Laparoscopic treatment of large gastrointestinal stromal tumors (> 5 cm)

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Abstract

Introduction: *Although laparoscopic techniques are currently a recognized type of treatment of small stromal tumors (GISTs) of the stomach, their application in the case of larger tumors has been the subject of debate.*
Aim: *To evaluate the technical feasibility, safety and early results of the laparoscopic treatment of large GISTs with a diameter of more than 5 cm.*
Material and methods: *A retrospective analysis was performed using data on patients who underwent laparoscopic surgery for gastric GIST in the period from 2009 to 2016. The patients selected for the study were divided into two groups based on the diameter of the tumor: patients who developed a tumor with a diameter smaller than or equal to 5 cm (group 1), and those whose tumors exceeded 5 cm in diameter (group 2). The following factors were established and compared for the two groups: duration of surgery, amount of intra-operative blood loss, length of hospital stay, and the number and nature of post-operative complications.*
Results: *No deaths occurred in the 30-day post-operative period, and no statistically significant differences regarding complications in the post-operative period were observed. In group 2, statistically significantly more pronounced blood loss and longer hospital length of stay were observed. No difference in the duration of surgery between the investigated groups was observed.*
Conclusions: *It appears that the surgical treatment of GISTs with a diameter of more than 5 cm by means of minimally invasive procedures is a viable and safe alternative.*

Key words: *gastrointestinal stromal tumors, laparoscopy, gastric wedge resection.*

Introduction

Gastrointestinal stromal tumors (GIST) are the most common type of mesenchymal neoplasms [1]. Their predominant primary location is the digestive system. It is estimated that between 40% and 70% of GISTs occur in the stomach [2]. The main treatment of localized, initially resectable tumors is surgery aimed to completely remove the affected tissue with a margin of the healthy surrounding tissue, as determined by macroscopic observation. The removal of regional lymphatic tissue seems to be unnecessary, since GISTs rarely metastasize to lymph nodes [3]. Given this fact, it appears that minimally invasive procedures can play a significant role in the treatment of this type of neoplasm. Laparoscopic surgery was first used to treat a small GIST of the stomach in 1992 [4]. The application of this method gradually became more widespread, but was still limited to the removal of small tumors with presumably very low potential for malignancy. As minimally invasive procedures developed and more knowledge and ex-

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perience was gained, laparoscopy became a viable option for the treatment of tumors with a higher potential for malignancy. Although laparoscopic techniques are currently a recognized type of treatment of small stromal tumors of the stomach, their application in the case of larger tumors has been the subject of debate [5, 6].

Aim

The objective of the present study was to evaluate the technical feasibility, safety and early results of the laparoscopic treatment of large GISTs with a diameter of more than 5 cm.

Material and methods

A retrospective analysis was performed using data on patients who underwent laparoscopic surgery for gastric GIST at the 2nd Department of General Surgery at the Jagiellonian University in Krakow in the period from 2009 to 2016. The group selected for the analysis included patients with an initially resectable tumor for whom the histopathological examination of the surgical specimen confirmed the occurrence of a gastrointestinal stromal tumor. The patients who were excluded from the analysis were those who had undergone neoadjuvant treatment with tyrosine kinase inhibitors, patients diagnosed with distant metastases, patients with an additional malignant neoplasm, and patients who had undergone laparotomy.

The medical records of patients were analyzed in terms of their eligibility for surgery, peri-operative care, and the clinical and pathomorphological features of the removed tumors. The malignancy potential of GISTs was established based on the ESMO 2012 guidelines. The diameter of the tumor was defined as its largest dimension observed in the course of the histopathological examination. The amount of blood loss and the duration of the surgery were determined based on the information included in the medical records by the surgeons and anesthesiologists involved in the procedure. The American Society of Anesthesiologists (ASA) scale was used to determine surgery-related risk, while the Clavien-Dindo classification was used to evaluate post-operative complications.

