Review Article

The gist of surgical margins in GIST: a narrative review

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Abstract: The role of margin status as a prognostic factor in gastrointestinal stromal tumour (GIST) remains a matter of debate. It is clear that R2 resection is predictive of poor outcomes, but the impact of R1 versus R0 surgery on survival varies among studies. The occurrence of spontaneous or iatrogenic rupture may explain this heterogeneity in survival and recurrence rates in the literature. Even if residual disease and rupture do have an impact on the prognosis of GIST patients, their role needs to be better clarified, also in the perspective of introducing one or both of these parameters in a proper staging system. Again, the role of margin status should be deeply investigated in order to give clinicians a reliable safety when planning peri-operative strategy. Although GIST should be managed by a multidisciplinary team in a referral center and there is no doubt that R0 surgery without rupture of the tumour is the gold standard, in everyday clinical practice this result is not always reasonably achievable: in some cases surgery may leave a microscopic residual and manipulation of large tumours may result in spillage of neoplastic cells in the abdominal cavity. In this review article, the effect of margins itself and the existence of other possible factors influencing prognosis of GIST patients are explored.

Keywords: Gastrointestinal stromal tumour (GIST); microscopically positive margins; R1 resection; tumour rupture; prognostic factors

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Introduction

Gastrointestinal stromal tumours (GISTs) are rare mesenchymal malignancies, even though they represent the most frequent sarcomas of the gastrointestinal (GI) tract with an incidence of 1 case per 100,000 per year. They arise most commonly in the stomach but can affect any part of the GI tract from the oesophagus to the rectum (1,2). The vast majority of GISTs in adults have *KIT* gene mutations and about 20–25% of them have different molecular alterations such as PDGFRA mutations, RAS pathway mutations and SDH alterations; rarely none of them can be found.

Even though the advent of tyrosine-kinase inhibitors (TKIs) has revolutionised the treatment of advanced/metastatic tumours and TKIs may dramatically change

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the surgical strategy in several patients, surgical resection remains the cornerstone of the treatment for localised GIST (2).

A complete resection with no residual tumour is the main goal of cancer surgery. Patients with macroscopic residual cancer after operation [R2 resection according to American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) R classification] definitively have the poorest prognosis (3). Consequently, it would be also intuitive that patients with microscopically positive margins (R1) after resection of primary GIST would have worse prognosis than patients with negative ones (R0). However, giving the biological and clinical-pathological heterogeneity of GISTs, it may be difficult, in some cases, to relate prognosis to the mechanistic consequence—if any—of microscopic residual disease left behind after surgery or to the primary features of the tumour itself. Indeed, R1 resection rate in GISTs ranges from 3.5% to 33% and it tends to occur more frequently in high risk GIST with aggressive presentation status, as large lesions or metastatic neoplasms (4-6).

In this paper we aim to review the prognostic role of surgical margins in GISTs.

The following terms have been used for the initial research on PubMed: GIST, gastrointestinal stromal tumor, prognostic factors, surgical margin, microscopically positive margins, residual tumor, tumor rupture, recurrence. All relevant English-written papers, including both original articles and reviews, published up to October 2020 were reviewed. We present the following article in accordance with the Narrative Review reporting checklist (available at https://ls.amegroups.com/article/view/10.21037/ls-20-139/rc).

Margins and risk of recurrence: classifications and guidelines

Knowledge about GIST has greatly increased in the past 20 years. Considering all GISTs as potentially malignant tumours, it has been necessary to create appropriate risk stratification to predict recurrence. The historically accepted prognostic factors in primary GISTs after resection include size, mitotic count (7) and site of the lesion (8).

Other prognostic factors have been explored in latest years: peripheral blood inflammation markers such as neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR) (9), or genotypic features such as the expression of PDL1 (programmed cell death ligand 1) (10).

None of these factors, however, has been introduced in a commonly used staging system and they are not employed in everyday clinical practice.

