

STUDY PROTOCOL

Robotic, Laparoscopic and Open Surgery for Gastric Cancer Compared on Surgical, Clinical and Oncological Outcomes: Establishing a Multi-Institutional Registry

IMIGASTRIC

International study group on Minimally Invasive surgery for Gastric Cancer

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SUMMARY

Gastric cancer represents a great challenge for health care providers and requires a multidisciplinary approach in which surgery plays the main role. Over the last two decades, minimally invasive surgery has been progressively developed, first with the advent of laparoscopy and more recently with the utilization of robotic surgery. These approaches immediately aroused a great interest in high volume centers performing gastric surgery, and many studies have been conducted on minimally invasive surgical techniques in comparison with open surgery. Minimally invasive surgery appears to offer many advantages including reduced postoperative pain, rapid recovery of gastrointestinal function and a shorter hospital stay. Although the feasibility of minimally invasive gastrectomy was demonstrated, especially in the treatment of early gastric cancer, there are many questions to be answered.[1] Thus, a number of issues related to minimally invasive surgical techniques are currently debated, including the limitations in performing an effective extended lymph node dissection and, within this context, the advantages of using the robotic system, the reproducibility of a total laparoscopic technique (rather than laparoscopic assisted technique) and the long-term oncological results.

A multicenter study with a large number of patients is now needed to further investigate the safety and efficacy as well as long-term outcomes of robotic surgery, traditional laparoscopy and the open approach.

BACKGROUND

Introduction

Gastric cancer constitutes a major health problem and is rampant in many part of the world. By some estimates, it is the fourth most common cancer[2]. In different Eastern Asian countries where screening is widely performed, early detection is often possible. In other parts of the world, it continues to pose a major challenge for health care professionals.

Surgery is the primary treatment for patients without metastatic disease. Subtotal gastrectomy is the preferred approach for distal gastric cancers. Whereas, proximal gastrectomy and total gastrectomy are indicated for proximal gastric cancers[3].

Resection should include lymph node dissection; however, the extent of lymphadenectomy remains controversial. Gastrectomy with D2 lymph node dissection is the standard treatment for curable gastric cancer in Eastern Asia. In the West, D2 dissection is considered to be a recommended but not required procedure. However, there is uniform consensus that the removal of an adequate number of nodes, 15 or greater, is beneficial for staging purposes.

Minimally invasive surgery (MIS) is progressively emerging in the management of gastric cancer through the development of new surgical devices and the advancement of surgical techniques.

Starting with Kitano[4], who performed the first laparoscopy-assisted distal gastrectomy in 1994, the use of laparoscopy continued to grow, and more recently, robotic-assisted gastrectomy was reported in 2003 by Hashizume[5]. Robotic gastrectomy has rapidly spread because of its potential technical advantages, such as the precision of movements using the articulated instruments and a three-dimensional view.

MIS is generally accepted as an alternative to open surgery in the treatment of Early Gastric Cancer[1], whereas for Advanced Gastric Cancer, the reliability of this approach depends largely on the proper execution of D2 lymph-node dissection[6, 7].

To date, many technical aspects of the surgical treatment are still controversial, and lack solid evidence regarding both short-term clinical and long-term oncological outcomes[8].

In particular, it is debated whether a complete and safe lymph-node dissection is possible with MIS. Robotic technology could overcome the difficulties of traditional laparoscopy, but the theoretical advantages in lymph-node dissection have not yet been proven and verified.

Recent meta-analyses have been performed are poor due to the small number of studies with good quality[9-13].

There are several limitations of the current literature that have been highlighted including the different baseline characteristics of patients, the relatively small number of samples size, the high heterogeneity of data, the lack of basic features regarding the procedures such as the type of surgical reconstruction and the inadequate or non-accessibility of data regarding both the short-term period and the oncological follow-up.

This project aims to create the most extensive multicenter database of patients receiving gastric surgery using the robotic, laparoscopic or open approach, involving institutions with experience in gastric and minimally invasive surgery[14].

Relevant Literature and Data

- Lymph-node dissection

Following the first published experience of laparoscopic gastrectomy with lymph node dissection for early gastric cancer[4], several studies comparing laparoscopic vs. open gastrectomy have demonstrated the benefits of laparoscopy with regards to perioperative outcomes.[15-20]

In patients with cancer, however, these advantages are weighed heavily against the concerns about surgeons' ability to maintain strict oncologic principles when the operation is performed using minimally invasive surgical techniques. Encouraging evidence from several randomized control trials and retrospective reviews suggests that there is no difference in the oncologic outcomes such as tumor recurrence and long-term survival between patients undergoing laparoscopic vs. open gastrectomy (OG) for early gastric cancer[21-23].