All patients in the analyzed group had undergone laparoscopic treatment involving a wedge resection or local excision of a stomach tumor. In the peri-operative period, an enhanced recovery after surgery (ERAS) protocol was followed.

The patients selected for the study were divided into two groups based on the diameter of the tumor: patients who developed a tumor with a diameter smaller than or equal to 5 cm (group 1), and those whose tumors exceeded 5 cm in diameter (group 2).

The following factors were established and compared between the two groups: duration of the surgery, amount of intra-operative blood loss, length of hospital stay, and the number and nature of post-operative complications.

The study was approved by an Ethics Committee.

Statistical analaysis

All analyzed data were processed using the StatSoft Statistica v. 13 software. The results are presented as the mean. The χ^2, Shapiro-Wilk, and Mann-Whitney tests as well as Student's *t*-test were applied for the calculations as required. The results were considered statistically significant when the *p*-value was lower than 0.05.

Results

In the analyzed period, 46 patients (33 women and 13 men) received laparoscopic treatment for stomach GISTs at the 2nd Department of General Surgery at the Jagiellonian University in Krakow. Mean age was 64.39 years. A demographic analysis of the investigated group of patients is shown in Table I.

Histopathological examinations confirmed that radical resection (R0 margins) had been performed for all patients in the analyzed group. Conversion to classic open surgery was not necessary for any of the patients, and none of them experienced an intra-operative tumor rupture. In group 2, i.e. the group of patients with large GISTs, statistically significantly more pronounced blood loss (68.1 vs. 25.2 ml) and longer hospital length of stay (4.9 vs. 3.2 days) were observed. Nevertheless, none of the patients had to receive packed red blood cells in the peri-operative period. No differences in the duration of the surgery between the investigated groups were observed. Relevant results are shown in Table II.

No deaths occurred in the 30-day post-operative period, and no statistically significant differences regarding complications in the post-operative period were observed. However, it should be noted that two of the patients in group 2 required reoperation

Table I. Demographic data for the investigated group of patients

Parameter	Group 1	Group 2	*P*-value
Number of patients, *n* (%)	34 (73.9)	12 (26.1)	–
Females, *n* (%)	28 (82.4)	5 (41.7)	0.0092
Males, *n* (%)	6 (17.6)	7 (58.3)	
Age, mean ± SD [years]	63.1 ±13.6	68.3 ±14.1	0.2344
BMI, mean ± SD [kg/m^2]	29.1 ±6.5	28.5 ±4.8	0.8849
ASA 1, *n* (%)	–	1 (8.3)	0.1806
ASA 2, *n* (%)	26 (76.5)	7 (58.3)	
ASA 3, *n* (%)	8 (23.5)	4 (33.3)	
Location, *n* (%):			0.9174
Cardia	4 (11.8)	2 (16.7)	
Lesser curvature	8 (23.5)	2 (16.7)	
Greater curvature	18 (52.9)	7 (58.3)	
Antrum	4 (11.8)	1 (8.3)	
Histological subtypes, *n* (%):			0.6038
Spindle cell	21 (61.8)	9 (75.0)	
Epithelioid	7 (20.7)	1 (8.3)	
Mixed	6 (17.6)	2 (16.7)	
ESMO risk classification, *n* (%):			0.0019
Very low	11 (32.4)	–	
Low	18 (52.9)	5 (41.7)	
Moderate	5 (14.7)	5 (41.7)	
High	–	2 (16.7)	

Table II. Early results of laparoscopic treatment

Parameter	Group 1	Group 2	*P*-value
Operative time, mean ± SD [min]	96.7 ±39.0	108.6 ±34.9	0.1845
Intraoperative blood loss, mean ± SD [ml]	25.2 ±20.8	68.1 ±40.2	0.0029
Length of hospital stay, mean ± SD [days]	3.2 ±1.1	4.9 ±2.7	0.0266
Patients without complications, *n* (%)	31 (91.2)	9 (75)	0.1757
Patients with complications, *n* (%)	3 (8.8)	3 (25)	
Clavien-Dindo 1, *n* (%)	2 (5.8)	1 (8.3)	0.0965
Clavien-Dindo 2, *n* (%)	1 (3)	–	
Clavien-Dindo 3, *n* (%)	–	2 (16.7)	
GISTs confirmed before operation	8 (23.5)	5 (41.7)	0.2408

– one due to bleeding from the short gastric vessels in the postoperative period, the other due to symptoms of a severe obstruction of the gastrointestinal tract associated with the stapling of the stomach at the location at which the tumor had been excised. The remaining complications did not require surgical intervention (grade I and II in the Clavien-Dindo classification).

