Name of Journal: World Journal of Gastrointestinal Surgery

Manuscript NO 82497

Manuscript Type: Minireviews

Impact of tumour rupture risk on the oncological rationale for the surgical treatment choice of gastrointestinal stromal tumours

Answering Reviewers

The Author thanks the Peer Reviewers for their supportive contribution to this artiche.

The following changes have been made in the Abstract:

Reviewer #1:

a)Please explain the abbreviation GIST in the firt time reported in introduction.

The requested explanation has been added to Introduction :

Tumour rupture in gastrointestinal stromal tumours (GISTs) has not been consistently defined in published studies.

b) Insert a new paragraph in introduction section reporting the purpose of the manuscript.

The final paragraph in Introduction section. " This review highlights the prognostic value of tumour rupture in GISTs and emphasizes the need to carefully take into account and minimize the risk of tumour rupture when choosing surgical strategies for GISTs." has been modified: "This review analyses the concept of tumour rupture and its prognostic value in GISTs and highlights the impact of the risk of tumour rupture during surgical treatment for these tumours. Additionally, it emphasize the need to carefully take into account and minimize the risk of tumour rupture when choosing surgical strategies for GISTs."

c) In TNM classificasion section please add a short description of TNM in GISTs.

The following sentences have been added to "TNM Classification of GISTs":

"In the TNM Classification of GISTs T(tumour) staging is dependent on the size of the tumour (T1: ≤ 2 cm; T2: > 2 cm and ≤ 5 cm; T3 : > 5 and ≤ 10 cm; T4: >10 cm) and not on the depth of local invasion. TNM Staging is dependent on the site (gastric and omental GISTs have a better prognosis than small bowel GISTs or other less common intestinal GISTs), size (T), regional lymph node (N) status and mitotic rate (low mitotic rate: 5 or fewer per 50 high power fields; high mitotic rate: over 5 per 50 high power fields)."

d)Please add a sentence for other prognostic factors such as synchronous GISTs (PMID: 33447349.)

The following sentence has been added to Introduction section :

"However, in addition to tumour rupture, different factors may also impact GIST prognosis. Synchronous GISTs and another primary tumour can significantly increase in the possibility for recurrent disease, resulting in a worse prognosis and a more aggressive course than a single GIST [6]."

The reference suggested by the Reviewer #1 has been added (reference #6) and the reference list has been updated.

Reviewer #2:

1. (p.5, l.23) in the case of smaller tumors, the predictive value…: Please specify the size of smaller tumors.

The words in round brackets has been added to the sentence :

"(median tumour size of all patients in their study was 1.5 cm; range 0.3-5 cm)"

2. (p.5, l.28) comparable to surgical resection for smaller tumors…: Please specify the size of smaller tumors.

The sentence has been modified : "However, it might be comparable to surgical resection for selected smaller tumours(< 3 cm in size)."

3. (p.6, l.1) a high mitotic index…: Please specify the high mitotic index.

The definition of high mitotic rate has been added in "TNM Classification of GISTs" section:

"TNM Staging is dependent on the site (gastric and omental GISTs have a better prognosis than small bowel GISTs or other less common intestinal GISTs), size (T), regional lymph node (N) status and mitotic rate (low mitotic rate: 5 or fewer per 50 high power fields; high mitotic rate: over 5 per 50 high power fields)".

The revised manuscript has been submitted to a professional English language editing service.

A new language certificate has been provided along with the manuscript.

According to the suggestions of ***Company editor-in-chief*** Figure 1 has been added to the manuscript and the content of the manuscript has been improved as reported in the following revision file (track-changes version) :

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Impact of tumour rupture risk on the oncological rationale for the surgical treatment choice of gastrointestinal stromal tumours

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Supportive foundations: This study is not supported by funding sources.

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Abstract

Tumour rupture of gastrointestinal stromal tumours (GISTs) has been considered to be a remarkable risk factor because of its unfavourable impact on the oncological outcome. Although tumour rupture has not yet been included in the current TNM Classification of GISTs as a prognostic factor, it may change the natural history of a low-risk GIST to a high-risk GIST. Originally, tumour rupture was defined as the spillage or fracture of a tumour into a body cavity, but recently, new definitions have been proposed.These definitions distinguished from the prognostic point of view between the major defects of tumour integrity, which are considered tumour rupture, and the minor defects of tumour integrity, which are not considered tumour rupture. Moreover, it has been demonstrated that the risk of disease recurrence in R1 patients is largely modulated by the presence of tumour rupture. Therefore, after excluding tumour rupture, R1 may not be an unfavourable prognostic factor for GISTs. Additionally, after the standard adjuvant treatment of imatinib for GIST with rupture, a high recurrence rate persists. This review highlights the prognostic value of tumour rupture in GISTs and emphasizes the need to carefully take into account and minimize the risk of tumour rupture when choosing surgical strategies for GISTs.