These results support not only the safety and feasibility of minimally invasive gastrectomy for the treatment of cancer but suggest that the use of these techniques may provide an oncologically sound long-term outcome for patients with cancer.

Nodal clearance is still regarded as an important factor influencing long-term survival, although agreement on the definition of lymphadenectomy between Japan and Western countries is still lacking. More lymph nodes retrieved can improve the accuracy of staging and lead to a more precise prognostic assessment[24]. In addition, a more thorough lymph node dissection may improve prognosis[25].

Although the use of limited lymphadenectomy in laparoscopy is widespread, the application of laparoscopic D2 dissection procedures, have not commonly been established worldwide to date[26]. Laparoscopic dissection of the lymph nodes around the superior mesenteric vein (LN #14v), celiac axis (LN #9), and splenic artery (LN #11) can be technically difficult using minimally invasive

surgical technique. In recent meta-analyses, the number of nodes harvested is significantly higher in open surgery[27-29], but some studies indicated no significant differences between the number of nodes collected in open versus laparoscopic surgery.[30, 31]

To clarify this and other issues, Vinuela et al.[7] performed a meta-analysis on laparoscopic versus open distal gastrectomy for gastric cancer, considering not only randomized controlled trials but also high-quality nonrandomized studies. Thus far, this represents the best evidence on the role of laparoscopic surgery for gastric cancer. In fact, twenty-five studies were included, of which 6 were RCTs and 19 were Non-RCTs including 3055 patients (1658 LG and 1397 OG). They found that the retrieval of lymph nodes was significantly higher in the OG group by 3.9 nodes ($P < 0.001$), although significant heterogeneity in lymphadenectomy type was observed between the groups. However, the authors show that the proportion of patients with less than 15 harvested nodes was similar ($P = 0.09$), which suggests that adequate nodal pathological staging is not compromised by the laparoscopic technique. The authors concluded that the extent of lymph node dissection could be a factor that may decrease the number of nodes retrieved after LG. Certainly a D2 dissection is technically more challenging, and achieving a good extended laparoscopic lymph node dissection will require a steep learning curve.

Studies evaluating robotic gastrectomy reported conflicting results. Pugliese et al. compared robotic gastric surgery (RGS) vs. laparoscopic gastric surgery (LGS) with regard to D2 lymph node dissection. In their study, the average number of resected nodes was 31 by LGS and 25 by RGS, but the authors did not report on its statistical significance [32].

In a study by Woo and colleagues[33], the number of lymph nodes retrieved for each approach was sufficient and did not differ by either method. D2 lymph node dissections were safely performed in 105 of 236 patients treated by robotic surgery, with an average of 42.4 nodes. In addition, it was reported by this author that 23.3% of the patients in the robotic group were confirmed as having lesions deeper than T2 and the safety and feasibility in the use of robotic assistance in treating advanced gastric cancer with D2 lymph node dissection was suggested.

A study by Huang et al.[34] indicated that there was a significant difference in the extent of lymphadenectomy among the robotic, laparoscopic and open techniques. The number of retrieved lymph nodes was similar between open and robotic groups but the laparoscopic group revealed fewer retrieved lymph nodes than both the open and robotic groups. The authors explained that they encountered technical difficulty with performing a laparoscopic D2 lymphadenectomies, so they performed D2 lymphadenectomies in only 18.8% of patients in the laparoscopic group but in 88.1% of the patients in the open group and 87.2% of patients in the robotic group.

With the aid of robotic instruments, the authors found that the lymphadenectomy was facilitated compared to the traditional laparoscopic approach, especially in the infrapyloric and suprapancreatic regions. A study by Caruso et al.[35], which considered patients who had undergone a gastrectomy with D2 lymph node dissection, confirmed no significant difference between the number of lymph nodes obtained using the robotic vs. open procedures (28.0 ± 11.2 vs. 31.7 ± 15.6 , respectively). In addition, the comparison between the robotic and laparoscopic techniques performed by Junfeng and colleagues[36] showed that the number of retrieved LNs was higher in the RGS group. Further analysis of retrieved LNs found significant differences of lymph node tier 2 between the two groups.

The reason provided by the author is that there are certain technically demanding lymph node stations, such as No. 7, No. 8a, No. 9, and No. 11 p in the second tier, and robotic surgery may provide better exposure and may facilitate the surgical dissection.

Yoon and colleagues[37] compared robotic vs. laparoscopic total gastrectomy. In their study, robotic total gastrectomy revealed no definite benefit regarding the number of retrieved LNs. The number of retrieved LNs for the robotic total gastrectomy and laparoscopic total gastrectomy groups was 42 vs. 39, respectively. The number of retrieved LNs in the N2 area did not differ significantly either (12 LNs by robot, 11 LNs by laparoscopy).

