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ORIGINAL ARTICLE – SARCOMA

Is Peritoneal Tumor Penetration of Prognostic Importance in Gastrointestinal Stromal Tumors?

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ABSTRACT

Background. Peritoneal tumor penetration (PP) strongly affects prognosis in gastrointestinal carcinomas. In gastrointestinal stromal tumor (GIST), its significance in the absence of tumor rupture has not been subjected to detailed analysis.

Methods. Patients undergoing complete resection for non-metastatic GIST from 2000 to 2017 were identified in the regional sarcoma database at Oslo University Hospital. Patients with extraperitoneal tumors (esophagus, rectum) or ruptured tumors were excluded from the study. Rupture was defined according to the Oslo criteria, and PP was assessed via routine histopathologic examination by sarcoma pathologists.

Results. The study enrolled 341 patients. The median follow-up period was 51 months (range 0–175) months. In 82 (24%) of the 341 patients, PP was recorded. There were 32 recurrences, 9 in patients with PP and 23 in patients without PP. Despite statistically significant associations between PP and established risk factors (size, mitotic index, non-gastric location), the 5-year recurrence-free survival rate did not differ between the patients with PP (86%) and those without PP (90%) (hazard ratio 1.25; 95% confidence interval 0.58–2.70; $P = 0.577$). Adjuvant imatinib was administered to 53 of 97 patients in the high-risk category. The recurrence rates did not differ between the PP-positive and PP-negative patients in either group.

Conclusions. In GIST, PP without tumor rupture appears not to influence prognosis. This lack of prognostic significance may reflect unexplored differences between epithelial and mesenchymal malignancies.

Peritoneal tumor penetration (PP), an acknowledged adverse characteristic of gastrointestinal carcinomas,[1–4] has not been subjected to dedicated scrutiny in gastrointestinal stromal tumor (GIST). Tumor size, mitotic index, non-gastric tumor location, and tumor rupture are established risk factors for recurrence in GIST, and some or all of these variables are included in the various classification systems and predictive nomograms currently in clinical use.[5–10]

Tumor rupture, a high-risk feature in the modified National Institutes of Health (NIH) consensus classification,[7] signifies seeding of malignant cells through a breach in the peritoneum, but PP is explicitly excluded from the Oslo definition of tumor rupture.[11,12] After complete resection of localized disease, recurrence rates reported in recent series range from 14 to 26%.[13–15] Peritoneal metastasis accounts for approximately two-thirds of recurrences, distributed evenly between isolated peritoneal disease and concurrent peritoneal and organ metastases.[15,16]

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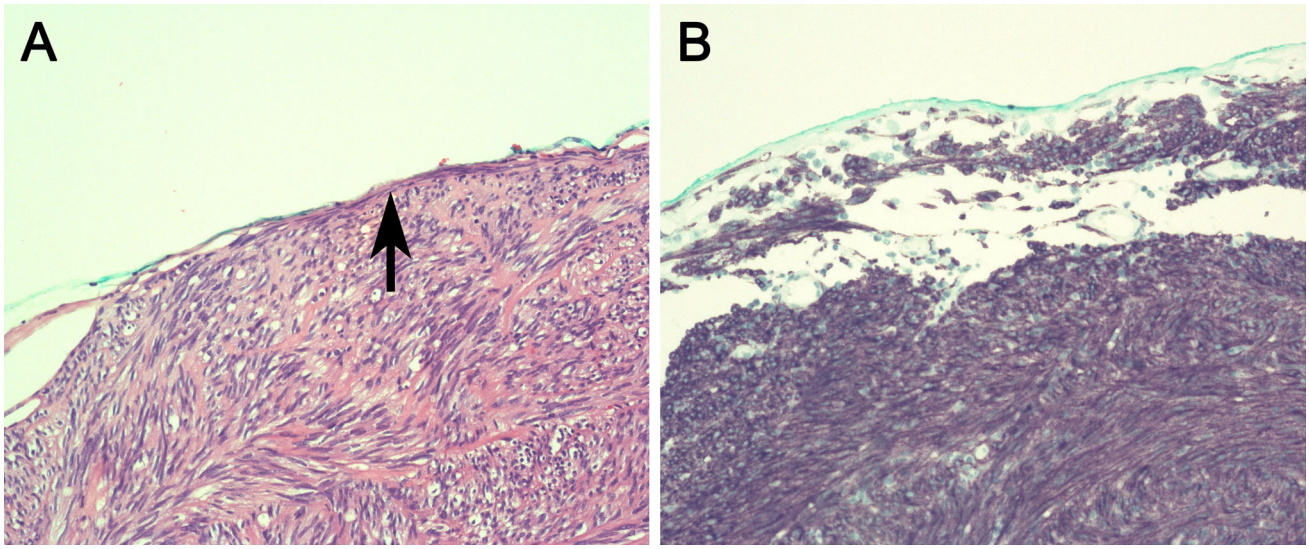

