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Prognostic Impact of Positive Microscopic Margins (R1 Resection) in Patients with GIST (Gastrointestinal Stromal Tumours): Results of a multicenter European study

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ABSTRACT

Background: Although several prognostic factors in GIST have been well studied such as tumour size, mitotic rate, or localization, the influence of microscopic margins or R1 resection remains controversial. The aim of this study was to evaluate the influence of R1 resection on the prognosis of GIST in a large multicentre retrospective series of patients.

Methods: From 2001 to 2013, 1413 patients who underwent surgery for any site of GIST were identified from 61 European centres. 1098 patients were included, excluding synchronous metastases, concurrent malignancies, R2 resection or GIST recurrence. Tumour rupture (TR) was reclassified according to the Oslo sarcoma classification. Cox proportional hazards ratio and Kaplan-Meier survival estimates were used to analyse 5-year recurrence-free survival (RFS)

Results: Of 1098 patients, 38 (3%) underwent R1 resection with a risk of TR of 11%. The 5-year RFS was 89.6% with a median follow-up of 81 months [range: 31.2-152 months]. On univariate analysis, lower RFS was significantly associated with R1 resection [HR=2.13; p=0.04], high risk score according to the modified NIH classification, administration of adjuvant therapy [HR=2.24; p<0.001] and intraoperative complications [HR=2.82; p<0.001]. Only intraoperative complications [HR=1.79; p=0.02] and high risk according to the modified NIH classification including the updated definition of TR [HR=3.43; p=0.04] remained significant on multivariate analysis.

Conclusion: This study shows that positive microscopic margins are not an independent predictive factor for RFS in GIST when taking into account the up-dated classification of TR. R1 resection may be considered a reasonable alternative to avoid major functional sequelae and should not lead to reoperation.

Keywords : GIST, R1 resection, microscopic positive margins, tumor rupture.

Abbreviations : TR : Tumour rupture, GIST : Gastro-intestinal Stromal Tumour, GI : Gastrointestinal, RFS : Recurrence Free Survival, TKI : tyrosine kinase inhibitor, NIHC : National Institute of Health classification,

INTRODUCTION

Gastro-intestinal stromal tumours (GISTs) are the most common mesenchymal tumour of the gastrointestinal (GI) tract with an annual incidence of 14-20 cases per million. GIST typically occur in older adults, mostly in the stomach (60%) and small bowel (30%) [1]. GISTs are heterogeneous tumours because of their variable biological and clinical behaviour, between unexpectedly discovered benign tumours, to perforated or bleeding malign tumours [3,4]. Imatinib Mesylate is the first effective medical treatment for metastatic GIST, neo-adjuvant treatment for locally advanced tumours, and patients with high risk tumours after operation. [4] Radical surgery with negative microscopic margins (R0) is the gold standard for primary, localized, resectable GISTs in current guidelines [4, 5, 6, 7, 8, 9].

However, the prognosis of positive microscopic resection margins (R1) and the potential therapeutic adjustment resulting from R1 resection (revision surgery, adjuvant treatment or surveillance) remain controversial in the current recommendations [4, 8, 9]. Indeed, several studies [5, 6, 7] have evaluated the prognostic value of R1 margin in GIST, with controversial results, partly due to the retrospective nature or the relatively small sample size of these studies. Three recent meta-analysis suggested that R1 resection resulted in a significantly shorter RFS/DFS than R0 resection for GISTs. However, in the first, the analysis excluding cases without tumour rupture cases showed that RFS was not significantly different between the R0 and R1 groups [10], and in the others, adjuvant imatinib could potentially attenuate the negative influence of R1 resection on recurrence-free survival (RFS) in GISTs [11, 12].

The introduction of a strict definition of tumour rupture by the Oslo Sarcoma Group in 2016 aimed

to provide a standardized and consistent criterion for identifying cases of tumour rupture. Before this definition, the term "tumour rupture" was often subject to interpretation during surgery, leading to inconsistent definitions and potentially including cases that were classified as R1 resections [13]

Two recent studies seem to support the notion that tumour rupture, as defined by the Oslo Sarcoma Group, is a critical factor influencing the overall survival of GIST patients, more so than R1 margin, regardless of whether adjuvant Imatinib therapy is administered [14].