Son and colleagues[38], critically highlights that Yoon included cases of limited LN dissection in which the proportions were not indicated. Thus, a more detailed comparison of these parameters could not be performed. In the Son study, the RGS group had a significantly greater number of retrieved LNs from extragastric nodes (stations 7-14v), suprapancreatic nodes (stations 7-12a), and nodes from the splenic hilum, including splenic artery (stations 10 and 11), although the total retrieved LNs did not differ significantly from laparoscopy. However, Son's study[38] found that RGS yielded significantly greater number of retrieved LNs around splenic vessels and splenic hilum compared with those obtained by a laparoscopic approach.

- Reconstructive stages

The possibility of safely achieving intracorporeal anastomosis in place of extracorporeal procedures is currently being debated.

Currently, there are no available studies comparing minimally invasive gastric surgery for intracorporeal versus extracorporeal anastomosis. The advent of robotic surgery has provided a noticeable boost to the possibility of performing completely intracorporeal sutures. Robots can help surgeons because of the precise three-dimensional view and the instruments with seven degrees of

freedom. Recent studies reported that a robot-sewn anastomosis for reconstruction in gastric cancer is feasible[39] and can easily be performed by surgeons with less experience in minimally invasive surgery[36]. In a recent study, robotic assistance compared to standard laparoscopy significantly improved intra-corporeal suturing performance and the safety of novices in the operating room, thus significantly shortening the learning curve[40]. Three-dimensional vision allows for significant improvement in performance times and reduction of error rates for both inexperienced residents and advanced laparoscopic surgeons[41].

- Blood loss

Many studies in the literature place great attention on evaluating blood loss because it appears to correlate with the post-operative recovery, and in addition, there is a concern over the possibility that cancer cell dissemination may increase with greater operative bleeding or lymphatic leakage[42, 43].

Most studies report favorable results for MIS versus open surgery with respect to blood loss. This is confirmed by a study by Vinuela et al.[7], who reported an estimated blood loss for LGS that was significantly less than that of OG ($P < 0.001$). Generally, robotic gastrectomy has been reported to have some advantages over laparoscopic or open surgery in reducing perioperative bleeding.

Kang et al.[44] showed that patients staged T1 or T2 and N0 or N1 experienced less blood loss in RGS than in LGS. The author explained that LGS has limited range of motion which may cause more bleeding, especially during the dissection of technically demanding lymph node stations #6, #14, #7, #8, and #9. Thus, the author highlighted that most bleeding occurred due to limitations of motion and visualization. The scaled motion of the robot arm and the three-dimensional images in RGS potentially led to a more precise dissection with less bleeding.

Woo et al.[33] confirmed that robotic surgery can result in significantly less blood loss compared to laparoscopic surgery.

Both Kang and Woo also reported an interesting result, which is that blood loss in the laparoscopic group revealed larger variability compared to robot-assisted surgeries indicating a more consistent surgical procedure.

Junfeng et al.[45] highlighted in a subgroup analysis of the elderly, patients undergoing RGS lose less blood, which translates to shorter recovery. However, there are conflicting studies, such as that of Eom et al.[46] who found greater blood loss after RGS compared with LGS.

In addition, Son et al.[38] similarly found higher blood loss after RGS. In this case, the author postulated that this was due to the surgeon's competence in laparoscopy and some limits of

robotic surgery, including the absence of tactile feedback and lack of various robotic instruments such as a suction-irrigator and endostaplers. Moreover, the author highlighted that macroscopic manipulation speeds and shifts of scene in the robotic system were not as quick as in the laparoscopic approach, and the robotic system also need longer time for instruments change compared to that of laparoscopic surgery.

- Surgical Stress

One clinical merit of MIS, as reported by different authors, is the reduction of surgical stress compared to open gastrectomy. Robotic surgery has been postulated to reduce the surgical stress response by decreasing surgical injury compared to standard laparoscopic surgery, hypothesizing that the stress response is proportional to the extent of operative trauma. However, Hyun et al.[47] reported Granulocyte:Lymphocyte (G:L) ratio results and did not find a significant difference in surgical stress between RGS and LGS. Moreover, Park et al.[48] evaluated the systemic surgical stress response by measuring the serum levels of C-reactive protein (CRP), fibrinogen, interleukin (IL)-6, IL-10 and tumor necrosis factor (TNF- α). In addition, oxidative stress was evaluated by determining the serial plasma levels of total bilirubin. The results revealed no evidence for reduced systemic stress response.