FIG. 1 Histologic slides illustrating **a** peritoneal tumor penetration (*arrow*) (hematoxylin–eosin stain) and **b** peritoneal tumor affection without penetration (CD117 stain)

Given the high incidence of peritoneal recurrence in GIST, a prognostic impact of peritoneal involvement similar to that in carcinomas with a propensity for peritoneal dissemination (i.e., gastric and colonic cancer) could be expected. This study aimed to assess the significance of PP in a population-based cohort of GIST patients.

METHODS

Patients undergoing complete resection (R0 or R1) for non-metastatic GIST from January 2000 to September 2017 were identified in the prospectively maintained sarcoma database of Oslo University Hospital (OUH). The OUH is the sarcoma center for the South-East Region of Norway (population 2.9 million) that receives patients for surgery, oncologic treatment, and follow-up evaluation. Because PP is a relevant feature of only abdominal tumors, patients with extraperitoneal (esophagus, rectum) GISTs were excluded from this analysis. Patients with tumor rupture according to the Oslo criteria (tumor spillage or fracture, piecemeal resection, incisional biopsy, blood-tinged ascites, gastrointestinal perforation through the tumor, and microscopic adjacent infiltration) also were excluded (Fig. S1).[11,12] Pathologic slides from specimens excised at other institutions were reexamined by a sarcoma pathologist at OUH.

During the study period, the Department of Pathology at OUH introduced a reporting template that includes a required field for recording serosal involvement. Before the introduction of this template, the tumor–peritoneum relationship was described in an individual fashion. Slides were reexamined if the original report was inconclusive. Only peritoneal defects or tumor extension to the peritoneal surface was considered PP; incomplete peritoneal penetration was not (Fig. 1). Transperitoneal core needle biopsy did not influence the assessment of PP.

In 2004, adjuvant treatment with imatinib 400 mg daily was introduced for high-risk patients according to the (modified) NIH criteria[7] who could be enrolled in the Scandinavian Sarcoma Group (SSG) XVIII/Arbeitsgemeinschaft Internistische Onkologie (AIO) trial (1 versus 3 years),[17] and from 2008, adjuvant imatinib was standard therapy for high-risk patients. Details regarding adjuvant treatment and follow-up evaluation have been presented in previous reports.[11,12]

Sites of first recurrence were categorized as peritoneal metastases (locoregional within the dissection field or distant peritoneal), organ metastases, or concurrent peritoneal and organ metastases. Recurrence-free survival (RFS) was measured from the date of surgery to recurrence, verified on biopsy or as indisputable on computed tomography (CT). The patients without recurrence were censored at the date of the latest CT. The patients who died of surgical complications were censored at the date of surgery. The study was approved by the Data Protection Officer at OUH.

Statistical Analysis

Relationships between PP and clinicopathologic variables were investigated using contingency tables and Fisher's exact test or a linear-by-linear-association Chi square test as appropriate. Survival was estimated using the Kaplan–Meier method and compared using the log-rank test. Hazard ratios (HRs) were calculated using the Cox proportional hazards regression model. Data analysis was

TABLE 1 Clinical and pathological characteristics of abdominal GIST patients without tumor rupture or metastases *n* (%)