Therefore, the aim of our study was to assess the true prognostic significance of the R1 margin by analysing a large series of primary GISTs regardless of tumour location, taking into account major TR in NIH modified classification, while respecting the Oslo definition [15].

PATIENTS AND METHODS

Population

From 2001 to 2013, 1413 patients who underwent surgery in 61 French-speaking European centers (members of AFC, Association Française de Chirurgie) for a local or metastatic GIST were identified. Data from these consecutive adult patients were collected retrospectively through a dedicated Website (<http://www.chirurgie-viscerale.org>). Population parameters and follow up were retrieved from clinical records in all patients through standardized forms. When missing, additional data were obtained from e-mail exchanges or phone calls with the referral center.

Patients were included if they underwent surgery with complete macroscopic resection (laparotomy or laparoscopy) including enucleation, with or without neoadjuvant or adjuvant therapy. All tumour locations and sizes were included.

Patients with synchronous metastatic disease, concurrent malignancies, R2 resection during surgery, GIST recurrence, or patients who received endoscopic resection were excluded from the study.

Patients were eligible for inclusion if they received surgery with complete macroscopic resection (laparotomy or laparoscopy) including enucleation, with or without neoadjuvant or adjuvant therapy. All location and all size of tumours were included.

Pretreatment work-up and surgical approach

Pretreatment investigations were standardised according to the guidelines of the European Society for Medical Oncology (ESMO) that were applicable at the time of surgical treatment [9] The surgical approach was determined according to the size and location of the tumour according to the same guidelines. Intraoperative complications were defined as any deviation from the ideal intraoperative course occurring between skin incision and skin closure. Only grade 2-4 were considered [16]

Post-operative course

Postoperative morbidity was divided into surgical complications (including anastomotic leak, intra-abdominal abscess, surgical site infection and bleeding necessitating blood transfusions, reoperation, and others) and medical complications (including urologic, pulmonary, cardiovascular, thromboembolic, neurologic complications, and others). The severity of complications was assessed according to the Clavien-Dindo classification, and only complications of at least grade II were considered for the analysis of overall morbidity[17].

Therapeutic strategies and follow-up

All cases were discussed during multidisciplinary team meetings. Decisions regarding the need for neoadjuvant and adjuvant tyrosine kinase inhibitors (TKI's) were made at the discretion of the local multidisciplinary teams in accordance with National and European guidelines [9, 18]. A regular follow-up with clinical examination and CT scan was recommended for at least 5 years, with a frequency depending on the recurrence risk according to the ESMO guidelines [9]. Recurrences were categorised as locoregional, or distant recurrence. RFS was calculated from the date of primary tumour surgery to the first evidence of recurrence censoring patients without recurrence at 5 years of follow-up.

Histopathologic analysis

European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines [4, 9] recommend complete resection of GIST with a negative surgical margin (R0) with an intact pseudocapsule, without a specific definition of a negative margin. Presence of residual tumour after treatment was coded in our study according to the current R classification, part of the TNM system [19]. This classification applies to the dissection surfaces of the tumour. Tumour relation to the peritoneum and TR is without implication for R status [20] so we analysed separately R1 resection and major TR and excluded R2 resection. In 2016, the Oslo Sarcoma Group proposed a clear-cut definition to code TR, based on a small intestine GIST population, and further applied to gastric GIST in 2018 [15, 21]. This definition has been approved by NCCN Guidelines from October 2020 [4] and updated ESMO Guidelines from January 2022 [9].

- Major defect, which identify patients at particularly high risk of recurrence, included: Tumour fracture/spillage, blood-tinged ascites, bowel perforation at tumour site, microscopic tumour infiltration into adjacent organ (T4b) even if resected in bloc, piecemeal resection, and surgical biopsy. (Fig1) [15] The peritoneum is without relevance to R status, so a GIST with negative gastrointestinal margins even removed with piecemeal resection, is still an R0 resection [8, 21].
- Minor defect included: Iatrogenic peritoneal laceration, peritoneal tumour penetration (T4a), and R1 resection [15].