Key words: Gastrointestinal stromal tumours; Tumour rupture; Residual tumour; Resection margin; Prognostic factors; Surgical treatment.

Core tip: Tumour rupture is a remarkable risk factor that can change the natural history of low-risk GISTs to a high-risk GIST. This review analyses the concept and prognostic value of tumour rupture in GISTs and highlights the impact of the risk of tumour rupture on the choice of surgical strategy.

INTRODUCTION

Tumour rupture in gastrointestinal stromal tumours (GISTs) has not been consistently defined in published studies. Although many studies have found an increased risk of recurrence and lower survival rates in patients with tumour rupture, other studies have not found any unfavourable prognostic effect. This is likely due to differences in tumour rupture definitions [1]. Tumour rupture has been considered to be a remarkable (often surgery-related) risk factor that can change the natural history of a low-risk GIST to a high-risk GIST, heavily impacting the long-term outcome [2-5]. However, in addition to tumour rupture, different factors may also impact GIST prognosis. Synchronous GISTs and another primary tumour can significantly increase in the possibility for recurrent disease, resulting in a worse prognosis and a more aggressive course than a single GIST [6].

This review analyses the concept of tumour rupture and its prognostic value in GISTs and highlights the impact of the risk of tumour rupture during surgical treatment for these tumours. Additionally, it emphasize the need to carefully take into account and minimize the risk of tumour rupture when choosing surgical strategies for GISTs.

THE CONCEPT OF TUMOUR RUPTURE IN GISTs

Originally, tumour rupture was defined as the spillage or fracture of a tumour into a body cavity, but recently, new definitions have been proposed. According to these new

definitions, the constant factor of all major defects of tumour integrity that qualify for tumour rupture (i.e., tumour fracture and/or tumour spillage in the abdominal cavity, blood-stained ascites, gastrointestinal perforation at the tumour site, microscopic transperitoneal adjacent organ infiltration, piecemeal resection or intralesional dissection, and incisional biopsy)[7,8] is substantial peritoneal exposure to tumour cells. This should be considered a remarkable risk factor because of potential peritoneal contamination. In contrast, minor defects of tumour integrity (such as those caused by core needle biopsy, microscopic peritoneal tumour penetration, iatrogenic superficial tumour capsule laceration or microscopically positive margins) are not considered tumour rupture [7-9].

THE IMPACT OF TUMOUR RUPTURE ON THE PROGNOSIS OF RESECTED GISTS

The impact of R1 resection on the oncological outcome of resectable gastrointestinal stromal tumours is debated. A systematic review and meta-analysis indicated that a microscopically positive margin could significantly impact disease-free survival but had no influence on overall survival. Moreover, adjuvant imatinib treatment could reduce the risk of recurrence for R1 resected primary GISTs [9].

Rutkowski et al. noted that GIST is a tumour growing under the mucosa and may be often ulcerated; consequently, the mucosal margin from the gastrointestinal lumen is not clinically meaningful. The authors indicated that the margins of clinical importance that are relevant to assess R status (i.e., R0, R1 or R2) are the peritoneal cavity side, which disruption entails tumour rupture, lateral margins or proximal and distal resection margins of the stomach/intestine wall, whose excision should be verified[11].

However, regarding the residual tumour classification of GISTs, it should be considered that not all tumour ruptures are classified as R1 or R2 resection. Nishida highlighted that peritoneum involvement is unrelated to R status; thus, a GIST disrupted in terms of peritoneal penetration otherwise resected with negative margins is still considered an R0 resection[8]

In their systematic review and meta-analysis, Kong et al. analysed the impact of R1 resection on the survival outcome of resectable GISTs with and without tumour rupture. They found that when tumour rupture cases were included, R1 resection resulted in a

significantly shorter recurrence-free survival or disease-free survival than R0 resection, but the differences in recurrence-free survival and disease-free survival between R0 and R1 resection vanished when tumour rupture cases were excluded [12]. The results of most recent studies suggest that R1 resection does not influence the oncological outcome of resectable GIST compared with R0 resection; consequently, reresection may not be necessary when a positive microscopic margin exists. Moreover, R1 resection would not be considered an indication for adjuvant imatinib treatment in the absence of other high-risk factors as well as tumour rupture [12-17]. However, tumour rupture is significantly associated with the occurrence of R1 resection [12]. Mc Carter and colleagues noted that the significant risk factors associated with a positive microscopic resection margin are tumour size ≥ 10 cm, location and intraperitoneal rupture, and found that the risk of disease recurrence in R1 patients was driven largely by the presence of tumour rupture [18].

