Quality of surgery and outcome in localized gastrointestinal stromal tumors treated within an international intergroup randomized clinical trial of adjuvant imatinib

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Quality of Surgery and Outcome in Localized Gastrointestinal Stromal Tumors Treated Within an International Intergroup Randomized Clinical Trial of Adjuvant Imatinib

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IMPORTANCE The association between quality of surgery and overall survival in patients affected by localized gastrointestinal stromal tumors (GIST) is not completely understood.

OBJECTIVE To assess the risk of death with and without imatinib according to microscopic margins status (R0/R1) using data from a randomized study on adjuvant imatinib.

DESIGN, SETTING, AND PARTICIPANTS This is a post hoc observational study on patients included in the randomized, open-label, phase III trial, performed between December 2004 and October 2008. Median follow-up was 9.1 years (IQR, 8-10 years). The study was performed at 112 hospitals in 12 countries. Inclusion criteria were diagnosis of primary GIST, with intermediate or high risk of relapse; no evidence of residual disease after surgery; older than 18 years; and no prior malignancies or concurrent severe/uncontrolled medical conditions. Data were analyzed between July 17, 2017, and March 1, 2020.

INTERVENTIONS Patients were randomized after surgery to either receive imatinib (400 mg/d) for 2 years or no adjuvant treatment. Randomization was stratified by center, risk category (high vs intermediate), tumor site (gastric vs other), and quality of surgery (R0 vs R1). Tumor rupture was included in the R1 category but also analyzed separately.

MAIN OUTCOMES AND MEASURES Primary end point of this substudy was overall survival (OS), estimated using Kaplan-Meier method and compared between R0/R1 using Cox models adjusted for treatment and stratification factors.

RESULTS A total of 908 patients were included; 51.4% were men (465) and 48.6% were women (440), and the median age was 59 years (range, 18-89 years). One hundred sixty-two (17.8%) had an R1 resection, and 97 of 162 (59.9%) had tumor rupture. There was a significant difference in OS for patients undergoing an R1 vs R0 resection, overall (hazard ratio [HR], 2.05; 95% CI, 1.45-2.89) and by treatment arm (HR, 2.65; 95% CI, 1.37-3.75 with adjuvant imatinib and HR, 1.86; 95% CI, 1.16-2.99 without adjuvant imatinib). When tumor rupture was excluded, this difference in OS between R1 and R0 resections disappeared (HR, 1.05; 95% CI, 0.54-2.01).

CONCLUSIONS AND RELEVANCE The difference in OS by quality of surgery with or without imatinib was associated with the presence of tumor rupture. When the latter was excluded, the presence of R1 margins was not associated with worse OS.

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Invited Commentary

Supplemental content

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Gastrointestinal stromal tumors (GISTs) are rare malignancies of the GI tract, predominantly occurring in the stomach and small bowel. Surgery is the cornerstone of therapy for localized tumors. A macroscopic complete resection with negative margins (R0) is the recommended goal.[1,2] However, the ultimate significance of a positive microscopic margins resection (R1) for GIST is controversial: in several studies it was found to be a significant prognostic indicator of overall outcomes,[3-5] while others failed to find any effect on relapse-free survival (RFS) or overall survival (OS).[6-8] Actually, the outcome of patients with R1 resections remains unclear. Existing series are generally composed of retrospective institutional analyses from relatively small numbers of patients with wide-ranging tumor heterogeneity. The only evaluation of this question in a prospective series of patients, included in 2 consecutive studies on adjuvant imatinib,[9] did not show an effect of R1 resections on RFS, regardless of the use of adjuvant imatinib. Of note, those 2 studies included tumor rupture in the definition of R1 resection, which is known to entail per se a dismal prognosis.[10,11] This post hoc substudy is based on the data collected in the European Organization for Research and Treatment in Cancer (EORTC) 62024 trial, which is, to our knowledge, the largest prospective randomized trial on adjuvant imatinib in patients undergoing a resection of primary localized GIST.[12,13] The aim of this study was to assess the association of an R1 resection with OS and RFS with and without adjuvant imatinib therapy and separating tumor rupture from the R1 group.