- Complications

The meta-analysis of Vinuela and colleagues[7] reported that LGS was associated with a significant reduction in overall complications ($P < 0.001$), medical complications ($P = 0.002$) and minor surgical complications ($P = 0.001$) compared to open surgery. Major surgical complications were comparable between the two groups. The authors hypothesized that significantly decreased medical and minor surgical complications could be explained by the reduced invasiveness of the laparoscopic technique and is consistent with the reduction in the length of hospitalization observed in the LGS group. In contrast, the current largest RCT, from the Korean Laparoscopic Gastrointestinal Surgery Study Group, found no significant difference in the rate of complications between the laparoscopic and open approach ($P = 0.13$).[15]

Vinuela et al.[7] highlighted that they did not have the ability to analyze long-term complications, such as incisional hernias or adhesive bowel obstructions, because this finding was not evaluated in any studies, but it could be an additional factor in favor of LGS that should be taken into account. Consistent data are emerging regarding the robotic approach.

Woo and colleagues[33] supported the safety of RGS, which in his study presented similar complication rates as laparoscopy.

Hyun et al.[47] investigated short-term postoperative outcomes by using the Clavien-Dindo (C-D) classification. This metric allows complications to be reported in an objective, reliable, and reproducible manner based on the degree of the complication.

The total complications assessed by the C-D classification system were not significantly different between the RGS and LGS groups. In particular, the frequency of Grade IIa complications was higher in the RGS (31.5 %) group than the LGS group (16.8 %), but this difference was not statistically significant. The RGS group had a higher total number of complications than the LGS group, but most of these complications were minor and could be treated nonsurgically. Conversely, the LGS group had more major complications that required surgical, radiologic, or endoscopic intervention than the RGS group.

A study by Son[38] confirmed a similar incidence of postoperative complications in RGS and LGS ($P = 0.374$). In this report, complications in the RGS group were found in 8 of 51 patients (16 %) and in 13 of 58 LGS patients (22 %). The severity of complications, measured according to the C-D Classification [23], was similar between the two groups ($P = 0.883$). In addition, Yoon [37] reported a complication rate for the RGS group (16.7%) was comparable with that for the LGS group (15.4%) ($P = 0.866$).

It was reported that major complications included mostly leakages and strictures of the anastomotic sites without major bleeding in either group. However, the authors specified that because they performed all of the anastomoses extracorporeally, the major complications did not differ significantly between the two groups. In addition, the authors demonstrated that minor complications in the RGS group were more frequent than in the LGS group, but the difference was not significant. The authors hypothesize that excessive robotic movement and improper positioning of the trocar in the abdominal wall may have been the cause of more wound infections and abdominal wall hematomas. On the contrary, Park[48] showed that postoperative complications occurred more frequently in the RGS group than the LGS group, although most were minor and managed conservatively. However, the incidence of severe complications requiring an additional invasive procedure did not differ significantly between the groups.

In a study by Huang[34], anastomotic leakage was the main cause of operative morbidity. In particular, the leakage rate was higher in the robotic group than in the open and laparoscopic groups (7.7 vs. 4.6 vs. 4.7%, respectively). However, the authors reported that the robotic phase ended after

completing the lymph node dissection, and then the same reconstructive technique was used as in laparoscopic gastrectomy.

Therefore, the authors stated that the highest rate of leakage in the RGS group cannot be attributed to the robotic system itself, but other confounding factors.

- Post-operative recovery

MIS has demonstrated several advantages over open surgery with regard to early post-operative outcomes. In particular, all meta-analyses on laparoscopic versus the open approach have demonstrated a shorter hospital stay in the LGS group, and these results are a consistent finding across all studies. Additionally, there is some evidence (Kim[49] and Woo[33]) of better short-term surgical outcomes for robotic gastrectomy compared to the laparoscopic approach, although the benefits appear to be restricted to hospital stay. According to these authors, patients who underwent robotic gastrectomy could be discharged at an earlier date than patients who underwent open or laparoscopic gastrectomy.

Kim et al.[49] reported that the postoperative hospital stay in the RGS group was significantly shorter than in the OG and LGS groups (RGS: 5.1 ± 0.3 ; LGS: 6.5 ± 0.8 ; OG: 6.7 ± 1.4 ; $P=0.001$).

In addition, the study by Woo et al.[33], identified a significantly larger percentage of patients in the robotic group discharged by postoperative day 5 (48.8% of the LGS group vs. 61.0% of the RGS group; $P=0.04$).

These results appear to confirm what has been observed by Hiki[50], who asserted that manually handling organs during gastrectomy is an important contributor to the inflammatory response after surgery. The smaller robot instruments may induce less inflammation than the instruments used for other procedures. Thus, postoperative bowel recovery in the robotic group may occur sooner. A study by Kang[44] included some operations performed with an intracorporeal technique, with the consequent advantage of having only a small incision for specimen extraction. In addition, he highlighted, as previously stated by Hur[39], that in the suture technique, handling was made much easier by the scaled motion of the robot arm, and thus, complete robot-sewn anastomosis was possible and easy. In these cases, Kang demonstrated that small and infra-umbilical wounds create less pain, and patients were more satisfied.

