The American Journal of Surgery 221 (2021) 549–553

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

Original Research Article

Positive microscopic surgical margins: Is there an association with survival in resected small gastrointestinal stromal tumors?

Dhruv J. Patel, BS [a, *], Sujay Kulshrestha, MD [b], Corinne Bunn, MD [b], Michael Littau, BA [a], Sonya Agnew, MD [b], Marshall S. Baker, MD, MBA [b, **]

[a] Loyola University Chicago Stritch School of Medicine, USA
[b] Department of Surgery, Loyola University Medical Center, USA

ARTICLE INFO

Article history:
Received 17 July 2020
Received in revised form
14 December 2020
Accepted 18 December 2020

Keywords:
GIST
R1 resection
Laparoscopic
Overall survival

ABSTRACT

Background: Few studies evaluate the relationships between surgical approach, histologic margin, and overall survival in gastrointestinal stromal tumor. We test the hypothesis that margin positive resection is associated with compromised overall survival.

Methods: We queried the National Cancer Data Base to identify patients undergoing resections for gastrointestinal stromal tumors ≤3 cm in size between 2010 and 2015. Multivariable logistic regression was used to identify factors associated with positive microscopic margins on final pathology. Cox proportional hazard methods were used to evaluate factors associated with overall survival.

Results: 2064 patients met inclusion criteria; 135 (6.5%) had a microscopically positive surgical margin. On multivariable regression, minimally invasive approach was not associated with risk of a positive margin (OR 1.06 95% CI [0.71, 1.59]). On Cox analysis, positive margin status was not associated with OS (R1: 1.03, CI [0.46–2.31], reference R0).

Conclusions: Positive microscopic surgical margins are not associated with compromised overall survival in patients undergoing resection of small gastrointestinal stromal tumors. Minimally invasive surgical approaches do not compromise oncologic outcomes in these cases.

Introduction

The National Comprehensive Cancer Network (NCCN) currently recommends resection to negative histologic margins (R0) as first-line treatment for patients with gastrointestinal stromal tumors (GIST). NCCN guidelines also advise that re-resection is "not generally indicated" for tumors initially resected to microscopically positive resection margins (R1). These guidelines are based on prior studies that have compared clinical outcomes for patients undergoing R0 and R1 resection for GIST. The majority of these have been under-powered single-institution series.[1] While these studies have consistently shown no association between resection margin and overall survival, they uniformly include very small numbers of patients with R1 resection.

Minimally invasive surgical approaches are being increasingly used in the surgical resection of small gastrointestinal stromal tumors. These approaches facilitate patient recovery but do not provide the same degree of tactile control as traditional open approaches do. This is especially true for small tumors that are difficult to see and "feel" laparoscopically. The use of these approaches may have a material impact on our ability to clear the surgical margin. Prior studies on the importance of resection margin in GIST primarily include patients who have undergone open surgical resection. Few control for tumor size, histologic grade, and the use of minimally invasive surgical approaches.

In the current study, the National Cancer Data Base (NCDB) was used to evaluate factors associated with R1 resection and overall survival among patients undergoing resection for small GIST (≤3CM). Our analysis is adjusted for surgical approach and tumor location. Our expectation was that patients undergoing minimally invasive approaches and those with tumors originating in locations other than the stomach would have a higher likelihood of having an R1 resection but that there would be no associated effect on overall survival.

* Corresponding author.
** Corresponding author.
E-mail addresses: dpatel27@luc.edu (D.J. Patel), marshall.baker@lumc.edu (M.S. Baker).

https://doi.org/10.1016/j.amjsurg.2020.12.038
0002-9610/

Table 1
Demographic and pathologic characteristics of patients receiving resection for GIST ≤3CM by margin status.