In the two Holmebakk's studies, a major defect of tumour integrity was an independent risk factor in multivariable analysis, together with mitotic index, tumour size and age. A minor defect did not influence prognosis. [15;21] Accordingly, in the present study, only major defects were considered as tumour rupture.

Thus, tumours were classified according to the modified National Institute of Health Classification (NIHC) based on size, mitotic index, primary tumour site and major TR with incorporation of the

up-dated definition [22] (Table 1)

Risk category	Tumour Size (cm)	Mitotic index (per 50 HPF)	Primary Tumour Site
Very low risk	<2,0	≤5	Any
Low risk	2,1-5	≤5	Any
Intermediate risk	2,1-5	>5	Gastric
	<5	06-10	Any
High risk	5,1-10	≤5	Gastric
	Any	Any	Tumour Rupture
	>10	Any	Any
	Any	>10	Any
	>5,0	>5	Any
	2,1-5	>5	Non-gastric
	5,1-10	≤5	Non-gastric

Table 1 : NIH Modified Classification (Joensuu criteria) of recurrence risk

Statistical analysis

Qualitative variables were compared by Chi² tests. Quantitative variables were compared by Student's t-tests. Survival data were collected at 5 years. Survival was analysed using the Kaplan-Meier method and (when valid) the log-rank test.

Cox regression models were built to assess the relationship between post-surgery recurrence and the studied variables. Variables significantly associated with univariate analyses were then included in a multivariate regression model. The validity conditions of all of these models were checked. All statistical analyses were performed with R software (version 3.5), and the threshold for statistical significance was set to 5% [23].

RESULTS

Patients characteristics

The population flow chart is shown in Figure 1. A total of 1098 patients were included. Surgical resection was macroscopically complete (R0) in 1060 (97%) and incomplete (R1) in 38 tumours (3%).