Median age: years (range)	66 (14–93)
Sex (male:female)	168:173
Median follow-up: months (range)	51 (0–175)
Surgery at sarcoma center	229 (67.2)
Surgery outside the sarcoma center	112 (32.8)
Elective surgery	322 (94.4)
Emergency surgery	19 (5.6)
Surgical access	
Open	292 (85.6)
Laparoscopic	46 (13.5)
Endoscopic	3 (0.9)
Surgical mortality	2 (0.6)
Tumor location	
Stomach	254 (74.5)
Small intestine	82 (24.0)
Colon	4 (1.2)
Extragastrointestinal	1 (0.3)
Median tumor size: cm (range)	4.5 (0.5–26.0)
Mitotic index, per 50 HPF: median (range)	2 (0–130)
Modified NIH risk classification[a]	
Very low risk	26 (7.6)
Low risk	143 (42.1)
Intermediate risk	74 (21.8)
High risk	97 (28.5)
R0 resection	314 (92.1)
R1 resection	27 (7.9)
Core needle biopsy	
No	308 (90.3)
Yes	33 (9.7)
Peritoneal penetration	
No	259 (76.0)
Yes	82 (24.0)
Adjuvant imatinib treatment	
No	288 (84.5)
Yes	53 (15.5)
Median duration: months (range)	12 (< 1–60)
Neoadjuvant imatinib treatment	
No	333 (97.7)
Yes	8 (2.3)
Median duration: months (range)	9 (5–14)
Recurrence	
No	309 (90.6)
Yes	32 (9.4)
Median time to recurrence: months (range)	23 (11–104)
Site of first recurrence	
Peritoneal	10 (31)
Distant organ	14 (44)
Peritoneal and distant organ	8 (25)

GIST gastrointestinal stromal tumor, *HPF* high-power fields of the microscope, *NIH* National Institutes of Health

[a]One patient at unspecified risk of recurrence was excluded

performed using SPSS version 25.0 (SPSS Inc, Chicago, IL, USA), and *P* values lower than 0.05 were considered statistically significant.

RESULTS

From the original cohort of 410 patients undergoing complete surgery for non-metastatic GIST,[15] patients with esophageal or rectal GIST and patients with tumor rupture were excluded from the study, leaving 341 patients (173 females and 168 males) for analysis. The median age of these patients was 66 years (range, 14–93 years). The median follow-up period was 51 months (range, 0–175 months) for the patients without recurrence. There were 254 gastric GISTs (74.5%) and 87 non-gastric GISTs (25.5%). Further characteristics are presented in Table 1. In the high-risk category, 97 patients (28.5%) remained after the exclusion of those with tumor rupture.

Peritoneal Penetration

The study recorded PP in 82 patients (24%). No association could be detected between PP and the patients' age or sex; nor was the incidence of PP influenced by emergency surgery or surgery outside the sarcoma center (Table 2). However, for non-gastric tumors, large tumors, and tumors with a high mitotic index, the rate of PP was higher. This was particularly pronounced for tumors larger than 10 cm and tumors with more than 10 mitoses per 50 high-power fields (HPFs), reflected in an association between PP and risk category. The peritoneum was penetrated by 38 (39%) of 97 high-risk tumors compared with 43 (23.3%) of 243 tumors not at high risk ($P < 0.001$).

Recurrence

Of 32 patients with disease recurrence, 9 had PP and 23 had no PP, corresponding to estimated 5-year RFS rates of 86% and 90% respectively (HR 1.25; 95% confidence interval [CI] 0.58–2.70; $P = 0.577$) (Fig. 2a). Only four recurrences were recorded for patients with primary tumors not at high risk, one patient at intermediate risk (PP-positive) and three patients at low risk (PP-negative). One

TABLE 2 Peritoneal tumor penetration related to clinical and pathological characteristics

