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Surgical treatment of primary gastrointestinal stromal tumors (GISTs): Management and prognostic role of R1 resections

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ABSTRACT

Background: Surgery represents the best treatment for primary gastrointestinal stromal tumors (GISTs). The aim of this study is to analyse outcomes of surgical management in order to evaluate the influence of microscopically R1 margins on survival and recurrence in patients affected by GISTs.
Methods: The study reviewed retrospective data from 74 patients surgically treated for primary GISTs without metastasis at diagnosis. Clinical and pathological findings, surgical procedures, information about follow up and outcomes were analyzed.
Results: Recurrence rate was low and no patients died in the R1 group during the follow up period. The difference in recurrence free survival for patients undergoing an R0 (n = 54) versus an R1 (n = 20) resections was not statistically significant (76% versus 85% at 3 years, logrank test p-value = 0,14; 63% versus 86% at 5 years, logrank test p-value = 0,48)
Conclusions: Microscopically positive margin has no influence on overall and relapse-free survival in GIST patients. Thus, when R0 surgery implies major functional sequelae, it may be decided to accept possible R1 margins, especially for low risk tumors.

Introduction

Gastrointestinal stromal tumors (GISTs) represent the most frequent mesenchymal neoplasms of the digestive tract.[1] They are poorly responsive to radiotherapy and conventional chemotherapy, therefore the commercial introduction of tyrosine kinase inhibitors (TKIs) has represented a turning point in the treatment of these neoplasms.[2] Imatinib mesylate is the gold standard for the treatment of metastatic disease, but it is also used both in neoadjuvant treatment for unresectable or "borderline" tumors and in an adjuvant form for high-risk postoperative recurrence tumors.[3,4] However, surgery remains the first choice of treatment for primary GIST and can be curative.[5–9]

In clinical practice, we tend to distinguish between metastatic and localized disease and, in cases of disease susceptible to radical surgery, the risk of recurrence is quantified. Over the years, several attempts have been made to classify the GISTs based on their clinical behavior and to identify the prognostic parameters capable of influencing the outcome of the disease.

Numerous factors have been studied, such as the presence of tumor necrosis, the degree of cellular atypia, the presence of ulceration, the state of the surgical margin, but the correct definition of the prognostic importance of these factors is made difficult by the small size of the cohort study and the retrospective nature of these studies. The main prognostic factors evaluated for GISTs have been collected by the Union for International Cancer Control tumor, node and metastasis classification of malignant tumors (UICC TNM 8th Ed.).[10]

The aim of this study is to define the prognostic value of the microscopic surgical margin, estimating relapse-free survival (RFS) and overall survival (OS) in patients undergoing surgical treatment for primary GISTs. Outcomes and clinical-pathological characteristics were analyzed and the results were compared with the most recent literature.

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Material methods

After approval by our institutional review board, we retrospectively collected and analyzed the data of 74 patients who had surgery with both R0 and R1 for primary GIST in the General and Oncological Surgery Department of the "Paolo Giaccone University Hospital" (University of Palermo) between 2003 and 2017. All patients gave a detailed informed consent. The only exclusion criterion was the presence of metastases at the time of diagnosis. So, the analysis was conducted only on patients with localized disease at diagnosis, including those who received adjuvant/neoadjuvant treatment with Imatinib mesylate.

The diagnosis of GIST was confirmed by the histopathological examination and the immunohistochemical expression of c-KIT (CD117) and/or CD34. Genetic analysis for the mutational status of c-KIT and PDGFRα genes was performed on 44 of the 74 patients. In all patients, macroscopically complete resection of the tumor was performed and surgical margins were assessed for the existence of microscopic residual tumor in the post-operative phase.

We analyzed clinical parameters of the patients such as gender, age and clinical presentation of the disease. Tumors were characterized by primary localization, size, mitotic index, histological subtype and mutational status.