Characteristics	R0	R1	P
Number of Patients	1929	135	
Year of Diagnosis			0.781
2010	232 (12%)	20 (15%)	
2011	296 (15%)	16 (12%)	
2012	318 (17%)	20 (15%)	
2013	369 (19%)	26 (19%)	
2014	352 (18%)	28 (21%)	
2015	362 (19%)	25 (19%)	
Age			0.738
≤55	586 (30%)	47 (35%)	
56–65	557 (29%)	38 (28%)	
66–75	520 (27%)	33 (24%)	
≥76	266 (14%)	17 (13%)	
Race			0.973
White	1349 (70%)	91 (67%)	
Black	355 (18%)	27 (20%)	
Hispanic	108 (6%)	8 (6%)	
Asian	95 (5%)	7 (5%)	
Other	21 (1%)	2 (2%)	
Sex			0.405
Male	787 (41%)	60 (44%)	
Female	1142 (59%)	75 (56%)	
Charlson-Deyo Score			0.993
0	1387 (72%)	97 (72%)	
1	395 (21%)	28 (21%)	
2	109 (6%)	7 (5%)	
≥3	38 (2%)	3 (2%)	
Income			0.912
<$38,000	306 (16%)	21 (16%)	
$38,000-$47,999	424 (22%)	32 (24%)	
$48,000-$62,999	505 (26%)	32 (24%)	
≥$63,000	690 (36%)	50 (37%)	
Insurance			0.332
Uninsured	54 (3%)	8 (6%)	
Private Insurance	951 (49%)	68 (50%)	
Medicaid	87 (5%)	6 (4%)	
Medicare	800 (42%)	49 (36%)	
Other Government	16 (1%)	2 (2%)	
Unknown	21 (1%)	2 (2%)	
Facility			0.832
Community	135 (7%)	11 (9%)	
Comprehensive	666 (36%)	44 (34%)	
Academic	774 (42%)	57 (45%)	
Integrated Network	267 (15%)	16 (13%)	
Tumor Site			<0.001
Stomach	1449 (75%)	84 (62%)	
Small Intestine	360 (19%)	33 (24%)	
Colon	61 (3%)	2 (2%)	
Rectum	59 (3%)	16 (12%)	
Tumor Size (CM)			0.191
≤1	455 (24%)	29 (22%)	
1.1–2.0	544 (28%)	50 (37%)	
2.1–3.0	930 (48%)	56 (42%)	
Tumor Grade (mitoses per 50 HPF)			0.910
Low (≤5)	1669 (95%)	120 (95%)	
High (>5)	93 (5%)	7 (6%)	
Surgical Approach			0.434
Open	763 (40%)	58 (43%)	
MIS	1166 (60%)	77 (57%)	

Methods

Data source, sample selection, and variables examined

The National Cancer Data Base (NCDB) is a facility-based dataset that is a joint project of the American Cancer Society and the Commission on Cancer (CoC) of the American College of Surgeons (ACS).[2] The NCDB captures an estimated 70% of newly diagnosed cancers being treated in the United States annually at nearly 1500 accredited hospitals. The ACS and CoC have not reviewed and are not responsible for the findings and conclusions of our analysis.

Table 2
Multivariable logistic regression analysis of factors associated with R1 resection for GIST ≤3 cm.

Characteristics	OR (95% CI)	P
Age	1.00 (0.98–1.02)	0.909
Sex		
Male	1 (ref)	1 (ref)
Female	0.95 (0.65–1.40)	0.792
Income		
<$38,000	1 (ref)	1 (ref)
$38,000-$47,999	0.81 (0.43–1.53)	0.525
$48,000-$62,999	0.87 (0.48–1.58)	0.649
≥$63,000	1.03 (0.59–1.82)	0.909
Charlson-Deyo Score		
0	1 (ref)	1 (ref)
1	1.18 (0.74–1.88)	0.492
2	1.16 (0.51–2.63)	0.722
≥3	1.32 (0.39–4.54)	0.655
Facility		
Community	1 (ref)	1 (ref)
Comprehensive	0.77 (0.37–1.60)	0.480
Academic	0.85 (0.41–1.74)	0.651
Integrated Network	0.72 (0.31–1.65)	0.433
Insurance		
Uninsured	1 (ref)	1 (ref)
Private Insurance	0.34 (0.15–0.77)	0.010
Medicaid	0.28 (0.08–1.00)	0.050
Medicare	0.31 (0.13–0.74)	0.009
Other Government	0.73 (0.13–3.95)	0.712
Unknown	0.32 (0.04–2.81)	0.303
Tumor Site		
Stomach	1 (ref)	1 (ref)
Small Intestine	1.83 (1.15–2.92)	0.011
Colon	0.56 (0.13–2.39)	0.437
Rectum	5.26 (2.67–10.4)	<0.001
Tumor Size (CM)		
≤1	1 (ref)	1 (ref)
1.1–2.0	1.35 (0.79–2.28)	0.272
2.1–3.0	0.86 (0.50–1.45)	0.565
Tumor Grade (mitoses per 50 HPF)		
Low (≤5)	1 (ref)	1 (ref)
High (>5)	0.94 (0.39–2.26)	0.888
Surgical Approach		
Open	1 (ref)	1 (ref)
MIS	1.06 (0.71–1.59)	0.764