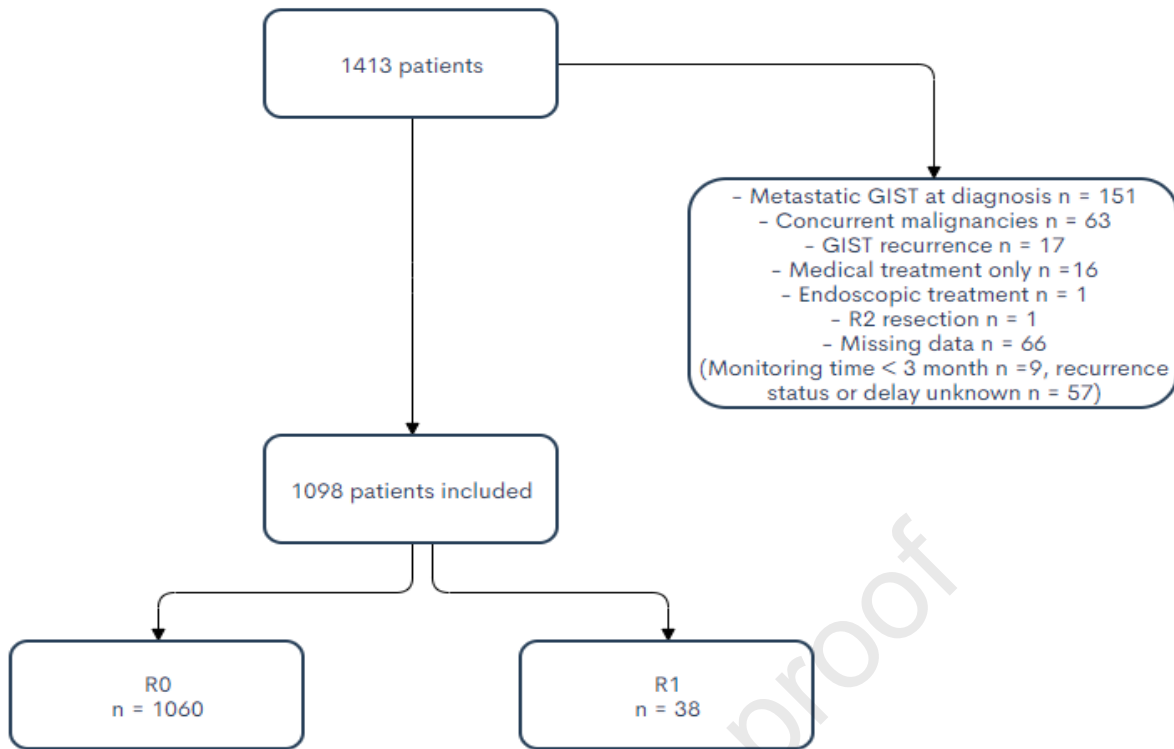


Figure 1. Flow Chart

Characteristics of the overall population are shown in Table 2. At presentation, the mean age of the patients was 63 years. They were mostly in good general condition, with 80% of patients having a WHO score of 0 to 1. Of these, 55 (5%) received neoadjuvant TKI and 21% received adjuvant TKI. The risk of relapse was calculated according to the NIHC classification: 6% of patients were classified as very low risk, 31% as low risk, 19% as intermediate risk and 43% as high risk. Intraoperative complications occurred in 83 patients (8%) and mostly included surgical complications necessitating transfusion (84%) . 5-year recurrence occurred in 114 patients (10%).

	No.	%
Follow-up time (months)	81.3	-
Age, yr median (DS)	63,29 (13)	
Sex		
Male	595	(54%)
Female	503	(46%)
BMI		
Underweight (<18.5)	439	(40%)
Normal Weight (18,5-25)	38	(3%)

Overweight (25-30)	375	(34%)
Obesity (>30)	145	(13%)
NA	101	(9%)
ASA score		
1	381	(35%)
2	502	(46%)
3	184	(17%)
4	11	(1%)
NA	20	(2%)
Tumour site		
Esophagus	29	(3%)
Stomach	722	(66%)
Duodenum	84	(8%)
Small intestine	217	(20%)
Colon	7	(1%)
Rectum	31	(3%)
Other	8	(1%)
Tumour size (cm)		
≤2	92	(8%)
]2;5]	464	(42%)
]5;10]	360	(33%)
≥10	165	(15%)
NA	17	(2%)
Neoadjuvant therapy		
No	1043	(95%)
Yes	55	(5%)
Adjuvant therapy		
No	861	(78%)
Yes	226	(21%)
NA	11	(<1%)
Joensuu criteria		
Very low risk	70	(6%)
Low risk	342	(31%)
Intermediate risk	213	(19%)
High risk	473	(43%)
Type of resection		
R0	1060	97
R1	38	3
Tumour rupture		
No	980	(89%)
Yes	118	(11%)

Laparotomy			
	No	273	(25%)
	Yes	810	(74%)
	NA	15	(1%)
Intra-operative complications			
	No	1013	(92%)
	Yes	83	(8%)
	NA	2	(0%)
Post-operative complications			
	No	877	(80%)
	Yes	203	(18%)
	NA	18	(2%)
Surgical complications			
	No	971	(88%)
	Yes	109	(10%)
	NA	18	(2%)
Type of surgical complications			
	No surgery complication	971	(88%)
	Fistula	23	(2%)
	Deep abscess	5	(0%)
	Bleeding	26	(2%)
	Other	45	(4%)
	Association	9	(1%)
	NA	19	(2%)
Recurrence at 5 years			
	No	984	(90%)
	Yes	114	(10%)
Local recurrence			
	No	1038	(95%)
	Yes	52	(5%)
	NA	8	(<1%)
Lymph Node recurrence			
	No	1080	(98%)
	Yes	11	(1%)
	NA	7	(1%)
Distant recurrence			
	No	1005	(92%)
	Yes	90	(8%)
	NA	3	(<1%)

Table 2 : Characteristics of patients and tumours

The characteristics of the R0 and R1 populations are described in Table 3. We observed no difference between the two groups in terms of age, sex, BMI, ASA score, neoadjuvant or adjuvant therapy, intraoperative complications, NIHC and major TR. We observed a significantly higher proportion of patients undergoing laparotomy ($p=0.025$) or postoperative surgical complications in the R1 resection group ($p<0.001$), which was consistent with tumour size, which was significantly higher in the R1 resection group ($p=0.001$).