According to the Armed Forces Institute of Pathology (AFIP) criteria (or Miettinen's criteria), the tumors were classified into risk categories, in order to define the risk of malignant behavior. Risk stratification was performed on the basis of the main prognostic factors: mitotic count, size and primary tumor site. Mitotic rate was defined as the count of mitosis per 50 high-power fields (<5/50 HPF,> 5/50 HPF); tumor size was estimated from the largest diameter of the neoplasm (<2 cm, from 2 to 5 cm, from 5 to 10 cm,> 10 cm); the localizations of primary tumors were stomach, duodenum, ileum and rectum.

A variety of instrumental investigations such as Ultrasound (US), Computed Tomography scan (CT), Magnetic Resonance (MR) and Positron Emission Tomography (PET) were used during preoperative diagnosis, staging and follow-up of the patients. Endoscopic biopsies and endoscopic ultrasound-guided biopsies were performed in some cases. Contrast-enhanced ultrasound (CEUS) assessed hepatic lesions following surgery time.

The main goal of surgical treatment was a complete resection with negative margins and intact pseudocapsule. Operations were performed with an open technique or with a minimally invasive surgical technique (laparoscopic and/or endoscopic approach). Surgical procedures were mainly chosen depending on the tumor size and site. Patients underwent elective or emergency surgeries. Some tumors were removed during surgical procedures for other pathologies.

Pathological examination of surgical margins classified resections as R0 (no residual tumor) and R1 (microscopic residual tumor or hemoperitoneum or tumor rupture). R2 surgeries (macroscopic residual tumor) were not included in the study. We analyzed possible surgical and pathological factors associated with R1 resection.

Imatinib mesylate was administered as adjuvant treatment for high-risk recurrence patients after surgery, as neoadjuvant treatment for unresectable or borderline tumors and as first-line treatment in cases of recurrent disease. Response to medical treatment with Imatinib mesylate was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) together with the Choi criteria,[11] considering changes in MR signal intensity, CT density and 18FDG-PET uptake.

A review of hospital records and a direct interview with patients or their relatives were performed to collect information related to the follow-up period. The association of clinical-pathological variables and R0/R1 surgeries with tumor recurrence was evaluated.

Statistical analysis included the Kaplan-Meier method to estimate RFS and OS of the R0 and R1 patients and the logrank test to evaluate differences between the survival curves.

Results

Clinical features

Our series included 38 women and 36 men with a mean age at diagnosis of 61,6 years (range: 33–81 years). The most common symptoms and clinical signs were abdominal pain, dyspeptic disorder, gastrointestinal bleeding and anemia. The neoplasia suddenly became symptomatic in 4 patients because of intestinal occlusion (n = 2) and hemoperitoneum (n = 2). Some patients (n = 18; 24,3%) were asymptomatic and their tumors were incidental findings during instrumental investigations (n = 10; 13,5%) or after surgery (n = 8; 10,8%) for other pathologies.

Tumor pathologic characteristics

In all patients, the disease was localized at the time of diagnosis. Primary tumor sites included 50 (67,6%) in the stomach, 22 (29,7%) in the small intestine (18 in the ileus, 4 in the duodenum) and 2 (2,7%) in the rectum.

Tumor size, mitotic counts and status of surgical margins were reported in all pathological reports. The median tumor size was 5.5 cm (range 1–15 cm). Mitotic count was <5/50 HPF in 72,9% of cases and >5/50 HPF in 27,1%. Margin status was classified as R0 in 54 (72,9%) tumors and R1 in 20 (27,1%). Histological subtypes were not available in all surgical specimens: 32 spindle cell tumors (66,8%), 8 epithelioid cells (16,7%), 8 mixed types (16,7%) for a total of 48 findings.

According to Miettinen's risk stratification, GISTs were classified as follows: 16 (21,6%) high risk, 14 (18,9%) intermediate risk, 16 (21.6%) low risk and 28 (37,8%) very low.