	Total $n = 341$	No penetration $n = 259$	Penetration $n = 82$	P value
Age ≥ median	178	136 (76.4)	42 (23.6)	0.899
Age < median	163	123 (75.5)	40 (24.5)	
Males	168	129 (76.8)	39 (23.2)	0.800
Females	173	130 (75.1)	43 (24.9)	
Elective operation	322	245 (76.1)	77 (23.9)	0.786
Emergency operation	19	14 (74)	5 (26)	
Surgery at sarcoma center	229	171 (74.7)	58 (25.3)	0.500
Surgery outside sarcoma center	112	88 (78.6)	24 (21.4)	
R0 resection	314	238 (75.8)	76 (24.2)	1.000
R1 resection	27	21 (78)	6 (22)	
Gastric tumor location	254	201 (79.1)	53 (20.9)	0.029
Non-gastric tumor location	87	58 (66.7)	29 (33.3)	
[a]*Tumor size (cm)*				0.004
≤ 5.0	193	155 (80.3)	38 (19.7)	
5.1–10.0	113	84 (74.3)	29 (25.7)	
> 10.0	34	19 (56)	15 (44)	
[b]*Mitoses per 50 HPF*				0.012
0–5	269	213 (79.2)	56 (20.8)	
6–10	29	22 (76)	7 (24)	
> 10	34	20 (59)	14 (41)	
Modified NIH classification				0.001
Very low risk	26	21 (81)	5 (19)	
Low risk	143	117 (81.8)	26 (18.2)	
Intermediate risk	74	62 (84)	12 (16)	
High risk	97	59 (61)	38 (39)	
Adjuvant imatinib				0.008
No	288	227 (78.8)	61 (21.2)	
Yes	53	32 (60)	21 (40)	
Neoadjuvant imatinib				0.099
No	333	255 (76.6)	78 (23.4)	
Yes	8	4 (50)	4 (50)	

Values are numbers (%)

[a]One patient with indeterminate tumor size excluded

[b]Nine patients with unspecified mitotic index excluded

[c]One patient at unspecified risk of recurrence excluded

HPF high-power fields of the microscope, *NIH* National Institutes of Health

patient who could not be allocated to a risk category had PP and relapsed. The nonsignificant prognostic nature of PP was not influenced by tumor site. The 5-year RFS rates with and without PP for gastric tumors were respectively 90% and 95% (HR 1.67; 95% CI 0.52–5.32; $P = 0.389$) (Fig. 2b) and for non-gastric tumors were respectively 82% and 73% (HR 0.65; 95% CI 0.23–1.84; $P = 0.420$) (Fig. 2c). The HRs for recurrence with PP in patients with tumors at different locations and in different risk categories are presented in Table 3.

In patients without PP, the site of the first recurrence was the peritoneum in 7 patients, a distant organ in 10 patients, and both sites concurrently in 6 patients. The corresponding figures for the patients with PP were three, four, and two.

Adjuvant Treatment

Adjuvant imatinib was administered to 53 patients, all at high risk of recurrence, for a median of 12 months (range < 1–60 months) (Table 1). Of 44 high-risk patients who received no postoperative therapy, 13 underwent surgery before the introduction of adjuvant imatinib, 5 had tumors with genotypes associated with primary resistance