Moreover, Song[51] reported that patients who underwent robotic surgery tended to ambulate earlier, felt less pain, and are were able to be discharged from hospital earlier. They also appeared to be satisfied despite the higher overall cost. The author concluded that the robotic surgical system

could serve as a tool for experienced laparoscopic surgeons to perform robot-assisted surgery in initial cases with certain level of skill.

In addition, a study by Park[48] reported that postoperative fluid discharge from the drain was reduced in patients who received RGS, presumably related, as suggested above, to less manipulation of intraabdominal organs during the surgical procedure. Other studies that have reported the results of the two MIS approaches did not reveal significant differences.

In particular, Junfeng[36] reported that robotic surgery is comparable to conventional laparoscopic surgery regarding time of first flatus, days to eating a liquid diet, and length of hospital stay. In a study by Son [38], postoperative restoration of bowel function, measured by postoperative day of flatus passage, resumption of water intake, soft diet, and hospital stay, though being slightly in favor of laparoscopy, were not significantly different between the two groups. However, other authors reported that due to the increase of robot-assisted gastrectomy cases, the surgical outcomes may improve[37, 44].

For example, Kang[44] reported that RGS patients had longer average hospital stays than LGS patients (9.81 days vs. 8.11 days, $P=0.042$). However, in subgroup analysis, a robotic subgroup designated by the authors as an "experienced group" demonstrated similar hospital stays as the LGS group (8.66 days vs. 8.11 days, $P=0.522$).

- Survival in curable gastric cancer

The 5-year survival after curative open or laparoscopic gastrectomy for locoregional gastric cancer ranges between 19 and 81%[52-56]. Obviously, survival rates depend on the proportion of EGC patients included. For a laparoscopic series, Huscher[53] reported a 59% cumulative 5-year survival but not stratified survivals for EGC and AGC. Tanimura[57] demonstrated for T2N1 pathology, there were equal survival rates for open vs. laparoscopic gastrectomy. Lee and Kim[54] reported a recurrence rate of 16% and a 3-year survival rate equal to the 5-year survival rate.

Studies on robotic surgery reporting data on oncologic follow-up are rare. In particular, there is no long-term comparison between the robotic and open approaches, whereas only 3 studies compared RGS to LGS. In these studies, RGS compared well to LGS regarding curative effect. Pugliese et al.[32] reported data on the oncologic follow-up comparing LGS to RGS. Both gastrectomy subgroups included EGC in approximately half the cases. However, the robotic group had a follow-up period of only 28 months. Thus, only a 3-year survival rate (85% vs. 78%) was reported, and the differences were not statistically significant.

In addition, Junfeng[36] conducted a short-term follow-up (median 17 months, range: 3–41 months).

The 3-year survival rate between the RGS and LGS groups were similar at 67.8 and 69.9 %, respectively ($P = 0.8$). His study also reported the survival rates in both groups according to lymph nodes metastasis. In this case, the 3-year survival rates for patients with node negative disease were 84.4 % in the RGS group versus 82.6 % in the LGS group, whereas the survival rates were 57.5 % in the RGS group versus 60.3 % in the LGS group for patients with positive nodal metastasis. No significant differences were found for either subgroup.

Son et al.[38] reported the longest follow-up study after RGS for gastric cancer, with a median follow-up of 70 months, and found no difference in overall survival ($p = 0.767$) or disease-free survival ($p = 0.67$). The 5-year overall survival rate was 89.5 % in the RGS group and 91.1 % in the LGS group while the 5-year disease-free survival rate was 90.2 % in the RGS group and 91.2 % in the LGS group.

RATIONALE

The research areas in the context of minimally invasive surgery are particularly directed to evaluate the possible advantages versus open surgery in perioperative outcomes and quality of life while respecting oncological principles.

Although there is growing attention concerning the role of MIS for gastric cancer, the current level of evidence on this topic is very low. For example, that there have been only 6 RCTs comparing laparoscopic versus open gastrectomy[15-17, 21, 22, 58] and no RCTs have been performed for robotic surgery.

In addition, the extreme heterogeneity of most studies is based on the absence of evidence-based practice guidelines.

Laparoscopic gastric surgery (LGS) is regarded as a technically feasible procedure as described in many reports that have demonstrated its safety, in particular for EGC; however, several studies have reported differences linked to the surgeon's experience and skill with laparoscopy, the hospital's volume and the surgeon's volume of gastrectomy procedure, and the accuracy of the preoperative diagnosis.

