ann Surg Oncol* 2015; **22**: 853–858.

Snapshot quiz

Snapshot quiz 16/5

Answer: Isolated hypoglossal nerve palsy. This is a rare complication following orotracheal intubation. Manipulation of the neck during intubation and/or direct compression of the nerve are proposed mechanisms of injury. Patients present with weakness/deviation of the tongue and dysphagia. Symptoms usually resolve within 6 months.