We queried the NCDB participant user files (PUF) for stomach, small intestine, colon, and rectum to identify individuals who received either a complete resection or a microscopic positive resection for GISTs ≤3CM between 2010 and 2015. We chose 3CM as our size criteria to allow for a reasonable population of patients with small, low-grade tumors that underwent an R1 resection. Eligible patients with GISTs were selected using the *International Classification of Diseases for Oncology* (third edition) site and histology codes (ICD-O-3 code 8936). Patients who received any treatment other than resection, those with metastatic disease, and those who had more than one type of malignancy were excluded from analysis. Additionally, patients who had a 30-day postoperative mortality were excluded from analysis.

Variables used in our multivariable regression and cox proportional hazard analyses were chosen a priori and included patient age, sex, race, income, insurance status, Charlson-Deyo comorbidity index, facility type, tumor site, surgical approach, and histologic grade. For surgical approach, laparoscopic, endoscopic and robotic procedures were both categorized as minimally invasive surgery (MIS). Converted cases were included in the MIS cohort in effort to perform an intention-to-treat analysis. The primary outcome was overall survival. The NCDB does not record any information regarding cancer-specific survival, cause of death, or

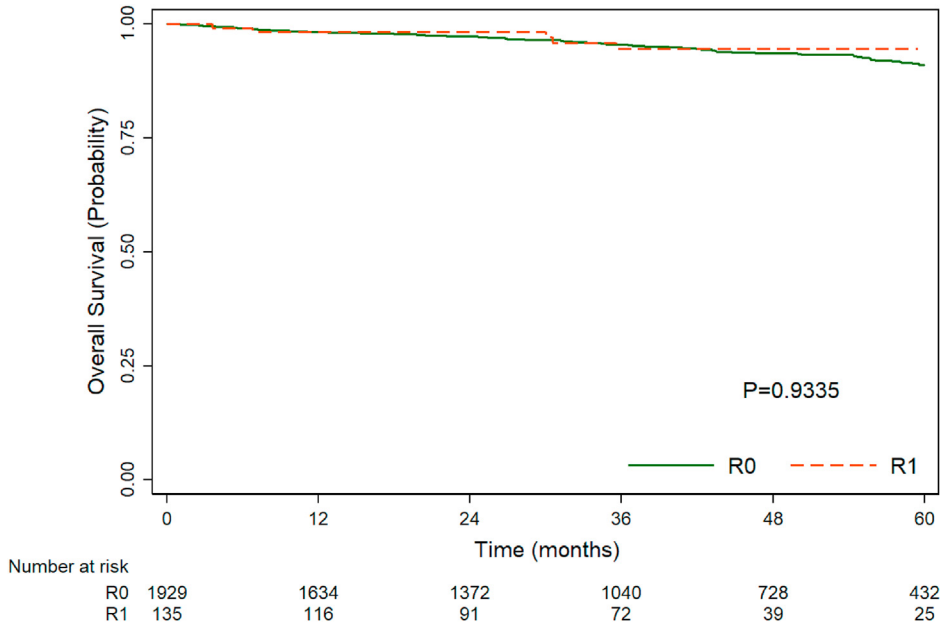

Fig. 1. Kaplan Meier overall survival by margin status for GIST ≤3CM
.

recurrence.

Statistical analysis

Baseline patient, hospital, and clinical characteristics for patients who underwent a margin negative resection and those who underwent a resection to a microscopically positive margin were evaluated using Pearson's chi-square tests. Multivariable logistic regression (MVR) was used to assess for association between studied variables and the likelihood of receiving a R1 resection. Kaplan-Meier methods were used to evaluate the association between each resection category and overall survival. Censored individuals were not included in calculation of survival estimates. Statistical significance on Kaplan-Meier analysis was assessed using log-rank testing. In order to control for the effects that age and comorbidities have on overall survival, we further compared overall survival patterns for patients within each resection category using Cox proportional hazard regressions. For the Cox analysis, variables that were statistically significant predictors of overall survival on univariate analyses and those variables considered potentially relevant determinants of survival were included in the multivariable model. The final model adjusted for the following independent variables: age, sex, income, Charlson index, insurance, facility type, surgical approach, margin status, tumor site, tumor size, and histologic grade. Variables including age, Charlson index, income, and insurance type are generally recognized as determinants of overall survival and were included a priori for that reason.