Over the past decade, robotic technology has provided new tools for minimally invasive surgery.

The potential underlined advantages of the use of the robotic system are essentially the following. The first advantage is the possibility of performing an extended lymphadenectomy to the level of the most complex lymph node stations, and the other advantage is to facilitate the performance of

an intracorporeal anastomosis. Current studies in the literature are inconsistent for both the aforementioned aspects.

The main problems found in clinical studies on robotic and/or laparoscopic versus open surgery for gastric cancer that should be overcome by a new study are as follows:

- In some comparative studies, there is selection bias in generating the comparative groups, in particular with regards to differences in the stage of the disease, who also could have been subjected to different extensive surgeries.
- Most studies do not clearly indicate the specific method of anastomotic technique such as intra- vs extracorporeal reconstruction. In centers that performed intracorporeal anastomosis, the data are often mixed with those of extracorporeal anastomosis.
- Some analyses of complications revealed that the anastomotic leak rate was twice as high after laparoscopic and robotic procedures than after an open approach, but there is a lack of information on the method of reconstruction.
- Almost all of the studies comparing laparoscopic and robotic surgery reported leaks. However, the same authors in most cases reported that the reconstructive phase of a robotic-assisted procedure was performed in a laparoscopic or open manner. In such a case, it is difficult to compare outcomes between the two techniques.
- There are significant discrepancies between studies concerning the length of hospital stay and postoperative management of patients.
- In several centers, the decision to receive laparoscopic vs robotic treatment is made by the patient after informed discussion about the two minimally invasive approaches as the patient often incurs the extra expense for robotic surgery.

Moreover, all of the studies that reported results in this field emphasize the need for large randomized trials. However, RCTs are difficult to perform and are very costly. In fact, in many countries, and especially those of East Asia, which also have significantly higher numbers of patients with gastric cancer than others, the patient himself decide whether to undergo robotic surgery because the patient will have to pay for the procedure.

There should be further consideration regarding the need for the detection of numerous surgical, clinical and oncological variables. Thus, it is imperative that a large number of patients is going to be enrolled. Therefore, a multicenter study is desirable.

At present, a multicenter registry may represent the best research method to assess the role of minimally invasive approaches in gastric cancer by comparing the methods to traditional open surgery[59].

Therefore, for this project, a large registry will be created by collecting data from the different participating centers to create a working basis for analyzing outcomes of interest and obtaining directions for further investigation.

METHODS

General Study Design:

The overall purpose is to develop and maintain an ongoing comprehensive multi-institutional database comprising of information regarding surgical, clinical and oncological features of patients undergoing surgery for gastric cancer with robotic, laparoscopic or open approaches and subsequent follow-up at participating centers.

The main objectives are:

- To determine the surgical, clinical, and oncological outcomes in both the short and long term
- To compare results according to the type of intervention, device used and manner of execution of different surgical phases
- To relate results of different surgeries with baseline characteristics of patients and stage of disease

The registry allows to retrospectively enter data of subjects with gastric cancer treated at the participating centers. Information gathered will be obtained from existing records, diagnostic tests and surgical interventions description.

Data Collection Tools

Information will be collected and recorded by all institutes through a specific online shared system. To facilitate and standardize data collection, speed up the creation of a shared database and ensure the security of sensitive data, a special online computerized web system has been developed.

The creation of a multi-institutional registry involves many obstacles. So, the following critical issues were considered.

As the investigators belong to centers located in different parts of the world, there is a high risk of generating transmission errors during the different stages of collection and submission of data.

In addition, each investigator may have difficulties in managing entered cases during different study steps, which could induce investigators to leave the study.

For these reasons, the intent was to make the entering and the sharing of data as easy as possible to increase the chances of success of the registry in the retrospective sense.

Therefore, a system of online submission and sharing of patient's data through a dedicated and protected website was planned.

The organizing committee of the registry with the cooperation of specialists in software programming, created a website that is accessible only to investigators using a password and username to login, which are provided after the accreditation of each participating center.

Data are not sent via email or spreadsheets but entered by each investigator directly through the web portal.

Once logged into the portal, the investigator is able to open a page where he can enter the required data of the patient by simply filling out a form and selecting the various features from dropdown lists made available for each parameter.

In fact, to facilitate the submission of information and their subsequent analysis, all of the features that have to be entered were previously standardized, and so data are selectable from the choices already made available, without the need to write or specify anything else.

Investigators have to provide the required data as completely as possible; however, the absence of certain information does not preclude sending the remaining data.

In fact, if some parameters are not recorded in patient files or are not provided because of an institute's policy, the investigator can send only the data of the variables at his disposal.