Mutational analysis was performed on a total of 44 tumors. There were 38 c-KIT mutations (34 of the exon 11 and 4 of the exon 9) and 2 PDGFRα mutation (exon 12); 4 patients were wild type (WT) for c-KIT and PDGFRα.

The patient demographics and tumor pathologic characteristics are summarized in Table 1.

Surgical treatment

A total of 90 surgeries were performed and were distributed as follows: 74 primary resection surgeries, 6 reoperations for complications, 2 re-excision surgeries after R1 resection, 4 resections of local recurrences, 4 liver metastasectomies.

The technical and procedural characteristics of primary resection surgeries are summarized in Table 2. In 8 cases, tumors were detected and removed during surgeries for other pathologies (gastric bypass, cholecystectomy, anti-reflux surgery). Most of the operations were elective (95%), only 4 were emergency surgeries because of intestinal obstruction (n = 2) and hemoperitoneum (n = 2). There was not operative death. Postoperative complications occurred in 7 patients: peritonitis due to anastomotic dehiscence (=2), supramesocolic abscess (=2), hemoperitoneum (=3). The median period of the post-operative recovery was 11 days approximately (range 3–36).

Surgical margins

The post-operative pathological examination classified surgical

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Table 1
Patient demographics and tumor pathologic characteristics.

	Number	%
Age		
- Mean age	61,6	
- Range	33–81 years	
Gender		
- Male	36	
- Female	38	
Tumor location		
- Stomach	50	67,6
- Duodenum	4	5,4
- Small Intestine	18	24,3
- Rectum	2	2,7
Tumor Size		
Mean size	5,52 cm	
>10 cm	15	20,3
>5–10 cm	18	24,3
2–5 cm	35	47,3
<2 cm	6	8,1
Mitotic rate		
<5/50 HPF	54	72,9
>5/50 HPF	20	27,1
Tumor margin at pathology		
- R0	54	72,9
- R1	20	27,1
Risk		
- High	16	21,6
- Intermediate	14	18,9
- Low	16	21,6
- Very low	28	37,8

margins as R0 in 54 (72,9%) patients and as R1 in 20 (27,1%). We analyzed the characteristics of R1 resections in order to identify factors associated with positive microscopic margins.

Positive microscopic margins occurred in 12 patients (60%) with a gastric localization of the GIST and in 8 patients (40%) with an ileal GISTs. Four tumors had a diameter <2 cm, 6 a diameter between 2 and 5 cm, 8 with a diameter between 5 and 10 cm, 2 a diameter> 10 cm. Mitotic counts turned out to be < 5/50 HPF in 14 (70%) and >5/50 HPF in 6 (30%) cases. The R1 group included 8 very low risk, 2 low risk, 6 moderate risk and 4 high risk tumors. Microscopically positive margins were obtained after minimally-invasive surgery in 14 cases (70%) and after open surgery in 6 cases (30%). Four R1 patients had received neoadjuvant therapy before the surgery. None of the above mentioned potential risk factors has been significantly associated with incomplete resection (Table 3).