In 2008, Joensuu presented a modification of NIH criteria, adding tumour rupture to the aforementioned prognostic factors (11). According to size, mitotic count, location and tumor rupture, patients affected by GIST are classified into four risk groups: high, intermediate, low and very low (11).

The tumour, node, metastasis (TNM) staging system developed by the UICC is similarly based on site, size and mitotic index, but it does not take into account tumor rupture (12).

Actually, margin status is considered as a component in none of the tumour staging systems.

Reports about the prognostic role of resection margins and the clinical value of R1 surgery are controversial and the therapeutic strategy after R1 resection remains uncertain. Also in latest GIST guidelines, indications for management appear vague: National Comprehensive Cancer Network (NCCN) guidelines report that re-resection is generally not indicated in R1 resection (13), while European Society for Medical Oncology (ESMO) guidelines invite to take into account the re-excision only if major morbidities are not expected and the site of the primary lesion can be found (2).

Many authors have reported about microscopic positive margins after GIST resection. The role of R1 on outcomes of patients resected for GIST is still debated, since also major series showed heterogeneous results. Indeed, various reports support margin status as a significant prognostic factor of overall outcomes while other authors did not find any association between the margin status and recurrence-free (RFS) or overall survival (OS) (4-6,14-16) (*Table 1*).

McCarter, analysing 819 patients in the ACOSOG Z9000 and ACOSOG Z9001 trials (6), did not find any statistically significant difference in RFS of patients undergoing an R1 *vs.* R0 resection of GIST, both in the imatinib and in the placebo group. When 3-year RFS was studied in R1 group, it has been observed that it was significantly worse in patients who experienced tumour rupture or intraperitoneal bleeding (60% *vs.* 80%, P=0.001); again, RFS in R1 and R0 patients was similar (79% *vs.* 80%, P=0.57) when all patients with tumour rupture were excluded from the analysis (6).

Results from a meta-analysis on the prognostic role of microscopically positive margins for surgically treated primary GIST comprising 12 studies (for a total number of 1,985 patients), revealed no statistically significant hazard ratio for the tendency of poor OS in R1 resection, both in

Table 1 Main characteristics of considered studies

Characteristics	McCarter, 2012, (6)	Åhlén, 2018, (14)	Cavnar, 2019, (5)	Hølmebakk, 2019, (15)	Gronchi, 2020, (17)
No. of patients	819	79	1000	410	905
R	R0 745, R1 72, R2 0, unknown 2	Wide 39, marginal 22, intralesional 18	R0 744, R1 118, R2 130, unknown 8	R0 363, R1 47	R0 743, R1 162
Rupture #	119 (14.8%)	*	§	52	97 [103]°
Recurrence	R0 26, R1 204	Wide 4, marginal 12, intralesional 15	–	70	–
5 year-OS	–	Wide 94.8%, marginal 77.3%, intralesional 77.7%	–	–	R0 93.9%, R1 84.4%
10 year-OS	–	–	–	–	R0 82.6%, R1 64.4%
3 year-DFS	R0 80%, R1 79%; R1 no rupture 80%, R1+ rupture 60%	–	–	–	–
5 year-DFS	–	Wide 100%, marginal 90.9%, intralesional 77.7%	–	R0 81.1%, R1 67%; rupture 35%, no rupture 88%	–

DFS, disease free survival; OS, overall survival; R, status of surgical margin; *, tumor rupture was included in the intralesional group, but the precise number was not reported; §, R2 margins include tumor rupture; °, the number in square brackets is the number of tumor rupture defined after surgery review.

patients receiving postoperative imatinib and in patients without adjuvant treatment; disease-free survival (DFS) in R1 patients was unfavourable compared to R0 patients but, notably, no significant difference between DFS in these subgroups of patients was observed when postoperative imatinib was administered (4).

Also, the results from the largest single-institution series recently published from Cavnar and colleagues, including 1,000 primary and/or metastatic GIST, showed no significant difference in OS between patients treated by R0 or R1 resection (5). Again, a recent retrospective multi-institutional study on 908 patients with localized GIST showed that 5-year RFS between R0 and R1 patients was significantly different both in the overall group and in patients underwent adjuvant treatment, but this difference was lost when patients with tumor rupture were excluded from the analysis (17).