Key Points

Question What is the association between quality of surgery and overall survival in patients affected by localized intermediate/high-risk gastrointestinal stromal tumors?

Findings In this cohort substudy using data from a randomized study on adjuvant imatinib, the microscopic margins status was not associated with a higher risk of recurrence or death regardless of the study arm.

Meaning In the subgroup of patients with no tumor rupture, microscopic margin status should not be considered per se an indication for adjuvant therapy.

Methods

This was an observational cohort substudy on patients from a randomized, open-label, multicenter phase III trial performed at 112 hospitals in 12 countries (Australia, Belgium, Denmark, France, Germany, Italy, New Zealand, Poland, Singapore, Spain, the Netherlands, and the United Kingdom).[12,13] Inclusion criteria of the randomized clinical trial included a histologically proven diagnosis of primary resected GIST, with positive immunostaining for tyrosine-protein kinase KIT (cluster of differentiation [CD] 117), with an intermediate or high risk of relapse on the surgical specimen according to the 2002 National Institutes of Health Consensus Diagnosis of GIST[14] as high risk (tumor size >10 cm; or mitotic rate >10/50 HPF; or tumor size >5 cm and mitotic rate >5/50 HPF) or intermediate risk (tumor size ≤5 cm and mitotic rate 6/50-10/50 HPF; or tumor size >5-10 cm and mitotic rate ≤5/50HPF). Surgery had to be performed from 2 weeks to 3 months before randomization, and surgical margins had to be either R0 or R1. Eligible patients were randomized (using minimization) after surgery to receive either imatinib (400 mg/d) for 2 years or no adjuvant treatment (the standard arm). Randomization was stratified by center, risk category (high vs intermediate), tumor site (gastric vs other), and quality of surgical margins (R0 vs R1). Neither patients nor investigators were masked to treatment allocation.

The trial procedures were already reported in detail.[12,13] The study was approved by the ethics committee of each participating institution. Written informed consent was obtained from all study participants. The primary end point of the main study was imatinib monotherapy failure-free survival (IFS),[12,13] determined from the date of randomization to the date of start of a new systemic treatment, a combination of imatinib with a new systemic treatment, or death from any cause, whichever occurred first. Secondary end points were relapse-free survival, overall survival, and incidence of adverse events. Results of the interim and final analysis have been reported elsewhere.[12,13]

Surgery was documented using surgical records and local pathology report. Furthermore, a surgical questionnaire on details of the operation (extent of resection, concordance of preoperative and intraoperative findings, complications, completeness of resection, and others) had to be completed. Surgeons from 5 countries, covering 8 languages, reviewed the full set of data that was available from 697 patients (76.7%).[15] In the protocol, tumor rupture occurring before or during intervention was included in the R1 category, but also analyzed separately. However, a clear definition of what to code as tumor rupture was lacking in the protocol. For the 697 operations reviewed centrally, tumor rupture was defined as any tumor spillage or fracture, laceration of the tumor capsule with or without macroscopic spillage, piecemeal resection, and incisional biopsy occurring either before or at the time of the operation. Patient, tumor, operative characteristics, factors associated with R1 resections, tumor rupture, and disease status were analyzed.

We did not follow the STROBE criteria because these apply to prospectively collected data in the context of an observational (nonrandomized) study. This is a retrospective analysis on an existing data set. Primary and secondary end points of this substudy were OS and RFS, respectively, in the different subgroups of R0 or R1 patients treated or not with adjuvant imatinib. These time-to-event end points were estimated using the Kaplan-Meier method[16] and compared between the R0/R1 using Cox models[17] adjusted for treatment and the study stratification factors (risk category and tumor site). The substudy was performed on the original data of the 908 randomized patients and repeated on the 697 patients for whom the complete set of data was available for central review. This analysis was assessed using a .05 significance level (2-sided test).