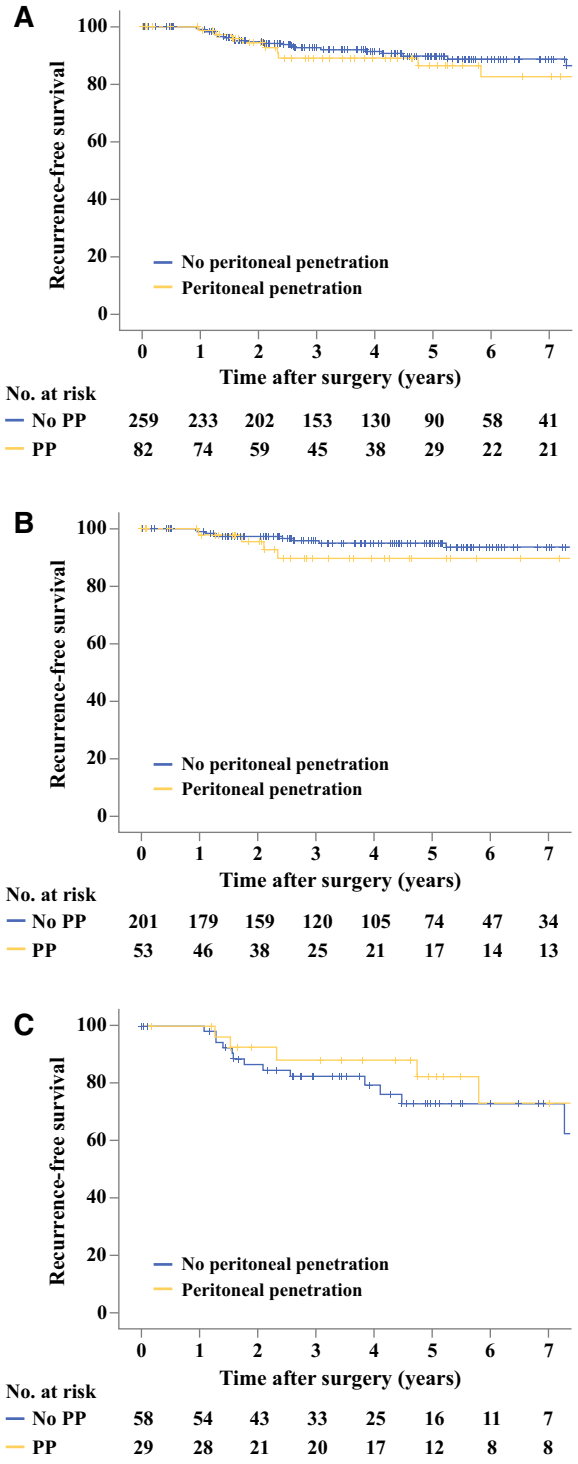

FIG. 2 Recurrence-free survival after resection of non-metastatic gastrointestinal stromal tumors without rupture. Peritoneal penetration versus no peritoneal penetration is shown in **a** the complete cohort, **b** gastric tumors, and **c** non-gastric tumors (esophageal and rectal GISTs excluded). **a** $P = 0.577$. **b** $P = 0.389$. **c** $P = 0.425$. All resulting from the log-rank test. *GIST* gastrointestinal stromal tumor

to imatinib, 10 were not referred or considered for medical treatment, and 8 were too old, had serious comorbidity, or had experienced surgical complications. In eight instances, adjuvant treatment was declined by the patient or the physician for other reasons. Among all 97 patients at high risk, 27 recurrences were experienced, 13 in patients who had received adjuvant treatment and 14 in patients who had not. The recurrence rates did not differ between the patients with and those without PP in any of these groups (Table 3).

DISCUSSION

In the current study, PP was subjected to a detailed analysis in a population-based cohort of primary GIST patients and found to be without prognostic significance. The impact of minor defects on tumor integrity, including PP, has been investigated previously by our group,[11,12] but specific studies analyzing PP in GIST have been lacking.

Patients with tumor rupture were excluded from this study. The risk of tumor rupture is a distinctive feature of sarcomatous abdominal tumors due to their size and fragility. It implies substantial contamination of the peritoneal cavity, is an established risk factor for recurrence,[9,15] and should not be confounded with PP. In contrast, PP is a characteristic common to both GIST and gastrointestinal carcinomas.

In the current series, PP was recorded in 24% of the GISTs. In gastric and colonic carcinomas, the incidence was respectively 20.4% and 7.9%, as reported by Sano et al.[18] and Gunderson et al.[4] in two large registry studies. In the former study of gastric cancer, the 5-year overall survival rate was reduced by 30% once the tumor penetrated the peritoneum (i.e., the difference between T3 and T4a tumors). The difference in 5-year survival rates between the T3 and T4a groups in the latter study of colon cancer varied from 10 to 30%.

Peritoneal metastases occur in 25–60% of gastric cancer patients with PP versus 5–21% of patients without PP.[2,19,20] In colon cancer, the rate of peritoneal metastasis increases from 9 to 50% with PP.[21] In GIST, according to the current analysis, no association seems to exist between PP and a peritoneal pattern of recurrence. Nevertheless, the peritoneum is the most common metastatic site in GIST because approximately two-thirds of patients who relapse have peritoneal disease, either as isolated peritoneal deposits or with concurrent organ metastases.[15,16]

Exfoliated cells from a primary abdominal or retroperitoneal tumor are thought to be the origin of peritoneal malignancy. However, a complex sequence of adhesion, penetration, proliferation, and angiogenesis must be induced for carcino- or sarcomatosis to become evident.[22] Differences between mesenchymal and epithelial