Two patients from group 1 (GIST ≤ 5 cm) were rehospitalized. One of them was admitted due to suspected bleeding from the upper gastrointestinal tract, which was eventually ruled out. In the case of the second patient, a small fluid collection in the vicinity of the stomach was observed in the post-operative period. Conservative management proved to be sufficient. In the group of patients with GISTs larger than 5 cm, no rehospitalization was necessary.

Discussion

The resection of a tumor with a margin (1–2 cm) of healthy surrounding tissue is a widely recognized method of treating initially resectable, localized gastrointestinal stromal tumors [3, 7, 8]. Due to the fact that the metastasis of GISTs to lymph nodes is very rarely observed (in fewer than 3% of all cases), the removal of the regional lymphatic tissue seems to be unnecessary. Although classic open surgery methods have been used for this purpose in the past, the development of minimally invasive surgical procedures has made laparoscopy an attractive alternative for the treatment of this type of neoplasm.

The advantages of laparoscopic techniques over classic surgery are well known and unquestionable. Laparoscopy reduces pain in the post-operative period, and allows the patient to be mobilized sooner after surgery, thereby shortening the length of hospital stay. It is also associated with better cosmetic effects compared to conventional surgery [9, 10]. These advantages and the fact that its application does not require extensive lymphangiectomy have given minimally invasive procedures a special place in the treatment of GISTs.

As per the guidelines formulated by the European Society for Medical Oncology (ESMO), laparoscopic treatment is indicated in the case of small tumors. The treatment of large tumors with minimally invasive procedures is not recommended due to the risk of intra-operative rupture [11], which is considered a very significant prognostic factor for the recurrence of the condition. At the same time, the tumor diameter that should mark the upper threshold for safe laparoscopic surgery has not been clearly defined. It is suggested that this value is around 4–5 cm. In the group we analyzed not a single intra-operative rupture was observed, despite the fact that the largest tumor that was removed had a diameter of 9.5 cm. Other authors have likewise not reported intra-operative tumor rupture, provided the appropriate surgical technique was applied and the tissues were dissected in a sufficiently gentle manner [12].

The largest tumor diameter which can be considered treatable by means of minimally invasive techniques seems to evolve as the experience of particular institutions grows and new reports are published. Numerous sources suggest that tumor diameter need not necessarily determine the technical feasibility of a surgical procedure [13–15]. Many authors have presented results which demonstrate that the laparoscopic treatment of GISTs larger than 5 cm is feasible, safe, and is not associated with increased risk of complications [12, 16–18]. It is suggested that the treatment of larger tumors may entail a longer duration of surgery, more pronounced blood loss, and a longer hospital length of stay.

In our study we did not observe a statistically significant difference in the duration of surgery between the two investigated groups of patients, even though the mean duration was longer for group 2 (GIST > 5 cm). In their report, Milone *et al.* also emphasized that the surgical removal of larger GISTs was not associated with statistically significantly longer duration [12]. On the other hand, Khoo *et al.* found that the laparoscopic treatment of GISTs larger than 5 cm entailed a significantly longer duration [16]. It seems that tumor size may indirectly affect the difficulty of the procedure and, subsequently, its duration. However, as indicated by the presented data, this dependence is not evident. This may be due to the fact that the difficulty and duration of a surgical intervention is not determined solely by tumor size, but also by its location. A tumor located in the vicinity of the greater curvature of the stomach is undoubtedly easier to remove and does not require extensive surgical site dissection.