Follow up and outcomes

Median follow-up time was 53 months (range 4–117). Disease relapsed in 14 (18,9%) of the all 74 patients at 6, 12, 14, 25, 29, 35 and 60 months after primary resections. Six relapses were local recurrences, 6 were liver metastases only, 2 was liver metastases with intraperitoneal dissemination. Relapses occurred after R0 resection in 12 (86%) cases and after R1 resection only in 2 (14%). Among patients with recurrences, 4 had low-risk and 10 high risk tumors. Adjuvant therapy was administered in 6 patients. Relapsing patients were treated as follows: 4 patients with local recurrence received surgical treatment plus Imatinib mesylate; 4 patients with liver metastases underwent metastasectomy plus Imatinib mesylate; the remaining 6 patients relapsing patients received only medical treatment with Imatinib mesylate. At the last update, 6 of the 14 relapsing patients died, 2 was alive with evidence of disease, and 6 had no evidence of disease. During long-term follow up of the entire sample, 8 (10,8%) patients died. None of them were in R1 group. The Kaplan-Meier curve of OS according to surgical margins (Fig. 1A) shows that none of the R1 patients (n = 20) died. In the R0 group (n = 54) the median survival time was 109 months: 8 patients died at 59, 59, 82 and 109 months after surgery, respectively. The difference in RFS for patients undergoing an R1 versus an R0 resections (Fig. 1A) was not statistically significant (logrank test p-value = 0.14). Recurrence rate was lower in R1 (10%) tumors than in R0 (22,2%) tumors. Five-years RFS (Fig. 1B) in R0 and R1 patients was 63% and 86%, respectively (logrank test p-value = 0.48). Three-years RFS was 76% in R0 patients and 85% in R1 patients (logrank test p-value = 0.14).

Table 2
Surgical procedures.

Tumour site	Surgical procedures	Surgical technique	
	n (%)	Mini-invasive	Open
Stomach			
Wedge resection	26 (52%)	22	4
Segmental resection	4 (8%)	4	–
Subtotal gastrectomy	2 (4%)	–	2
Subtotal/total gastrectomy with distal esophagectomy	4 (8%)	3	1
Enucleation	13 (26%)	12	1
Resection en bloc of stomach, spleen, body and tail of the pancreas	1 (2%)	–	1
Duodenum			
Subtotal resection of the duodenum	4 (18,2%)	–	4
Small intestine			
Ileal segmental resection	12 (54,5%)	10	2
Enucleation	5 (22,7%)	2	3
Small intestine/Stomach			
Subtotal gastrectomy and ileal segmental resection	1 (4,5%)	–	1
Rectum			
Anterior resection	2 (100%)	–	2
Total	74 procedures	53 (71,6%)	21 (28,4%)

Surgical Technique	n	%	*Median operative time*
Mini-invasive	**53**	**71,6%**	168 (60–330)
Laparoscopy	51	68,9%	
Endoscopy	2	2,7%	
Open	**21**	**28,4%**	150 (62–240)
Laparotomy	19	25,7%	
Conversion from laparoscopy to laparotomy	2	2,7%	

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Table 3
Factors associate with R1 resection.

	R0 n.	R1 n.	p value *
Tumor localization			0.156
Stomach	38 (70,4)	12 (60,0)	
Duodenum	4 (7,4)	–	
Small intestine	10 (18,5)	8 (40,0)	
Rectum	2 (3,7)	–	
Tumor Size			0.171
> 10 cm	12 (22,2)	2 (10,0)	
>5–10 cm	14 (25,9)	8 (40,0)	
2–5 cm	24 (44,4)	6 (30,0)	
< 2 cm	4 (7,4)	4 (20,0)	
Mitotic rate			0.956
< 5/50 HPF	40 (74,1)	14 (70,0)	
> 5/50 HPF	14 (25,9)	6 (30,0)	
Risk			0.313
High	12 (22,2)	4 (20,0)	
Intermediate	8 (14,8)	6 (30,0)	
Low	14 (25,9)	2 (10,0)	
Very low	20 (37,1)	8 (40,0)	
Surgical technique			0.956
Mini-invasive	39 (72,2)	14 (70,0)	
Open	15 (27,8)	6 (30,0)	

*p-value comes from Chi-squared test.