Table 1. Patient/Disease Characteristics by Quality of Surgical Margins According to Investigators' Assessment

Characteristic	No. (%) Quality of surgical margins: surgery R0 (n = 743)	R1 (n = 162)	Total (N = 905)
Age at randomization, y			
≤20	4 (0.5)	0	4 (0.4)
20-40	68 (9.2)	13 (8.0)	81 (9.0)
40-60	335 (45.1)	74 (45.7)	409 (45.2)
>60	336 (45.2)	75 (46.3)	411 (45.4)
Sex			
Male	375 (50.5)	90 (55.6)	465 (51.4)
Female	368 (49.5)	72 (44.4)	440 (48.6)
Perioperative tumor rupture			
No	NA	65 (40.1)	808 (89.3)
Yes	NA	97 (59.9)	97 (10.7)
Tumor site			
Small bowel	223 (30.0)	64 (39.5)	287 (31.7)
Gastric	444 (59.8)	58 (35.8)	502 (55.5)
Other	76 (10.2)	40 (24.7)	116 (12.8)
Risk category, new definition, local			
Low/intermediate risk	390 (52.5)	32 (19.8)	422 (46.6)
High risk	353 (47.5)	33 (20.4)	386 (42.7)
Tumor rupture			
Low/intermediate risk	0	28 (17.3)	28 (3.1)
High risk	0	69 (42.6)	69 (7.6)
Tumor size, cm			
<2	3 (0.4)	0	3 (0.3)
2-5	84 (11.3)	11 (6.8)	95 (10.5)
5-10	482 (64.9)	88 (54.3)	570 (63.0)
≥10	174 (23.4)	63 (38.9)	237 (26.2)

Abbreviation: NA, not applicable.

Table 2. Quality of Surgical Margins by Treatment Arm

Quality of surgical margins	No. (%) Treatment arm Observation	Imatinib adjuvant	Total
Surgery	454	454	908
R0	368 (81.1)	375 (82.6)	743 (81.8)
R1	85 (18.7)	77 (17.0)	162 (17.8)
R2	1 (0.2)	1 (0.2)	2 (0.2)
Unknown	0	1 (0.2)	1 (0.1)
Surgery review	354	343	697
R0	265 (75.1)	262 (76.4)	527 (75.7)
R1	83 (23.5)	80 (23.3)	163 (23.4)
R2	5 (1.4)	1 (0.3)	6 (0.9)

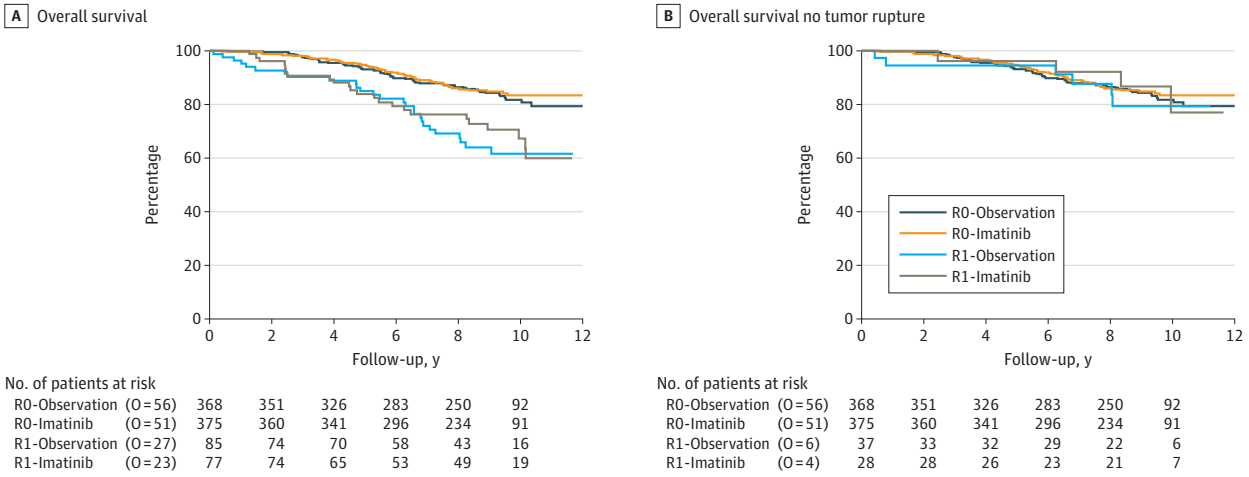
The randomized trial was registered with ClinicalTrials.gov identifier NCT00103168. This report is based on all data available on July 12, 2017.