		R0		R1		P-value
		No	%	No.	%	
		1060	(97%)	38	(3%)	
Follow-up time (months) m ± et		84.5	(56)	83.6	(58.2)	0,927
Age (years) m ± et		63,19	(13)	66,29	(13)	0,144
Sex						
	Male	577	(54%)	18	(47%)	0.39
	Female	483	(46%)	20	(53%)	
BMI						
	Underweight	422	(44%)	17	(52%)	0,626
	Normal Weight	36	(4%)	2	(6%)	
	Overweight	364	(38%)	11	(33%)	
	Obesity	142	(15%)	3	(9%)	
ASA score						
	1	372	(36%)	9	(24%)	-
	2	483	(46%)	19	(50%)	
	3	174	(17%)	10	(26%)	
	4	11	(1%)	0	(0%)	
Tumour site						
	Oesophagus	27	(3%)	2	(5%)	-
	Stomach	700	(66%)	22	(58%)	
	Duodenum	80	(8%)	4	(11%)	
	Small intestine	209	(20%)	8	(21%)	
	Colon	7	(1%)	0	(0%)	
	Rectum	30	(3%)	1	(3%)	
	Other	7	(1%)	1	(3%)	
Tumour size (cm)						
	≤2	88	(8%)	4	(11%)	0,001
]2;5]	452	(43%)	12	(32%)	

]5;10]	353	(34%)	7	(19%)	
	≥10	151	(14%)	14	(38%)	
Neoadjuvant therapy						
	No	1007	(95%)	36	(95%)	1,000
	Yes	53	(5%)	2	(5%)	
Adjuvant therapy						
	No	835	(80%)	26	(68%)	0.1
	Yes	214	(20%)	12	(32%)	
Joensuu criteria						
	Very low risk	66	(6%)	4	(11%)	0,335
	Low risk	333	(31%)	9	(24%)	
	Intermediate risk	208	(20%)	5	(13%)	
	High risk	453	(43%)	20	(53%)	
Tumour rupture						
	No	945	(89%)	35	(92%)	0,756
	Yes	115	(11%)	3	(8%)	
Laparotomy						
	No	270	(26%)	3	(8%)	0.036
	Yes	776	(74%)	34	(92%)	
Intra-operative complications						
	No	980	(93%)	33	(87%)	0.19
	Yes	78	(7%)	5	(13%)	
Postoperative complications						
	No	855	(82%)	22	(63%)	<0,001
	Yes	190	(18%)	13	(37%)	
Surgical complications						
	No	941	(90%)	30	(86%)	0.01
	Yes	104	(10%)	5	(14%)	
Recurrence (5 years)						
	No	954	(90%)	30	(79%)	0.03
	Yes	106	(10%)	8	(21%)	
Local recurrence						
	No	1008	(96%)	30	(79%)	<0,001
	Yes	44	(4%)	8	(21%)	
Lymph node recurrence						
	No	1043	(99%)	37	(97%)	0.324
	Yes	10	(1%)	1	(3%)	
Distant recurrence						
	No	974	(92%)	31	(82%)	0.02
	Yes	83	(8%)	7	(18%)	
Death all causes						

	No	996	(92%)	30	(81%)	<0,001
	Yes	53	(5%)	7	(19%)	

Table 3 : Characteristics of patients and tumours by surgical resection

Follow up and outcome: Recurrence Free Survival (RFS)

The 5-year RFS was 89.6% with a median follow-up of 81 months (range 31.2 to 152 months). 5-year RFS was 90% in the R0 tumours, and 79% in R1 tumours. The risk of recurrence was higher in R1 tumours (21%) than in R0 tumours (21% vs. 10%, $p=0.028$), and local recurrence was significantly higher in the R1 resection group (21% vs. 4%, $p<0.001$). The rate of death was not significantly higher in R1 tumours (3%) than in R0 tumours (1%).