Discussion

Our demographic data and clinical features was similar to those reported in literature.[12,13] As expected, the most frequent primary tumor site was the stomach. Our histopathological findings fit with those described in other series and revealed a higher presence of spindle cell subtype, compared to epithelioid and mixed subtype.[14,15] Molecular analysis showed increased frequency of KIT mutations, according to previous studies.[15–18] The prognostic value of the main clinical-pathological factors, such as mitotic counts, site and tumor size, was confirmed.[5,8,15,19] Therefore, in our series 60% of relapses occurred after resection of tumors with mitotic index >5/50 HPF and 70% in tumors with diameter >5 cm. Gastric tumors appear to be more favorable than those located in the bowel[20,21]: relapses were more frequent for tumors located in the small intestine. The recurrence rate was significantly associated with risk categories: more than 70% of relapses occurred in patients classified as high risk.

The aim of the present study was to evaluate the prognostic role of microscopically positive surgical margin, analyzing factors associated with R1 surgery and its influence on the RFS and OS of patients with primary GISTs. Although complete resection is the main goal of the surgical treatment for primary GISTs, the influence of the microscopically positive margins on the prognosis remains controversial. Surgical margin status was added as prognostic factor in the 2012 edition of the ESMO guidelines, but removed in the following editions.[22,23] The revised Union for International Cancer Control tumour, node and metastasis classification of malignant tumors (UICC TNM 8th Ed.),[10] included surgical resection margins among the “additional” prognostic factors for GISTs. Incomplete gross resection (R2) is associated with a high recurrence rate and short survival in GIST patients, but little is known about the outcomes of R1 patients.[5,19,24] This is because the few studies that analyzed the margin status were characterized by a retrospective approach, a small number of patients and mixed results. Some authors have found a worse prognosis in patients undergoing incomplete (R1) resection[25–28] while others have not observed any influence on the RFS and/or the OS.[13,24,29,30] In a prospective randomized study conducted in 819 patients with primary GISTs, the difference in RFS in patients who had R0 vs. R1 surgery was not statistically significant.[31]

In our study, the rate of R1 resection was 27,1% (n = 20) and it is within the range of those reported in other retrospective studies from the published literature.[19,25,30–32] The median follow-up time was 54 months (range of 4–117 months).

The Kaplan-Meier curve of OS according to surgical margins shows that none of the R1 patients (n = 20) died. In the R0 group (n = 54) the median survival time was 109 months: 8 patients died at 59, 59, 82 and 109 months after surgery, respectively. The difference in RFS for patients undergoing an R1 versus an R0 resections was not statistically significant (logrank test p-value = 0.14). Recurrence rate was lower in R1 (10%) tumors than in R0 (22,2%) tumors. Five-years RFS in R0 and R1 patients was 63% and 86%, respectively (logrank test p-value = 0.48). Three-years RFS was 76% in R0 patients and 85% in R1 patients (logrank test p-value = 0.14).

Our results do not show a significant prognostic role of the positive microscopic margin, since it does not influence the OS or the RFS of patients treated for primary GISTs.

Several studies identified some factors associated with R1 resection, such as intraoperative tumor rupture, high risk group and large tumors size.[33] In our study, there were no cases of tumor rupture. Some surgical and pathological factors (tumor site, tumor size, mitotic rate, risk group, surgical technique) were analyzed, but none of them has been significantly associated with incomplete resection. Finally, in agreement with the results of other authors,[34,35] even in our experience, the oncologic outcomes of laparoscopic resection of GISTs, were comparable to that of open procedure. But laparoscopic procedure compared to open resection, has the advantage of minimal invasion and is superior in postoperative recovery offering a shorter hospital stay.

The management of patients with positive microscopic margin on final pathologic analysis is undefined and the NCCN guidelines do not show any evidence that they require re-excision. The most recent ESMO guidelines suggest re-excision when the original site of the lesion can be identified and morbidity or functional deficit can be avoided.[14] A recent meta-analysis demonstrated the efficacy of adjuvant treatment in reducing the risk of recurrence for R1 patients, suggesting its administration.[36] Various authors consider recurrence risk assessment to be an important parameter in the decision-making process for the management of positive microscopic margins.[13] The multidisciplinary team should consider benefits and risks of clinical-instrumental monitoring, adjuvant treatment or re-excision. Among our patients, only 2 experienced repeat surgeries after R1 resection in order to excise the residual tumor. The adjuvant treatment with imatinib was administered to 6 of our R1 patients (30%), belonging to high (n = 4) and intermediate (n = 2) risk groups. The clinical-instrumental monitoring was used for 12 (6 very low, 2 low, 4 intermediate risk categories) of the R1 patients and no one relapsed. Recurrence occurred in 2 high-risk patients (10%) of the R1 group, 35 months after primary GIST resection and 7 months after the interruption of adjuvant therapy.