TNM CLASSIFICATION OF GISTs

In the TNM Classification of GISTs T(tumour) staging is dependent on the size of the tumour (T1: ≤ 2 cm; T2: > 2 cm and ≤ 5 cm; T3 : > 5 and ≤ 10 cm; T4: >10 cm) and not on the depth of local invasion. TNM Staging is dependent on the site (gastric and omental GISTs have a better prognosis than small bowel GISTs or other less common intestinal GISTs), size (T), regional lymph node (N) status and mitotic rate (low mitotic rate: 5 or fewer per 50 high power fields; high mitotic rate: over 5 per 50 high power fields).

In contrast to the TNM classification of gastrointestinal carcinomas, in the TNM classification of GISTs, i) involvement of the peritoneum is not prognostically graded as an unfavourable T (tumour) factor, i.e., T4a; and ii) after excluding tumour rupture, R1 may not be an unfavourable prognostic factor for GISTs. Moreover, tumour rupture, which may be the true unfavourable prognostic factor instead of R1, has not yet been included in the current TNM Classification of GISTs [19]. From a prognostic point of view macroscopic injuries to the pseudocapsule (which are considered tumour rupture) should be distinguished from microscopic breaks of the pseudocapsule on pathological

examination (that are not considered to be tumour rupture) [20]. However, the choice of surgical strategy should consider the unfavourable impact of an eventual tumour rupture on prognosis on prognosis and the risk of tumour rupture when performing a dissection on the tumour surface (pseudocapsule)., i.e., without clearance distance [21].

OPTIONS IN THE SURGICAL TREATMENT OF GISTs

Everett and colleagues emphasised that tumour enucleation is considered insufficient because it may leave behind a tumour-seeded pseudocapsule. Moreover, enucleation is associated with tumour rupture [22] and should not be performed even if it is useful to preserve a vital structure. Interruption of the pseudocapsule or incidental peritumoral disruption can change a curable disease to a poor prognostic tumour. Accurate handling is very important to avoid tumour rupture because GISTs are soft and fragile. This can be a problem in laparoscopic and endoscopic treatment of GIST because of the instrumental manipulation of the tumours. Small low-grade GISTs are often treated by endoscopic resection. However, Song and colleagues argued that in the case of smaller tumours (median tumour size of all patients in their study was 1.5 cm; range 0.3-5 cm), the predictive value of tumour rupture and mitotic index diminished, and the risk of peritoneal metastasis may not be increased, even in tumours ruptured during endoscopic resection [23]. Due to the risks of tumour rupture, tumour remnants, perforation and bleeding, endoscopic resection is not currently recommended as a routine treatment for GISTs of the upper or lower gastrointestinal tract. However, it might be comparable to surgical resection for selected smaller tumours(< 3 cm in size). Surgical resection is still considered the standard treatment for tumours ≥ 2 cm or if the tumour has a high mitotic index or mucosal ulceration [24]. However, a high mitotic index is mostly unknown before resection.

According to the most recent guidelines, the standard treatment for localized GISTs is complete surgical excision of the lesion, with no dissection of clinically negative lymph nodes. The goal is R0 excision, i.e., an excision whose margins are clear of tumour cells at least at the site of origin in the GI tract. In low-risk GISTs located in unfavourable locations,

R1 margins can be acceptable, given the lack of evidence that R1 surgery is associated with a worse overall survival.

A laparoscopic/robotic approach is clearly discouraged in patients who have large tumours because of the risk of tumour rupture, which is associated with a very high risk of relapse. For selected patients with small tumours in the upper or lower GI tract, endoscopic excision is an acceptable treatment strategy [25]. Three years of adjuvant imatinib is the standard treatment for resected ruptured GISTs, although the recurrence rate is prominently high [26], and five years of adjuvant imatinib treatment in patients with ruptured GISTs seems to be promising [27,28].

CONCLUSIONS

In the choice of a surgical strategy for GISTs, key points should be considered.

First, R1 resection cannot be a standard treatment for GISTs, and second, the risk of tumour rupture should be carefully evaluated and avoided. According to these key points, i) enucleation cannot be considered a standard treatment for GISTs localized in favourable resection sites; ii) laparoscopic/robotic excisions cannot be the standard treatments for large GISTs, and iii) endoscopic treatment cannot be considered a routine procedure for smaller GISTs(Fig.1) .

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Conflict of interest statement: No conflict of interest exists.

Figure Legends

Figure 1: Surgical strategies for gastrointestinal stromal tumours (GISTs) according to key points.