Results

In total, 908 patients were randomized between December 8, 2004, and October 20, 2008. There were 454 in the adjuvant imatinib arm and 454 in the observation arm. Median follow-up was 9.1 years (IQR, 8-10 years). In all, 162 patients (17.8%) had an R1 resection, and 97 of these patients (59.9%) had a tumor rupture (**Tables 1** and **2**).

Five-year OS rates were 93.9% (95% CI, 91.8-95.4) for patients with R0 resection vs 84.4% (95% CI, 77.7-89.3) for patients with R1 resection; 10-year OS rates were 82.6% (95% CI, 79.2-85.5) and 64.4% (95% CI, 55.1-72.3), respectively. There was a significant difference in OS for patients undergoing an R1 vs R0 resection of GIST, both overall (HR, 2.05; 95% CI, 1.45-2.89; $P < .001$) and by treatment arm (HR, 2.65; 95% CI,

Figure 1. Overall Survival (OS) by Treatment and Quality of Surgical Margins, Overall (A) and Without Tumor Rupture (B)



No. of patients at risk

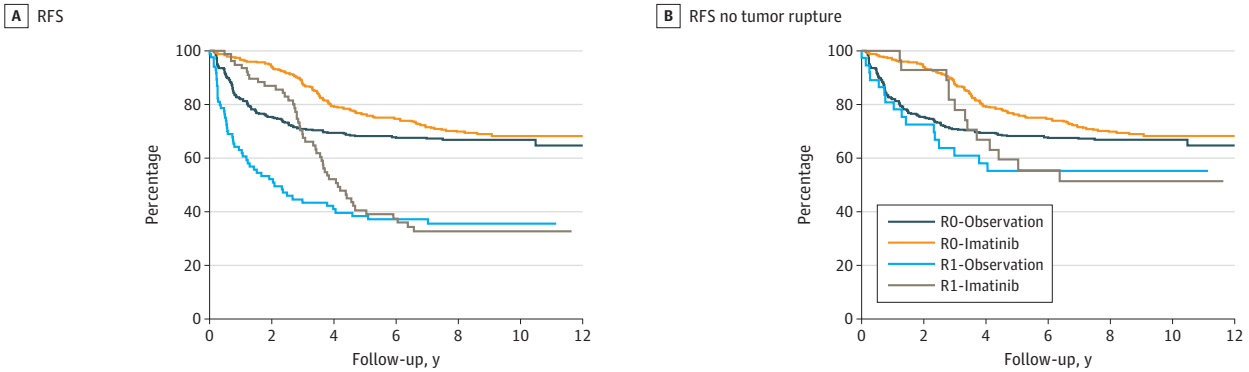
R0-Observation	(O=56)	368	351	326	283	250	92
R0-Imatinib	(O=51)	375	360	341	296	234	91
R1-Observation	(O=27)	85	74	70	58	43	16
R1-Imatinib	(O=23)	77	74	65	53	49	19

No. of patients at risk

R0-Observation	(O=56)	368	351	326	283	250	92
R0-Imatinib	(O=51)	375	360	341	296	234	91
R1-Observation	(O=6)	37	33	32	29	22	6
R1-Imatinib	(O=4)	28	28	26	23	21	7

O indicates observed events.