Conclusions

Surgery represents the best treatment of patients with localized GIST. Complete resection with microscopic negative margins and intact pseudocapsule is the main objective of the surgery. However, when R0 resection implies major functional sequelae to be achieved, despite neoadjuvant treatment, it may be decided to perform a less aggressive surgery without obtaining negative surgical margins. The lack of evidence for a worse outcome in patients undergoing R1 resection leads to accept microscopically positive surgical margins, especially in low-risk lesions. Despite a limitation of this study is its retrospective nature, our results by minimizing the significance of microscopically positive margins as an oncologic risk

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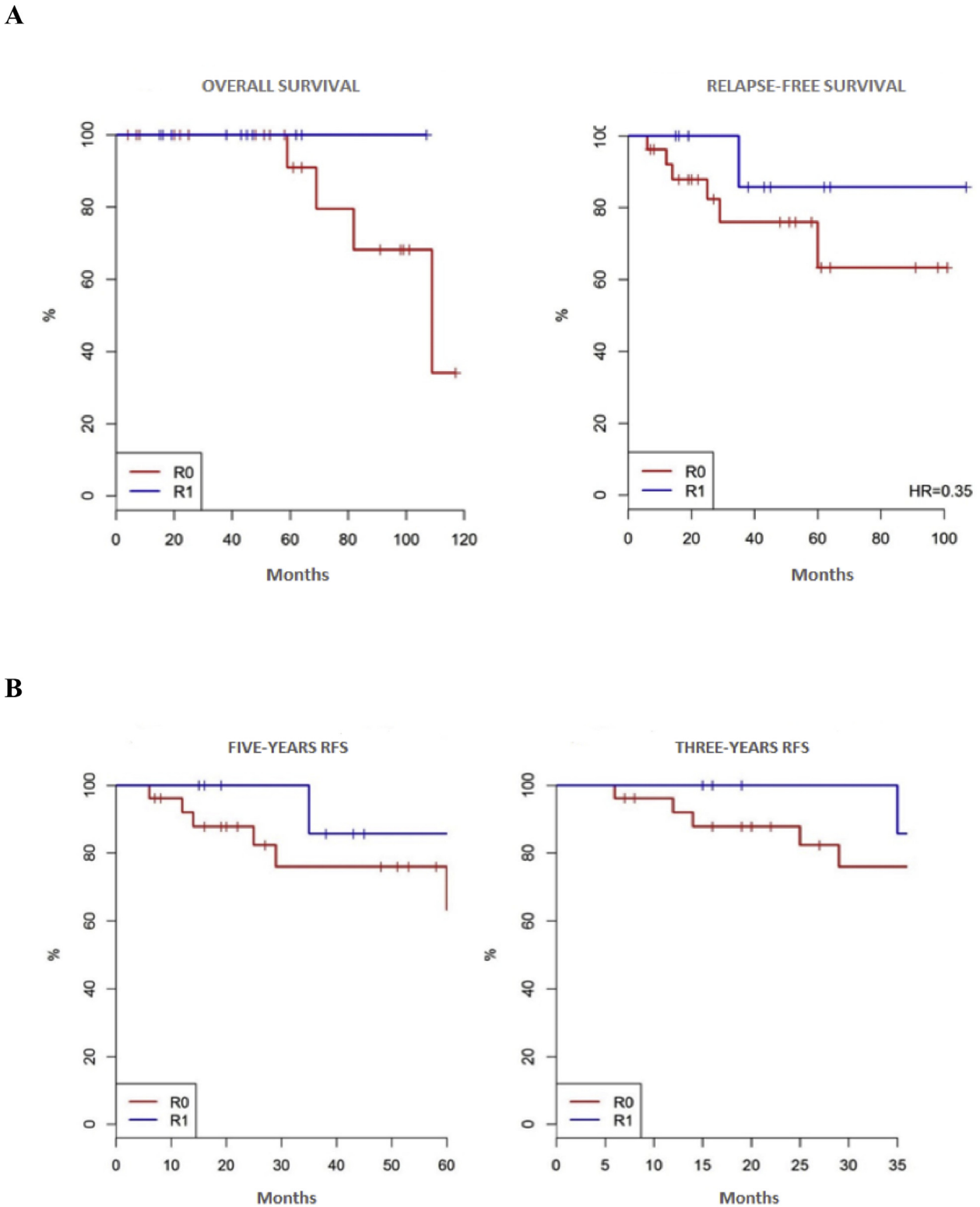