Analyses were performed using Stata/SE 15.1 statistical software (StataCorp LLC, TX). All tests were two-sided, and a P-value <0.05 was considered statistically significant.

Results

Univariate analysis of differences in patient outcome by margin status and surgical approach

2064 patients met inclusion criteria. 1533 (74%) of tumors originated in the stomach. The vast majority (>92%) of each cohort were well differentiated tumors. 135 (6.5%) of the total number of patients underwent an R1 resection. On univariate analysis, the only statistically significant difference between the patients undergoing R0 resection and those undergoing R1 resection was tumor location. Patients undergoing R1 resection were more likely to have tumors located in the small bowel (24% vs. 19%, $p < 0.001$) or rectum (12% vs. 3%) than those undergoing R0 resection (Table 1). The relatively high proportion of small bowel GIST in the R1 cohort appeared to be due to the fact that this subgroup included duodenal GIST. The proportion of patients with duodenal GIST that had an R1 resection was two-fold higher than it was for those undergoing resection of jejunal or ileal GIST (11.5% vs. 6.5%). This difference did not reach statistical significance ($p = 0.263$) most likely because the number of patients who received an R1 resection for a small bowel GIST was relatively small ($n = 33$). The bulk of the tumors in the study population as a whole were small gastric GISTs. The rate of R1 resection among gastric GIST was closer to the rate of R1 resection for jejunal/ileal GISTs (5.5% vs. 6.5%).

The proportion of patients undergoing an R0 resection who had an MIS approach was statistically identical to the proportion of patients undergoing an R1 resection who had an MIS approach. The surgical approach used did vary with tumor location but the overall rate of margin clearance did not vary by surgical approach. 1243 (60%) underwent an MIS approach to resection. 85 (7%) MIS procedures were converted to open. Patients with gastric GISTs were more likely to undergo an MIS approach than those with small bowel or rectal tumors (67.5% vs. 36.5%, $p < 0.001$). Patients with duodenal GISTs were more likely to undergo an open resection than those with jejunal or ileal GISTs (79.2% vs. 51.2%, $p < 0.001$). Patients undergoing an MIS approach did have a mean length of stay (days) that was shorter than those undergoing an open approach [(3.2 ± 4.6 and 5.8 ± 5.9, respectively), $p < 0.001$]. There was no statistically significant difference in 30-day readmission rates for patients undergoing an MIS or open approach [(2.8% vs. 4.2%, respectively), $p = 0.100$].

Table 3
Multivariable cox regression analysis of factors associated with 5-year overall survival for GIST ≤3 cm.

Characteristics	HR (95% CI)	P
Age	1.09 (1.06–1.11)	<0.001
Sex		
Male	1 (ref)	1 (ref)
Female	0.44 (0.30–0.66)	<0.001
Income		
<$38,000	1 (ref)	1 (ref)
$38,000-$47,999	0.92 (0.51–1.65)	0.779
$48,000-$62,999	0.69 (0.38–1.23)	0.209
≥$63,000	0.59 (0.33–1.06)	0.079
Charlson-Deyo Score		
0	1 (ref)	1 (ref)
1	0.98 (0.59–1.65)	0.951
2	2.55 (1.47–4.42)	0.001
≥3	2.29 (1.00–5.23)	0.049
Facility		
Community	1 (ref)	1 (ref)
Comprehensive	0.96 (0.44–2.08)	0.914
Academic	0.78 (0.36–1.72)	0.542
Integrated Network	1.04 (0.43–2.51)	0.926
Insurance		
Uninsured	1 (ref)	1 (ref)
Private Insurance	0.36 (0.12–1.06)	0.064
Medicaid	0.71 (0.17–3.03)	0.645
Medicare	0.44 (0.16–1.26)	0.128
Other Government	1.34 (0.23–7.66)	0.741
Unknown	1.60 (0.34–7.54)	0.552
Tumor Site		
Stomach	1 (ref)	1 (ref)
Small Intestine	1.31 (0.81–2.13)	0.274
Colon	0.56 (0.16–1.96)	0.364
Rectum	0.68 (0.20–2.32)	0.536
Tumor Size (CM)		
≤1	1 (ref)	1 (ref)
1.1–2.0	0.97 (0.54–1.74)	0.919
2.1–3.0	0.76 (0.43–1.33)	0.332
Tumor Grade (mitoses per 50 HPF)		
Low (≤5)	1 (ref)	1 (ref)
High (>5)	1.81 (0.90–3.65)	0.095
Surgical Approach		
Open	1 (ref)	1 (ref)
MIS	0.76 (0.50–1.15)	0.195
Margin Status		
R0	1 (ref)	1 (ref)
R1	1.03 (0.46–2.31)	0.945