Figure 2. Relapse-Free Survival (RFS) by Treatment and Quality of Surgical Margins, Overall (A) and Without Tumor Rupture (B)



No. of patients at risk

R0-Observation	(O=118)	368	266	233	205	178	74
R0-Imatinib	(O=107)	375	343	278	231	171	59
R1-Observation	(O=53)	85	43	33	26	20	8
R1-Imatinib	(O=48)	77	66	37	24	19	6

No. of patients at risk

R0-Observation	(O=118)	368	266	233	205	178	74
R0-Imatinib	(O=107)	375	343	278	231	171	59
R1-Observation	(O=16)	37	26	20	17	13	5
R1-Imatinib	(O=13)	28	26	18	14	12	4

O indicates observed events.

1.37-3.75; with adjuvant imatinib and HR, 1.86; 95% CI, 1.16-2.99; without adjuvant imatinib; **Figure 1**A). However, when patients with tumor rupture were excluded, this difference in OS between R1 and R0 resections disappeared (HR, 1.05; 95% CI, 0.54-2.01; Figure 1B). Subgroup analyses of the effect of R1 vs R0 resection by tumor location are shown in eFigure 1 in the Supplement.

A significant difference in RFS was also observed for patients undergoing an R1 vs R0 resection of GIST, both overall (HR, 1.98; 95% CI, 1.55-2.53; $P < .001$) and by treatment arm (HR, 2.32; 95% CI, 1.64-3.30; with adjuvant imatinib and HR, 1.81; 95% CI, 1.29-2.54; without adjuvant imatinib; **Figure 2**A). When patients with tumor rupture were excluded, this difference in RFS between R1 and R0 resections disappeared (HR, 1.35; 95% CI, 0.91-1.99; Figure 2B).

Finally, we adjusted the RFS and OS analyses for tumor size, location, and risk in addition to treatment in the patient population without tumor rupture, and no difference was observed between R0 and R1 resections (eTables 1 and 2 in the Supplement).

Central Surgery Review Results (697 Patients)

According to the surgery review, 163 of 697 patients (23.4) had an R1 resection (Table 2); 103 of these patients (63.2%) had tumor rupture (eTable 3 in the Supplement). Five-year OS rates were 94.0% (95% CI, 91.5-95.8) for patients with R0 resection vs 86.7% (95% CI, 80.3-91.1) for patients with R1 resection; 10-year OS rates were 84.0% (95% CI, 80.0-87.3) and 64.3% (95% CI, 55.2-72.1), respectively. The OS of patients undergoing an R1 was significantly worse than that of patients with R0 resection of GIST, both overall (HR, 2.18; 95% CI, 1.50-3.16; $P < .001$) and by treatment arm (HR, 2.99; 95% CI, 1.74-5.14 with adjuvant imatinib and HR, 1.66; 95% CI, 0.99-2.77 without adjuvant imatinib; eFigure 2A in the Supplement).

Again, the risk of death in R1 patients was largely associated with the presence of tumor rupture. When patients with tumor rupture were excluded, this difference in OS between R1 and R0 resections disappeared (HR, 0.88; 95% CI, 0.42-1.84; eFigure 2B in the Supplement). Subgroup analyses of the effect of R1 vs R0 resection by tumor location are shown in eFigure 3 in the Supplement.

There was also a significant difference in RFS for patients undergoing an R1 vs R0 resection of GIST, both overall (HR, 2.19; 95% CI, 1.68-2.86; $P < .001$) and by treatment arm (HR, 267; 95% CI, 1.81-3.92; with adjuvant imatinib and HR, 1.97; 95% CI, 1.36-2.85; without adjuvant imatinib; eFigure 4 in the Supplement).

Discussion

In this post hoc analysis of 908 patients treated with resection of localized intermediate-risk or high-risk GIST, randomly assigned to receive 2 years of adjuvant imatinib or observation, tumor rupture was associated with a worse prognosis independently of the study arm, while status of surgical margins without tumor rupture was not.

Limitations

One major limitation of our study is that data on how many surgeons were involved and the median number of operations per surgeon are lacking. The study was performed at 112 sites, and surgery was not standardized in the protocol of the randomized clinical trial and could also have been performed at another center, provided the surgical report was available. Therefore, we cannot exclude the presence of institution-level and/or surgeon-level differences that might have influenced at least in part our results.