TABLE 3 Univariate Cox regression analysis of recurrence-free survival for abdominal GIST patients without tumor rupture or metastases[a]

	No penetration		Penetration		HR (95% CI)[b]	*P* Value
	Recurrence-free	Recurrence	Recurrence-free	Recurrence		
All patients	236	23	73	9	1.25 (0.58–2.70)	0.577
Gastric location	191	10	49	4	1.67 (0.52–5.32)	0.389
Non-gastric location	45	13	24	5	0.65 (0.23–1.84)	0.420
Very low-intermediate risk	197	3	42	1	1.52 (0.16–14.82)	0.716
High risk	39	20	31	7	0.50 (0.21–1.18)	0.112
High risk with adjuvant imatinib	23	9	17	4	0.66 (0.20–2.16)	0.491
High risk without adjuvant imatinib	16	11	14	3	0.46 (0.13–1.64)	0.228

GIST gastrointestinal stromal tumor, *HR* hazard ratio, *CI* confidence interval

[a]One patient at indeterminate risk of recurrence who had peritoneal penetration and disease recurrence was excluded from analyses involving risk category

[b]HR for recurrence with versus without peritoneal penetration

malignancies in this respect may explain the benign nature of PP in GIST documented in this report, but have not been investigated to date.

In accordance with the Oslo definition, microscopic organ infiltration was considered tumor rupture, and patients with this disorder were excluded from the current study. Contiguous transperitoneal infiltration, equivalent to tumor stage pT4b in gastrointestinal carcinoma, is a somewhat controversial criterion of tumor rupture because it does not intuitively entail transcoelomic dissemination. However, in GIST, adjacent infiltration carries a particularly poor prognosis. In the sarcoma database at OUH, eight patients with collaterally infiltrating tumors are registered, all of whom relapsed despite complete multivisceral resections (unpublished data). Similar outcomes are indicated in the report by Yanagimoto et al.[23] Adjacent organ infiltration probably reflects biologic properties other than isolated PP, and these categories should be kept apart, as in carcinomas, whether microscopic adjacent infiltration be termed tumor rupture or not.

Recurrence was almost exclusively seen in high-risk patients, who by current standards now receive adjuvant treatment for 3 years. In the current study, nearly half of the patients at high risk received no postoperative treatment. For the patients without adjuvant therapy, PP did not confer a greater risk of recurrence than for those who received postoperative imatinib. The events were few, and the two groups were not exactly similar (median follow-up period, 51 versus 45 months; median tumor size, 8.3 versus 7.7 cm; median mitotic index, 6 versus 11; non-gastric location, 26 [59%] versus 20 [38%]), and the current data could not exclude a detrimental consequence of PP compensated by imatinib, although such an effect seems unlikely.

The current study had limitations related to both its retrospective design and the nature of the phenomenon under study. Assessment of PP was performed in routine histopathologic examination. Before the introduction of the reporting template, the serosal surface was described in an individual fashion, and some penetrations certainly were missed. However, only a few sarcoma pathologists have been engaged in these examinations, and a uniform practice can be presumed.

Of greater methodologic concern are the problems encountered in handling large fragile specimens and in selecting areas for microscopy. Artificial peritoneal damage, iatrogenically during surgery or during specimen transport or examination, may have been recorded as PP. Artificial damage is more likely to occur in large, high-risk tumors, and misclassification would therefore overestimate the negative impact of PP.

In the current study, PP was noted in 11 (24%) of the 46 resections (13.5%) performed laparoscopically. Peritoneal damage sustained during specimen extraction, misinterpreted as PP, would not have significantly influenced the analysis.

CONCLUSIONS

The current study showed that PP is common in GIST, but despite its association with recognized risk factors, PP appears not to influence prognosis. In this respect, GISTs behave differently from carcinomas, indicating unexplored dissimilarities between mesenchymal and epithelial malignancies.