Multivariable analysis for factors associated with positive resection margin

On MVR evaluating factors associated with surgical margin, the only factors associated with risk of a positive margin were insurance status and tumor location. Patients with private insurance and those with Medicare were considerably less likely to have a positive resection margin than those who were uninsured. Patients with tumors located in the small intestine (Odds Ratio 1.83, 95% CI [1.15, 2.92]) or rectum (OR 5.26, [2.67, 10.36]) were significantly more likely than those with gastric GISTs to undergo an R1 resection (Table 2). Use of the MIS approach was not associated with increased odds risk of an R1 resection relative to use of an open approach (OR 1.06, [0.71, 1.59]).

Survival analysis

The median follow-up time for all patients included in analysis of overall survival was 38.4 months. At that follow-up time, the survival rates between the R0 and R1 cohorts were 95.1% and 95.9%, respectively. On unadjusted Kaplan Meier analysis, there was no statistically significant difference in 5-year overall survival between patients who received a R0 resection and patients who received an R1 resection [(91% vs 95%, respectively), p = 0.9335] (Fig. 1). On multivariable Cox regression analysis adjusted for age, demographics, comorbidities, facility characteristics, surgical approach, tumor location, size, and histologic grade, the only variables independently associated with risk of death were age and presence of comorbid disease (Table 3). A positive histologic margin was not associated with an increased risk of death (HR: 1.03, 95% CI [0.46–2.31] nor was MIS compared to an open approach (0.76, [0.50–1.15]).

Discussion

In this study, we find that tumor location is a significant predictor of receiving an R1 resection for GIST ≤3CM while use of a minimally invasive approach to resection is not associated with an increased or decreased likelihood of residual microscopic disease after resection. Further, after adjusting for relevant covariates, R1 resection was not associated with overall survival. In addition to affirming the ability of MIS to achieve complete surgical resection of GISTs, these results suggest that R1 resection for small GISTs may not portend inferior survival compared to R0 resection. The role of resection in small GIST should be to eliminate the tumor but not compromise functional outcome by "chasing" a histologic margin.

Our findings are consistent with results from a previous post-hoc analysis of a randomized trial and a meta-analysis. Outcomes between R0 and R1 resection were compared among patient data from the American College of Surgeons Oncology Group (ACOSOG) clinical trials Z9000 and Z9001, both examining the efficacy of adjuvant imatinib for GIST.[3] In these trials, 745 patients underwent R0 (91%) and 72 patients R1 (9%) resections. Tumor location was found to be a significant predictor of R1 resection as patients with tumors in the rectum had an increased likelihood of being resected to microscopic positive histologic margins compared to tumors in the stomach (p = 0.004). There was no difference in recurrence free survival comparing R0 to R1 resection. Similarly, in a meta-analysis of twelve studies examining the prognostic role of R1 resection for GIST, eight studies tracked overall survival with four studies including patients who were treated with adjuvant imatinib (n = 253).[4] R1 resection (n = 67) was not associated with rates of overall survival. Both the post-hoc analysis and meta-analysis included patients with larger tumors (>3 cm) and included and adjusted for the use of adjuvant therapy. In the current study we examine a larger number of patients having undergone R1 resection for small GIST with no adjuvant therapy given. We identify no association between margin and survival.

Our results regarding the use of MIS for GIST are in agreement with a previous review of 5096 patients with GISTs from the NCDB.[5] 1895 (37%) patients received a laparoscopic resection while 3201 (63%) patients received an open resection for their tumors. There was no significant difference between the laparoscopic and open cohorts regarding the ability to obtain R0 margins at any tumor stage. After adjusting for covariates, the authors found the laparoscopic approach to not be a significant predictor of mortality (p = 0.06). Additionally, in a previous meta-analysis comparing outcomes between laparoscopic and open resection for GIST, 12 studies evaluated differences in length of stay between these two cohorts.[6] Patients who received a laparoscopic resection (n = 486) for GIST had a shorter length of stay (days) with a weighted mean difference of −3.42 [95% CI: (−4.37, −2.46)] relative to those undergoing open resection (n = 444).