Strengths

Of note in the 697 patients available for central review, inconsistencies of surgical reporting were found in 18% of patients.[15] However, the analysis performed on the centrally reviewed subgroup did not differ from the one performed on the whole series, taking into account the local investigator assessment.

Indeed, a clear definition of which conditions should have been coded as tumor rupture was not emphasized in the protocol. In 2018, a detailed classification was proposed by the Oslo Sarcoma Group[18-21]: rupture was defined as tumor spillage or fracture, piecemeal resection, incisional biopsy, gastrointestinal perforation to the abdominal cavity, blood-tinged ascites, or microscopic transperitoneal infiltration into an adjacent structure. In contrast, minor defects of tumor integrity (such as those caused by core needle biopsy), peritoneal tumor penetration, iatrogenic superficial tumor capsule laceration, or microscopically positive margins were not considered tumor rupture, and the outcome of these patients was shown to be similar with those patients whose tumor was removed without any minor defects.[9,20]

In our study, we defined tumor rupture as the report in the medical record of any tumor spillage or fracture, piecemeal resection, and incisional biopsy, occurring either before or at the time of the operation. In contrast, blood-tinged ascites, gastrointestinal perforation to the abdominal cavity, or infiltration of adjacent structures were not included in the tumor rupture category, while iatrogenic superficial laceration of the tumor capsule without tumor spillage was.

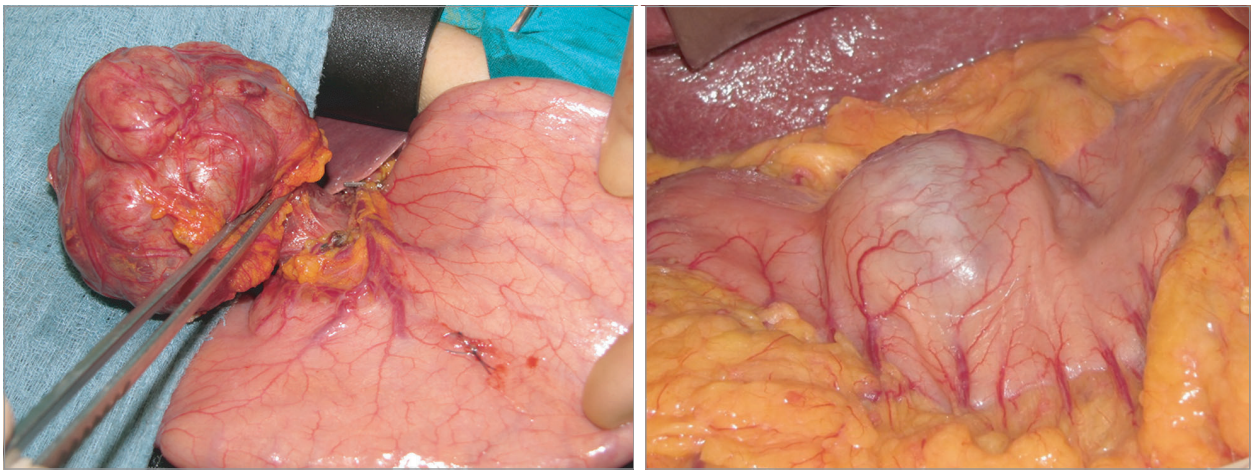
For the purpose of this analysis, we retained the original definition entered by the surgeon of the participating institutions and reviewed by the surgical subcommittee of the study. The worse prognosis associated with tumor rupture was confirmed.[12] While this difference may be predominantly associated with tumor biology, another possible explanation may have to do with the type of tumor ruptures. It is very unlikely to observe spillage/fracture or intra-abdominal bleeding in low- to intermediate-risk GIST. Most of the tumor ruptures observed in these patients may simply consist of iatrogenic superficial laceration of the tumor capsule with no spillage, something that is now shown to have a limited effect on prognosis.[20] This may have therapeutic implications because many guidelines recommend treatment of patients affected by localized ruptured GIST with postoperative imatinib until recurrence. Owing to the low risk of recurrence in case of minor defects with no spillage, some of these patients may be overtreated.