Fig. 1. A. Overall survival (left side) and relapse-free survival (right side) according to R0/R1 surgery. B. Five-years relapse-free survival (left side) and three-years relapse-free survival (right side) according to R0/R1 surgery.

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factor, encourage the use of a minimally invasive surgical approach in clinical practice, particularly in the treatment of low-risk GISTs.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

References

1. Miettinen M, Lasota J. Gastrointestinal stromal tumors. *Gastroenterol Clin N Am*. 2013;42:399–415.
2. Eisenberg BL, Judson I. Surgery and imatinib in the management of GIST: emerging approaches to adjuvant and neoadjuvant therapy. Educational Review. *Ann Surg Oncol*. 2004;11:465–475.
3. Miettinen Lasota J. Gatrointestinal stromal tumors (GISTs): definition, occurrence, pathology, differential diagnosis and molecular genetics. *Pol J Pathol*. 2003;54:3–24.
4. Miettinen M, Lasota J. Histopathology of gastrointestinal stromal tumors. *J Surg Oncol*. 2011;104:865–873.
5. Pierie JP, Choudry U, Muzikansky A, et al. The effect of surgery and grade on outcome of gastrointestinal stromal tumors. *Arch Surg*. 2001;136:383–389.
6. Roberts PJ, Eisenberg B. Clinical presentation of gastrointestinal stromal tumors and treatment of operable disease. *Eur J Cancer*. 2002;5:S37–S38, 38 Suppl.
7. Wu P, Langerman B, Ryan C, et al. Surgical treatment of gastrointestinal stromal tumors in the imatinib (STI-571) era. *Surgery*. 2003;134:656–665.
8. Bucher P, Egger JF, Gervaz P, et al. An audit of surgical management of gastrointestinal stromal tumors (GIST). *Eur J Surg Oncol*. 2006;32(3):310–314.
9. Cipolla C, Fulfaro F, Sandonato L, et al. Clinical presentation and treatment of gastrointestinal stromal tumors. *Tumori*. 2006;92:279–284.
10. Brierley JD, Gospodarowicz MK, Wittekind C, eds. *TNM Classification of Malignant Tumours*. eighth ed. Oxford: John Wiley & Sons, Inc.; 2016.
11. Choi H, Charnsangavej C. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinibmesylate: proposal of a new computed tomography response criteria. *J Clin Oncol*. 2007;25:1753–1759.
12. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. *Am J Surg Pathol*. 2005;29:52–68.
13. Demetri GD, von Mehren M, Antonescu CR, et al. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. *J Natl Compr Cancer Netw*. 2010;8(Suppl 2):S1–S41.
14. Casali PG, Abecassis N, Bauer S, et al. Gastrointestinal stromal tumours: ESMO–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(Supplement 4):iv68–iv78.
15. Fletcher CD, Berman JJ, Corless CC, et al. Diagnosis of gastro intestinal stromal tumours: a consensus approach. *Hum Pathol*. 2002;33:459–465.
16. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Arch Pathol Lab Med*. 2006;130:1466–1478.
17. Rubin BP, Singer S, Tsao C, et al. KIT activation is a ubiquitous feature of gastrointestinal stromal tumours. *Cancer Res*. 2001;61:8118–8121.