Numerous studies demonstrate that laparoscopy involves reduced blood loss and a shorter length of hospital stay compared with classic open surgery [17, 19]. At the same time, it can be expected that the treatment of larger tumors can lead to increased

intra-operative blood loss and requires a longer stay at the hospital. Such observations were indeed made for patients from group 2 (GIST > 5 cm) of our study; however, it should be emphasized that the observed blood loss was insignificant in all cases and the administration of packed red blood cells was not necessary. These findings are in good agreement with those reported in the available literature [20].

Milone *et al.* found no statistically significant difference in the rate of complications between patients receiving laparoscopic treatment due to large (> 5 cm) and small (< 5 cm) GISTs [12]. These data are consistent with those presented by other authors [19, 20], who also suggest that the most common complications are pulmonary in nature (infections, emboli). In our study we did not find a statistically significant difference in the rate of complications. The complications observed for patients with GISTs with a diameter of 5 cm or less were exclusively grade I and II in the Clavien-Dindo classification. In the group with GISTs larger than 5 cm, two patients required reoperation (grade III in the Clavien-Dindo classification). One of these patients was diagnosed with symptoms of severe obstruction of the gastrointestinal tract caused by an exaggerated narrowing of the stomach at the location of the resection. A reoperation involving the surgical correction of this site was necessary. It should, however, be noted that this complication occurred after one of the first laparoscopic procedures performed at our facility while treating a patient with a GIST. The experience gained over the course of time made it possible to avoid such complications in the case of 43 patients who had since been treated by means of this technique. The second patient who required reoperation experienced bleeding into the peritoneal cavity from the short gastric vessels. It is worth adding that the bleeding was not severe enough to put the patient at an immediate risk of death.

The application of minimally invasive procedures in most cases forces the surgeon to perform a mini-laparotomy in order to remove the surgical specimen. Smaller post-operative wounds are associated with a lower risk of infection at the site of the surgery and a lower risk of incisional hernia [21, 22]. The surgical removal of large tumors requires a mini-laparotomy to be performed over a larger area. In our study, we observed one incidence of surgical site infection in the group with GIST ≤ 5 cm and one such case in the group with GIST > 5 cm. Although literature data do not indicate a high frequency of complications with regard to wound healing, it is to be expected that a mini-laparotomy performed over a larger area to allow a larger tumor to be removed from the abdominal cavity may be associated with increased risk in this respect.

The GISTs develop in the deeper layers of the gastrointestinal wall [23] and are often covered by mucosa that does not exhibit any lesions. Successful histopathological verification often requires collecting a tissue sample from the deeper layers of the wall, whereas the collection of tissue samples during standard endoscopy may not be sufficient for positive verification [24]. Our data did not indicate statistically significantly higher efficacy of pre-operative verification in either group. Despite the fact that larger tumors are far more noticeable during endoscopic examination, collecting material suitable for biopsy is no easier in this case.

The available literature data do not show statistically significant differences in the 5-year survival rates of patients treated for large GISTs (5–10 cm) by means of either classic open surgery or laparoscopic surgery [25]. This provides yet another argument for a debate concerning the qualification of patients with large GISTs for treatment with minimally invasive procedures and the safety of such treatment.

Conclusions

It appears that the surgical treatment of GISTs with a diameter of more than 5 cm by means of minimally invasive procedures is a viable and safe alternative. Although it is associated with slightly larger intra-operative blood loss and a longer hospital length of stay compared to the treatment of smaller tumors, it does not involve an increased number of post-operative complications. The analyzed data show that the treatment of small and large GISTs using minimally invasive procedures does not entail too many notable differences. Taking into consideration these observations and the fact that laparoscopy has proven to be a viable and effective procedure for the treatment of small GISTs, it seems that it can play a significant role in the treatment of larger gastrointestinal stromal tumors. In fact, it may even become the treatment of choice in such clinical contexts.

Conflict of interest

The authors declare no conflict of interest.

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