There have been a few studies that have found evidence to suggest that R1 resection may carry an unfavorable prognosis for GIST. A single-institution analysis of 96 macroscopically resected GISTs between 1989 and 2006 at the University Hospital of S. Joao,

Porto, Portugal found a significant difference in the percentage of recurrence between R0 (n = 78/recurrence rate = 13%) and R1 (n = 18/recurrence rate = 28%) resections (p = 0.045).[1] On adjusted analysis, however, R1 resection was not a significant predictor of recurrence-free (p = 0.059) or disease specific survival (p = 0.57). In this paper, the authors acknowledged that their findings are limited by the small number of R1 resections in their study. Also, in a recent subset analysis of data collected from the European Organization for Research and Treatment of Cancer (EORTC) 62042 trial, the authors examined the outcomes of R0 (n = 743) and R1 (n = 162) resection among patients who were randomized to receive either adjuvant imatinib for two years or observation.[7] There was a statistically significant difference in ten-year overall survival between the R0 and R1 resection for both the imatinib-treated cohort (HR: 2.65, 95% CI [1.37–3.75]) and the observation cohort (HR: 1.86, 95% CI [1.16–2.99]). A similar significant difference between R0 and R1 resection was observed for RFS. After excluding patients in the R1 cohort who had tumor rupture, however, there was no significant difference in either overall survival or RFS between R0 and R1. Also, both the R0 (88%) and R1 (93%) groups consisted of primarily patients with tumors >5CM.

There are several limitations to our study. As a retrospective review, our study is limited by selection and omitted variable bias. The NCDB does not track several variables that may have relevance to our conclusion. These include tumor rupture, intraoperative and postoperative complication rates, and recurrence free survival. In addition, we are unable, because of limitations of the database, to differentiate between endoscopic and laparoscopic approaches to resection. We believe it is unlikely that tumor rupture would contribute to bias in this study given that we have focused on small tumors unlikely to carry significant risk of rupture. We do believe, however, that tumor recurrence may be a better measurement of outcome than overall survival for patients who receive resections for nonmetastatic small GIST which are primarily well differentiated. For our analysis on surgical approach, we were not able to evaluate the effect of MIS approach or different MIS approaches (endoscopic or laparoscopic) on intraoperative and postoperative complications. The NCDB does not record variables such as operative time, bleeding, or return to bowel function. Previous studies have demonstrated that MIS for GIST is associated with a significantly decreased operative time and intraoperative blood loss compared to the open approach along with a shortened return to bowel function and oral intake.[6]

Conclusion

We report the largest and most contemporary analysis of the effect of R1 resection on nonmetastatic GIST ≤3CM. Despite noted limitations, we find that MIS is not associated with risk of R1 resection or compromised overall survival and that R1 resection is not associated with a statistically significant reduction in overall survival. The decision to reoperate in effort to clear residual tumor should be made on a case by case basis but should certainly be used very sparingly to clear a histologic margin in small GIST.

References

1. Gouveia AM, Pimenta AP, Capelinha AF, de la Cruz D, Silva P, Lopes JM. Surgical margin status and prognosis of gastrointestinal stromal tumor. *World J Surg*. 2008;32(11):2375–2382. https://doi.org/10.1007/s00268-008-9704-8.
2. Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The national cancer data base: a powerful initiative to improve cancer care in the United States. *Ann Surg Oncol*. 2008;15(3):683–690. https://doi.org/10.1245/s10434-007-9747-3.
3. 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(1):53–60. https://doi.org/10.1016/j.jamcollsurg.2012.05.008.
4. 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. https://doi.org/10.1038/srep21541.
5. Inaba CS, Dosch A, Koh CY, et al. Laparoscopic versus open resection of gastrointestinal stromal tumors: survival outcomes from the NCDB. *Surg Endosc*. 2019;33(3):923–932. https://doi.org/10.1007/s00464-018-6393-8.
6. Xiong H, Wang J, Jia Y, et al. Laparoscopic surgery versus open resection in patients with gastrointestinal stromal tumors: an updated systematic review and meta-analysis. *Am J Surg*. 2017;214(3):538–546. S0002-9610(16)30932-1 [pii].
7. Gronchi A, Bonvalot S, Poveda Velasco A, et al. Quality of surgery and outcome in localized gastrointestinal stromal tumors treated within an international intergroup randomized clinical trial of adjuvant imatinib. *JAMA Surg*. 2020, e200397. https://doi.org/10.1001/jamasurg.2020.0397.