A general framework to interpret the heterogeneity of the results can be explained invoking the practice of including in multivariate analysis the parameters that showed significant values on univariable analysis, also known as the "*Table 2 fallacy*" (18). Indeed, there is for sure multicollinearity of many variables: the risk classes are numerically defined by mitosis, size and site, and—if not all three—the latter two reasonably influence the radicality of the surgical procedure.

Secondarily, administration of TKI varies among studies, periods and indications and its effect cannot be exactly appreciated. Also a lack of uniformity in procedures on the surgical specimen and in compilation of pathology reports may contribute to this discrepancy, as well as the presence of other possible confounding factors such as serosal perforation (19) or KIT mutations (20) that have not been systematically considered yet. A wide-shared common language among classification systems should be encouraged and up-graded.

Margins and rupture in GISTs: definitions

Differently from epithelial tumours of the gastro-intestinal tract that originate from the mucosa and progressively infiltrate the wall, GISTs may grow within the layers of the viscera leaving intact the overlying mucosa and/or it may ulcerate the mucosa while preserving the serosa. The pseudo-capsule (i.e., compressed normal tissue surrounding the lesion and covered by one layer of serosa

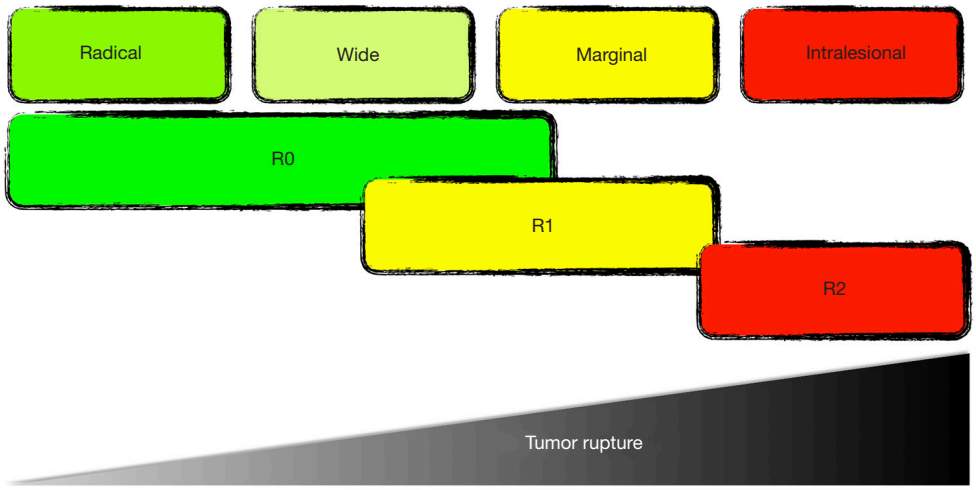

Figure 1 Comparison between Enneking's classification (radical, wide, marginal, intralesional) and UICC (Union for International Cancer Control) R classification (R0, R1, R2). Tumor rupture may occur in any type of resection (i.e., radical or wide resection with microscopically negative margins, but iatrogenic rupture during surgery).

in intraperitoneal organs) is an important component of GIST as it represents a sort of natural but very weak limit. Importantly, it could not be considered as a barrier since it may also contain neoplastic cells. A complete pathological analysis should evaluate the integrity of the pseudo-capsule and the status of lateral or circumferential margins (21). Although the UICC-R classification formally applies in the same way to epithelial and mesenchymal tumors, the meaningful margins to determine the quality of resection are actually different. Indeed, in GIST surgery the serous (from the peritoneal cavity) and lateral margins or proximal and distal resection margins of the stomach/intestine wall (21) are the most relevant, as well as the extent of the neoplasm through the wall of the involved organ; in epithelial cancers of the GI tract, instead, the assessment of the quality of resection is basically determined through the lateral margin due to the infiltrative growth pattern of carcinomas (22).