The web portal was designed as each investigator has a personal protected page that is not accessible to other participants. So, the investigator can display real time entered patients' data and manage their information. However, at the same time, the protection of data of each patient is guaranteed, and the data are editable only by the submitter.

In particular, the patient's sensitive information are only recognized by the investigator of the center to which the specific subject belongs. Moreover, the system provides the use of a reference code for each patient who also appears in the general shared registry instead of the name.

In this manner, it is hypothesized that the maximum chance of accuracy in the collection and maintenance of data can be achieved.

Therefore, each investigator has a two-function tool accessible via the web. The first provided function is a personal web page through which he can manage the data belonging to his institution, and the second function is the access to a shared web page on which there are data of all patients of the multi-institutional registry.

Specific aims:

AIM 1: To compare robotic and laparoscopic surgery to the open approach in terms of safety and feasibility based on the intraoperative and postoperative outcomes.

AIM 2: To verify the respect of oncological principles through minimally invasive approaches in relation to the stage and location of the tumor by comparing results to open surgery.

AIM 3: To verify whether minimally invasive approaches ensure the same effectiveness as open surgery in terms of overall survival and disease-free survival.

AIM 4: To compare the three treatment arms regarding recovery of gastrointestinal function considering the outcomes measured during the postoperative hospital stay.

AIM 5: To compare the incidence, types and severity of early postoperative complications after gastrectomy by the three approaches according to the Clavien-Dindo classification system[60]

AIM 6: To compare the intracorporeal to the extracorporeal anastomosis to evaluate post-operative recovery and complications.

AIM 7: To verify whether robotic gastrectomy, compared to laparoscopic or open techniques, is capable of reducing postoperative surgical stress.

ELIGIBILITY

Every patient is required to meet all of the inclusion criteria and none of the exclusion criteria.

Inclusion criteria:

- Histologically proven gastric cancer.
- Preoperative staging work-up performed by upper endoscopy and/or endoscopic ultrasound, and CT scan in accordance to international guidelines.
- Early Gastric Cancer[61, 62]
- Advanced Gastric Cancer[61, 62]
- Patients treated with curative intent in accordance to international guidelines[3, 63, 64]
- Patients with positive peritoneal cytology can be considered.

Exclusion criteria:

- Distant metastases: peritoneal carcinomatosis, liver metastases, distant lymph node metastases, Krukenberg tumors, involvement of other organs.
- Patients with high operative risk as defined by the American Society of Anesthesiologists (ASA) score > 4.
- History of previous abdominal surgery for gastric cancer.

- Synchronous malignancy in other organs.
- Palliative surgery cases.

DATA COLLECTION

Patient Demographics

- Sex, age, Body Mass Index (BMI kg/m²), surgical risks as assessed according to the American Society of Anesthesiologists (ASA score), neo-adjuvant therapy, concomitant illness, previous abdominal surgery.

Surgical Procedure details

- Type of surgical approach: open, laparoscopy, robotic
- Gastric resection and type of reconstruction[3]
- Anastomosis approach: intra-corporeal, extra-corporeal
- Anastomosis performance: linear stapler, circular stapler, hand-sewn, robot-sewn
- Extent of lymphadenectomy[3]: D1, D1+, D2, D2+
- Site and length of minilaparotomy
- Placement of intra-abdominal drain and nasogastric tube at the end of procedure

Tumor characteristics

- Tumor location: Upper third, Middle third, Lower third.
- Long diameter of tumor, depth of invasion (T classification), lymph node status (N classification)
- Number of metastatic lymph nodes and total number of nodes retrieved
- AJCC pathological stage[65]
- Histological type[66] and Lauren classification[67]

Operative findings

- Duration of surgery, estimated blood loss, conversion to open surgery, intraoperative complications, proximal resection margin, distal resection margin, number of retrieved lymph nodes, margin free of disease or infiltrated.

Post-operative clinical findings

- Time to start oral intake (post-operative day)
- Resumption of bowel function (post-operative day): time to peristalsis, time to first flatus
- Length of postoperative hospital stay
- Granulocyte to lymphocyte ratio (values before and after surgery)

Post-operative complications

- Type of complication, reoperation for complication
- Surgical complications after discharge: Time of occurrence from surgery, type, need of surgical intervention

Follow-up details

- Patient alive, not alive or lost at follow-up
- Disease-free or not at follow-up
- Time to onset of recurrence and site of recurrence

PRIMARY OUTCOME MEASURES:

- Safety and feasibility of minimally invasive procedures: rate of intraoperative complications, rate of conversion to open surgery, estimated blood loss.
- Respect of oncological principles: number of lymph nodes retrieved and rate of patients achieving R0 resection, at the histopathological analysis of the surgical specimen.
- Effectiveness of surgery: overall survival and disease-free survival achieved at 1, 3, 5 years from surgery.