As far as the status of microscopic surgical margins is concerned, these findings are consistent with other reports, both in retrospective and prospective series in GIST.[6-9] However, opposite observations were reported in soft tissue sarcoma of extremities or trunk wall: positive microscopic surgical margins are associated with a higher risk of local recurrence and death, especially for tumors located at critical sites.[22] The same is true for breast cancer, melanoma, gastric cancer, pancreatic cancer, and rectal cancer.[23-27]

On the contrary, in retroperitoneal sarcoma, the status of microscopic surgical margins is of limited prognostic value because the large size of these tumors at presentation along with their critical location in proximity to major vessels, nerves, bone, and intra-abdominal viscera limit the possibility of achieving a true negative-margin resection in most patients.[28] In addition, assessment of a positive margin based on a tissue section placed on a pathology slide in these sizable tumors is subject to numerous processing variables, such as number of samples and location, tissue contraction after resection, and fixation.

In GIST, this study confirmed that status of microscopic surgical margins were not associated with RFS and OS. Beside what is said about retroperitoneal sarcomas that may also apply to GIST, these results are also consistent with how surgical margins are reported in these tumors. In fact, the organ of origin of the tumor is sampled, while the tumor surface toward the abdominal cavity is not examined. Given the peculiar pattern of growth of these tumors, most of the time, the margins at risk are rather the one toward the abdominal cavity and not the ones on the surface of the organ of origin, but the current classification does not account for them (**Figure 3**A). This may not apply to some GIST that are indeed confined to the GI wall (Figure 3B), where a positive margin may be associated to a higher local recurrence risk, but this is left to be proven and is also counterbalanced by the low biologic risk these tumors often, if not always, in fact have. However, one exception does exist: positive margins for GIST located to the

Figure 3. Margins at Risk in Gastrointestinal Stromal Tumors (GISTs)



rectum have shown to be associated to a significantly higher local recurrence risk and eventually death.[29] Given their rarity and limited number in our study, we could not confirm this in our analysis. Indeed, rectal GISTs occur predominantly if not always in the lower third of the rectum outside the abdominal cavity. Status of surgical margins are easier to assess and their affect outcome is logical at least.

Therefore, with all the limitations of an observational cohort study, we believe that this study adds to the evidence and is consistent with many other reports[7-9] and recommendations[1,2] that the presence of positive microscopic margins should not be factored in decision-making about adjuvant therapy. However, every attempt should be made to reduce this likelihood from occurring. A multimodal approach, which includes a more liberal use of preoperative imatinib, is generally recommended whenever a positive margin over the organ of origin can be anticipated on a preoperative assessment. This is particularly true of rectal GIST.

Conclusions

In conclusion, for the studies on localized GIST to come and the daily management of our patients, we recommend to distinguish tumor rupture from microscopic positive surgical margins, because their associations with outcome were shown to be clearly different. While the former significantly affect prognosis and should be factored into the therapeutic decision-making, the latter without tumor rupture seems not, but it should still be avoided whenever possible because long-term effects on outcome cannot be ruled out at least in a proportion of patients.

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Author Contributions: Dr Marréaud and Ms Litière at the independent EORTC Charitable Trust in Brussels had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Gronchi, Bonvalot, Rutkowski, Hohenberger, Judson, van Coevorden, Marreaud, Blay, Casali.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Gronchi, Zaffaroni, Litiere, Blay.
Critical revision of the manuscript for important intellectual content: Bonvalot, Poveda Velasco, Kotasek, Rutkowski, Hohenberger, Fumagalli, Judson, Italiano, Gelderblom, van Coevorden, Penel, Kopp, Duffaud, Goldstein, Martin Broto, Wardelmann, Marreaud, Smithers, Le Cesne, Zaffaroni, Litiere, Blay, Casali.
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Supervision: Gronchi, Fumagalli, Martin Broto, Marreaud, Le Cesne, Blay, Casali.

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