In univariable analysis (table 4), 5-year RFS was significantly lower in case of R1 resection [HR = 2.13; $p=0.04$]. RFS was also significantly lower with adjuvant therapy [HR=2.24; $p<0.001$], high risk score according to modified NIHC including new definition of TR [HR=3.94; $p=0.02$], and intraoperative complications [HR =2.82; $p<0.001$].

		HR	CI95%	p
Surgical Resection	R1 VS R0	2,13	[1,04;4,38]	0,04
Age		1,00	[0,99;1,02]	0,615
Sex	M VS F	0,75	[0,51;1,09]	0,13
Joensuu Score	Low risk VS Very low risk	0,53	[0,14;1,99]	0,35
	Intermediate risk VS Very low risk	1,00	[0,28;3,64]	0,9972
	High Risk VS Very low risk	3,94	[1,25;12,46]	0,02
Intraoperative complications	Yes VS No	2,82	[1,74;4,57]	<0,001
Rupture	Yes VS No	1,22	[0,69;2,13]	0,5
Adjuvant therapy	Yes VS No	2,24	[1,54;3,27]	<0,001

Table 4. Recurrence-free Survival from univariate analysis ; *Hazard Ratio estimated with 95% confidence intervals and P-value from the cox proportional Hazard models*

In multivariate analysis (Table 5), only intraoperative complications [HR=1.79; $p=0.02$] and NIHC

high risk score [HR=3.43; p=0.04] remained significant (Table 5). R1 resection remained nonsignificant in multivariable analysis.

		HR	CI 95%	p
Surgical resection	R1 vs R0	1,8	[0,87;3,73]	0,11
Age		1,01	[0,99;1,02]	0,32
Sex	M vs F	0,76	[0,52;1,13]	0,17
NIH modified classification	Low risk vs very low risk	0,52	[0,14;1,98]	0,34
	Intermediate risk vs very low risk	0,88	[0,24;3,28]	0,86
	High risk vs very low risk	3,43	[1,07;11,01]	0,04
Intraoperative complications	Yes vs No	1,79	[1,07;2,99]	0,02
Adjuvant therapy	Yes vs No	1,14	[0,77;1,72]	0,50

Table 5 : Recurrence-Free Survival from multivariate analysis ; *Hazard Ratio estimated with 95% confidence intervals and P-value from the cox proportional Hazard models*

DISCUSSION

In this large multicentre GIST series, 5-year RFS was significantly lower for R1 resection, high risk according to the modified NIH classification, administration of adjuvant therapy and intraoperative complications in univariate analysis. However, only intraoperative complications and NIH modified high risk remained significant in multivariate analysis.

In a population of 1098 patients who underwent resection for GIST in a curative attempt, 3% had a R1 resection, which is in the range of other studies (1.7%-27%) but lower than the pooled incidence of 12.4% reported in the recent meta-analysis by Liu et al. [12]. This low rate may be explained by the quality of the surgery inside the AFC working group and FREGAT network, and our selection criteria particularly our choice to keep low risk tumours in the analysis, unlike other studies [14]. Published series generally include a small number of patients from retrospective analyses, especially in R1 patient groups [24].

Furthermore, despite the importance of an accurate analysis of tumour resection to determine the significance of R1 as a prognostic factor, there is variability in how margins are reported. Previous studies analysed "complete gross resection", which includes R0 and R1 resection [2, 25], while others have recently focused on microscopically positive margins (R1) [14, 26, 27], as in our study. Surgery with margin-negative resection (R0) is the recommended primary treatment for non-metastatic GIST in all guidelines [4, 8, 9], but recommendations are inconsistent regarding what to do after R1 resection. R1 resection is not considered an indication for reoperation in NCCN guidelines [4] and ESMO guidelines [9] in their most recent update. Asian guidelines do not comment on reoperation after R1 resection [8] Adjuvant treatment is recommended in case of R1 resection in Asian guidelines, but ESMO guidelines since their last update suggest that adjuvant treatment is useless after R1 resection. Similarly, NCCN guidelines do not recommend adjuvant treatment. [4, 8, 9].