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REFERENCES

1. Moriguchi S, Maehara Y, Korenaga D, Sugimachi K, Nose Y. Risk factors which predict pattern of recurrence after curative surgery for patients with advanced gastric cancer. *Surg Oncol.* 1992;1:341–6.
2. Roviello F, Marrelli D, de Manzoni G, Morgagni P, Di Leo A, De Stefano A, Italian Research Group for Gastric Cancer. Prospective study of peritoneal recurrence after curative surgery for gastric cancer. *Br J Surg.* 2003;90:1113–9.
3. O'Connell JB, Maggard MA, Ko CY. Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. *J Natl Cancer Inst.* 2004;96:420–5.
4. Gunderson LI, Jessup JM, Sargent DJ, Greene FI, Stewart AK. Revised TN categorization for colon cancer based on national survival outcomes data. *J Clin Oncol.* 2010;2:264–71.
5. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol.* 2002;33:459–65.
6. Miettinen M, Lasota J. Gastrointestinal stromal tumours: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Arch Pathol Lab Med.* 2006;130:1466–78.
7. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumour. *Hum Pathol.* 2008;39:1411–9.
8. Gold JS, Gönen M, Gutiérrez A, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. *Lancet Oncol.* 2009;10:1045–52.
9. Joensuu H, Vehtari A, Riihimäki J, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. *Lancet Oncol.* 2012;13:265–74.
10. Brierley JD, Gospodarowicz MK, Wittekind C (eds). *TNM classification of malignant tumours (UICC).* 8th ed. Oxford: Wiley; 2017.
11. Hølmebakk T, Bjerkehagen B, Boye K, Bruland O, Stoldt S, Sundby Hall K. Definition and clinical significance of tumour rupture in gastrointestinal stromal tumours of the small intestine. *Br J Surg.* 2016;103:684–91.
12. Hølmebakk T, Hompland I, Bjerkehagen B, Stoldt S, Bruland ØS, Hall KS, Boye K. Recurrence-free survival after resection of gastric gastrointestinal stromal tumors classified according to a strict definition of tumor rupture: a population-based study. *Ann Surg Oncol.* 2018;25:1133–9.
13. Bischof DA, Kim Y, Dodson R, et al. Conditional disease-free survival after surgical resection of gastrointestinal stromal tumours. *JAMA Surg.* 2015;150:299–306.
14. Nishida T, Cho H, Hirota S, et al. Clinicopathological features and prognosis of primary GISTs with tumor rupture in the real world. *Ann Surg Oncol.* 2018;25:1961–9.
15. Hølmebakk T, Bjerkehagen B, Hompland I, Stoldt S, Boye K. Relationship between R1 resection, tumour rupture, and recurrence in resected gastrointestinal stromal tumour. *Br J Surg.* 2019;106:419–26.
16. Rutkowski P, Nowecki ZI, Michej W, et al. Risk criteria and prognostic factors for predicting recurrences after resection of primary gastrointestinal stromal tumour. *Ann Surg Oncol.* 2007;14:2018–27.
17. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. *JAMA.* 2012;307:1265–72.
18. Sano T, Coit DG, Kim HH, et al. Proposal of a new-stage grouping of gastric cancer for TNM classification: international gastric cancer association staging project. *Gastric Cancer.* 2018;20:217–25.
19. Soga K, Ichikawa D, Yasukawa S, et al. Prognostic impact of the width of subserosal invasion in gastric cancer invading the subserosal layer. *Surgery.* 2010;2:197–203.
20. Huang B, Sun Z, Wang Z, et al. Factors associated with peritoneal metastasis in non-serosa-invasive gastric cancer: a retrospective study of a prospectively collected database. *BMC Cancer.* 2013;13:57.
21. Hompes D, Tiek J, Wolthuis A, et al. HIPEC in T4a colon cancer: a defendable treatment to improve oncologic outcome? *Ann Oncol.* 2012;23:3123–9.
22. Jayne D. Molecular biology of peritoneal carcinomatosis. In: Ceelen WP, editors. *Peritoneal carcinomatosis. A multidisciplinary approach.* New York: Springer; 2007.
23. Yanagimoto Y, Takahashi T, Muguruma K, et al. Reappraisal of risk classifications for primary gastrointestinal stromal tumors (GISTs) after complete resection: indications for adjuvant therapy. *Gastric Cancer.* 2015;18:426–33.