18. Joensuu H, Wardelmann E, Sihto H, et al. Effect of KIT and PDGFRA mutations on survival in patients with gastrointestinal stromal tumors treated with adjuvant imatinib: an exploratory analysis of a randomized clinical trial. *JAMA Oncol*. 2017;3:602–609.
19. DeMatteo RP, Lewis JJ, Leung D, et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg*. 2000;231:51–58.
20. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol*. 2006;23:70–83.
21. Miettinen M, Makhlouf H, Sobin LH, Lasota J. GISTs of the jejunum and ileum: a clinicopathologic, immunohistochemical and molecular genetic study of 906 cases before imatinib with long term follow up. *Am J Surg Pathol*. 2006;30:477–489.
22. ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012;23(Suppl 7):vii49–55.
23. ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2014;25(Suppl 3):iii21–i26.
24. Gouveia AM, Pimenta AP, Capelinha AF, et al. Surgical margin status and prognosis of gastrointestinal stromal tumor. *World J Surg*. 2008;32:2375–2382.
25. Langer C, Gunawan B, Schuler P, et al. Prognostic factors influencing surgical management and outcome of gastrointestinal stromal tumours. *Br J Surg*. 2003;90:332–339.
26. Unalp HR, Derici H, Kamer E, et al. Gastrointestinal stromal tumours: outcomes of surgical management and analysis of prognostic variables. *Can J Surg*. 2009;52:31–38.
27. Hinz S, Pauser U, Egberts JH, et al. Audit of a series of 40 gastrointestinal stromal tumour cases. *Eur J Surg Oncol*. 2006;32:1125–1129.
28. Ahmed I, Welch NT, Parsons SL. Gastrointestinal stromal tumours (GIST) – 17 years experience from mid trent region (United Kingdom). *Eur J Surg Oncol*. 2008;34:445–449.
29. Demetri GD, Baker LH, Benjamin RS, et al. Soft tissue sarcoma. *J Natl Compr Cancer Netw*. 2007;5:364–399.
30. Everett M, Gutman H. Surgical management of gastrointestinal stromal tumors: analysis of outcome with respect to surgical margins and technique. *J Surg Oncol*. 2008;98:588–593.
31. McCarter MD, Antonescu CR, Ballman KV, 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.
32. Hassan I, You YN, Shyyan R, et al. Surgically managed gastrointestinal stromal tumors: a comparative and prognostic analysis. *Ann Surg Oncol*. 2008;15:52–59.
33. Lin SC, Huang MJ, Zeng CY, et al. Clinical manifestations and prognostic factors in patients with gastrointestinal stromal tumors. *World J Gastroenterol*. 2003;9:2809–2812.
34. Biondi A, Grosso G, Mistretta A, et al. Laparoscopic vs. open approach for colorectal cancer: evolution over time of minimal invasive surgery. *BMC Surg*. 2013;13(Suppl 2):S12.
35. Biondi A, Grosso G, Mistretta A, et al. Predictors of conversion in laparoscopic-assisted colectomy for colorectal cancer and clinical outcomes. *Surg Laparosc Endosc Percutaneous Tech*. 2014;24(1):e21–e26.
36. Zhi X, Jiang B, Yu J, et al. Prognostic role of microscopically positive margins for primary gastrointestinal stromal tumors: a systematic review and meta-analysis. *Sci Rep*. 2016;6:21541.

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