Moreover, the resection margins that should be considered vary on the basis of site of the neoplasm: for GIST in stomach, small intestine and colon, resection margins correspond to organ transection surface, and less frequently dissection surface; for extra-peritoneal GISTs in oesophagus, duodenum and rectum, it is necessary to consider both transection and dissection surface while for extra-gastrointestinal GISTs, resection margins are entirely comprised in dissection surface (20). These aspects sustain the differences between the surgery for GIST and other sarcomas and surgery for epithelial tumours. As mentioned above, the pseudo-capsule is regarded as part of sarcoma as it may contain tumoral cells, hence, an oncologically safe dissection plan should run through normal tissue beyond it. In this context, in 1980 Enneking proposed a classification to describe the degree of radicality in orthopaedic oncology and extensively employed in sarcoma surgery; it is based on the relationship of the surgical margin to the neoplasm and its pseudo-capsular-reactive zone (23). It identifies four types of resection: intralesional, marginal, wide and radical. The application of this classification to GIST surgery, however, may generate conflicts with the UICC R classification (24): a marginal resection may leave (R1) or not (R0) residual disease on margins; in the same way, an intralesional resection may be R1 or R2 (15) (*Figure 1*). Indeed, besides biological and anatomical factors, tumour rupture certainly represents an impactful event, and in 2008, it has been introduced in NIH criteria modified by Joensuu (11).

Rupture may occur spontaneously before surgery or iatrogenically, due to intraoperative manipulation, independently of the surgical approach (i.e., laparoscopy or open). Both spontaneous and iatrogenic rupture are associated with poor prognosis with a long-term relapse rate of approximately 80% (25).

However, although the negative prognostic role of

tumour rupture has been demonstrated in a population-based study (26), a widely employed definition of tumour rupture is lacking and this could explain the great difference in incidence of rupture among studies, ranging between 1% and 27% (25).

Just recently, a classification has been proposed. The Oslo Sarcoma Group defined six types of rupture grouped as major defects: tumour spillage and/or tumour fracture, piecemeal resection or intralesional dissection, GI perforation at the tumour site, blood-stained ascites, microscopic tumour infiltration into an adjacent organ and surgical incisional biopsy. Other conditions, grouped as minor defects of tumour integrity include mucosal defects or tumour perforation into the GI lumen or GI intraluminal bleeding, microscopic peritoneal penetration of tumour cells or iatrogenic peritoneal damage, transperitoneal core- or fine-needle biopsy without complications and R1 resection (25). In the Norwegian studies minor defects showed no difference in RFS compared to that of patients with tumour integrity, while they showed significantly better RFS compared to that of patients with major defects (27,28). Hølmebakk and colleagues analysed data from their prospectively maintained dataset at the referral sarcoma centre of South Norway involving 410 patients undergoing complete resection of primary, non-metastatic GIST and they found that, when analysing the whole cohort, rupture and margin status R0 *vs.* R1 were related to RFS at the univariate analysis (5-year RFS non-rupture *vs.* rupture 88.0% *vs.* 35%, HR 9.55, 95% CI, 5.95–15.33, P<0.001; 5-year RFS R0 *vs.* R1: 81.1% *vs.* 67%, HR 2.49, 95% CI, 1.44–4.31, P=0.001), but when the analysis was adjusted by tumour rupture, margin status lost its significance (patients without tumour rupture, 5-year RFS R0 *vs.* R1 87.6% *vs.* 93%; HR 0.71, 95% CI, 0.17–2.98, P=0.638; patients with tumour rupture, 5-year RFS R0 *vs.* R1 37% *vs.* 31%, HR 1.31, 95% CI, 0.68–2.54, P=0.420) (15).

At multivariable analysis tumour rupture was selected as the only factor independently associated with RFS (HR 10.22; 95% CI, 6.09–17.16; P<0.001) (15).

Basically, all of the above-mentioned data suggest that in most cases, the prognostic impact of R1 margins may actually derive from the presence of concomitant tumour rupture.