The effect of R0 resection (vs. R1) on the prognosis remains controversial because several investigators between 2001 and 2020 have found it to be a main prognostic factor of RFS or OS [2, 11, 24, 28, 29] while others did not report any significance in terms of RFS or OS [21, 25, 26, 27, 30, 31, 32].

Three recent meta-analyses suggested that R1 resection resulted in significantly shorter RFS/DFS than R0 resection for GISTs, with results potentially confounded by the definition of tumour rupture and the administration of adjuvant TKI [10, 11, 12].

TR has been shown to be strongly associated with disease recurrence: It was first introduced as a risk factor by Rutkowski et al. in 2007, then confirmed in the modified National Institutes of Health (NIH) consensus criteria in 2008, and added in the 2012 edition of the ESMO guidelines [2, 22, 5, 9]. Indeed, GIST are fragile tumours and tend to rupture spontaneously into the peritoneal cavity or during surgery, increasing the risk of intra-abdominal implant tumours[22]. In clinical practice,

without predefined criteria, tumour rupture was usually a vague expression based on intraoperative judgement. This has led to inconsistent definitions of tumour rupture in reported series, sometimes including R1 resections or tumour spillage without consideration of gastrointestinal perforation into the abdominal cavity [14, 15]. In 2016, the Oslo Sarcoma Group proposed a clear definition for coding tumour rupture based on a small bowel GIST population and applied it to gastric GIST in 2018 [15, 21]. Major deficiencies identifying patients at high risk of recurrence included: tumour fracture, tumour spillage, hemorrhagic ascites, bowel perforation at the tumour site, microscopic tumour infiltration into adjacent organs (T4b in TNM classification) even if resected in one block, piecemeal resection and surgical biopsy (Fig1) [15, 21]. A strength of our study is that we have incorporated the updated definition of the Oslo Sarcoma Group into the Joensuu classification to assess the true prognostic significance of R1.

RFS was significantly lower with intraoperative complications [HR = 1.79; p=0.02], mainly transfusions (84%). There is no literature on the impact of intraoperative complications on recurrence-free survival in GIST, mainly because these events are rare.

The potential limitations of the study are as follows. Tumour mutational status has been shown to be associated with prognosis and response to adjuvant imatinib [33]. Due to the retrospective nature of our study, we could not analyse the impact of tumour mutational status on RFS as it was known in only 312 (28.4%) of 1098 patients.

Neoadjuvant treatment is currently recommended for locally advanced GIST [4, 9] and could hypothetically improve the oncological outcome by preventing TR during surgery and also improving the R0 resection rate [34] As patients were enrolled between 2001 and 2013 before the imatinib era, only 55 patients (5%) received neoadjuvant treatment. However, both R0 and R1 groups were comparable on this criterion at baseline.

During follow-up, only 60 patients (4.2%) died, of which only 19 were due to GIST. The analyses

of overall survival and cancer-specific survival were therefore underpowered, as is often the case in studies of non-metastatic GIST due to the relatively good prognosis of such tumours.

Conclusion

Our study confirms that R1 resection does not influence RFS in a large multi-centre cohort using the updated definition of tumour rupture. Although R0 resection remains the gold standard for localised GIST, R1 resection may be considered a reasonable alternative to avoid major functional sequelae and should not lead to reoperation.

Ethical Approval for Research

Data concerning the patients medical records were included in an online database, approved by the local comity of informatics and liberty (CIL) reference N°920361.

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Risk category	Tumour Size (cm)	Mitotic index (per 50 HPF)	Primary Tumour Site
Very low risk	<2.0	≤ 5	Any
Low risk	2.1-5	≤ 5	Any
Intermediate risk	2.1-5	> 5	Gastric
	< 5	6-10	Any
	5.1-10	≤ 5	Gastric
High risk	Any	Any	Tumour rupture
	> 10	Any	Any
	Any	>10	Any
	> 5.0	> 5	Any
	2.1-5	>5	Non-gastric
	5.1-10	≤ 5	Non-gastric

Table 1 : NIH Modified Classification (Joensuu Criteria) of recurrence risk

Prognostic Impact of Positive Microscopic Margins (R1 Resection) in Patients with GIST (Gastrointestinal Stromal Tumours): Results of a multicenter European study

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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