Residual disease and tumour rupture: clinical and therapeutic implications

A wide-shared definition of margins and rupture is not a mere theoretical issue but it is a pragmatic factor potentially affecting the daily clinical practice. Indeed, although tumour rupture is not always avoidable, the risk of spontaneous rupture may be lowered and iatrogenic lesions should be avoided.

Current guidelines invite to consider laparoscopy for small GISTs placed in favourable anatomic locations; the laparoscopic approach should instead be discouraged in patients with large tumours since they have a greater risk of intra-operative rupture (2,13,29). It is mandatory to handle with care the tumour during the operation; the pseudo-capsule should be preserved; the resected specimens should be removed from the peritoneal cavity in an extraction bag to prevent contamination of the abdomen with cancer cells or seeding of port sites, since this would mean a dramatic increase of the risk of recurrence.

Common oncological principles should be enhanced through a careful manipulation of the lesions: a "no-touch" technique has to be preferred. This term defines a series of manoeuvres such as grasping tissues surrounding the tumours instead of the neoplasm, holding the threads sutured at the normal serosa around the tumour, and using a laparoscopic stapler or bag during laparoscopic resection in order to minimise risk of rupture and tumour dissemination (30).

As it has been observed that rupture is related to tumour size, neoadjuvant therapy with TKI could be administered with the goal to devitalise the tumour; this could reduce its vulnerability and, consequently, the risk of rupture or bleeding during intraoperative manipulation (21). Despite the usefulness of the neoadjuvant therapy in selected patients, in the literature, rupture rate after neoadjuvant treatment is greatly variable, ranging from 0% to 21%. It is unknown the advantage of neoadjuvant therapy over prognostic consequences of rupture (25).

In case of intraoperative tumour rupture, intraperitoneal spillage of tumour cells and therefore occult peritoneal disease can be assumed to exist with a very high risk of intra-abdominal dissemination, peritoneal relapse and a subsequent negative impact on survival. Therefore, these patients should be considered for adjuvant imatinib therapy and also ESMO guidelines reconsider patients with tumour rupture as metastatic patients and propose a lifelong adjuvant therapy (2). Also, neoadjuvant TKI should be offered when R0 surgery is not feasible or it implies an extended demolitive surgery (2). The aim is to achieve cytoreduction and make it possible to perform a less mutilating surgery.

It is reasonable to evaluate an organ-sparing surgery for GIST in rare sites as rectum, duodenum or gastroesophageal junction as it is demonstrated that adjuvant therapy with imatinib can reduce the risk of recurrence in primary GIST after R1 surgery (21). Also Cavnar et al did not experienced any local recurrence in their subgroup of 30 patients with rectal GIST in the imatinib era—independently on the status of the surgical margins—while local relapse was observed in the pre-imatinib era in both R0 and R positive patients (31).

Intentional R1 treatments may also be considered in small GISTs categorised as low-risk tumours, which may be treated endoscopically and in which R1 resection does not negatively impact on the prognosis. Importantly, in this approach, GIST must be removed in one part and rupture must be avoided (25).

Regardless of the surgical approach, enucleation of the GISTs should be discouraged. It is considered as tumour rupture, because it may leave neoplastic cells behind owing to infiltration of tumor into or beyond the pseudocapsule (21). Whenever it is feasible, wedge resection should be considered, provided that margins are wide and the organ function is preserved. Otherwise, when GIST is adherent to other organs, an *en bloc* resection involving the contiguous organs should be performed (2,13,29).

Conclusions

Complete surgical excision is the standard of care for primary localised GISTs. The role of positive margins and tumour rupture as prognosticators has been studied in latest years, and we are going toward a deeper comprehension of their relationship and significance: indeed, it seems clear that prognosis is actually influenced by tumor rupture rather than by status of surgical margins.

Certainly, an improvement in the system of classification is desirable as a wide-shared standardised common language among sarcoma pathologists, surgeons and oncologists may give a stronger evidence-based support in clinical management of GIST patients.

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