SECONDARY OUTCOME MEASURES:

- Recovery of gastrointestinal functions and physical status allowing the discharge of the patient: time to peristalsis, time to first flatus, time to start oral intake and days of hospitalization after surgery until discharge.
- Early postoperative complications: rate of total complications, rate of specific surgical complications, severity of complications scored on the Clavien-Dindo classification system[60], assessed during hospitalization.
- Safety and efficacy of intracorporeal anastomosis: rate of anastomotic leakage, days of hospitalization after surgery until discharge.
- Postoperative surgical stress: Granulocyte-to-lymphocyte ratio[68] recorded and compared before and after surgery.

MAIN OUTCOMES DEFINITIONS AND CLASSIFICATIONS ADOPTED

Perioperative and oncological features

Operative time: the time between laparotomy and skin suture for OG and pneumoperitoneum induction and port-site closure for LG or RG (including, in this case, the time necessary to dock the robotic cart).

Blood loss: suction volume minus irrigation volume.

Description of type of procedure: Gastrectomy and extent of lymphadenectomy will be classified in accordance with the Japanese Gastric Cancer Association (JGCA) guidelines[3].

Postoperative Stress: As a surgical stress marker, the Granulocyte:Lymphocyte (G:L) ratio[68] will be analyzed comparing preoperatively and postoperative values.

Medications: These will be categorized into antibiotics and analgesics administered in the post-operative period.

Staging tumor: The stage will be described according to the Seventh Edition of the American Joint Committee (AJCC) on Cancer/International Union Against Cancer tumor node metastasis (TNM) classification for gastric cancer[65, 69].

Curative resection: This will be defined as an R0 resection using the AJCC residual tumor classification in accordance with the Japanese Gastric Cancer Association (JGCA) guidelines.[3]

Oncological follow-up: scheduled controls consisting of clinical examination, abdominal echography, cancer antigens serum levels, endoscopy or CT scan.

Postoperative Complications

Postoperative complication: any adverse event leading to a deviation from the normal postoperative course, occurring within 30 days of gastrectomy in or out of the hospital or after 30 days during the same hospital stay as the gastrectomy

Types of complication:

- Wound infection: superficial or deep surgical-site infection (SSI) based on the criteria of the Centers for Disease Control and Prevention[70]. Superficial incisional SSI involves either skin or subcutaneous tissue, and deep incisional SSI extends deep into the fascial layer.
- Organ/space SSI is classified separately and defined as an abscess and fluid collection confirmed by contrast-enhanced computed tomography (CT) of the abdomen and pelvis.
- Leak is defined as an anastomotic disruption at the gastroduodenostomy, gastrojejunostomy, esophagojejunostomy or jejunojunctionostomy, as well as staple-line disruption at the duodenal

stump. These are diagnosed by at least one of the following: extravasation of enteral contrast material on an upper gastrointestinal contrast study or abdominal CT, visualization of anastomotic defects on oesophagogastroduodenoscopy (OGD), persistent bilious fluid in the abdominal drain, or identification of intestinal spillage during exploratory laparoscopy or laparotomy.

- Bleeding will include both intraluminal and intraabdominal hemorrhages. Intraluminal bleeding is confirmed by OGD in patients with clinical signs and symptoms of upper gastrointestinal bleeding, such as melena, hematemesis or a substantial decrease in serum hemoglobin concentration. Intra-abdominal bleeding is diagnosed when at least one of the following are documented: blood-stained fluid in the intra-abdominal drains, bleeding vessels identified by angiography, and hemoperitoneum found on relaparotomy.
- Intestinal obstruction and ileus will be diagnosed based on clinical suspicion, signs of small intestinal dilatation on plain abdominal X-ray or CT or when an anastomotic stricture is confirmed on OGD.
- Other complications include surgical complications not classified by any of the above, such as pancreatitis, remnant stomach necrosis, as well as medical complications – cardiac, pulmonary, renal, hematological (disseminated intravascular coagulopathy) and neurological (stroke).

All of the surgical complications will be classified according to the Clavien-Dindo classification[60] system, which objectively categorizes postoperative outcomes according to treatment aggressiveness.

The 5 categories are as follows:

- grade I, any deviation from the normal postoperative course without the need for pharmacological treatment;
- grade II, requiring pharmacological treatment;
- grade III, requiring surgical, endoscopic, or radiological intervention;
- grade IV, life-threatening complications requiring intensive care unit (ICU) management;
- grade V, death of the patient.

Grade I will include fever after the third postoperative day that required antipyretics.

Any postoperative transfusion or antibiotics after postoperative day 3 will indicate grade II.

Pancreatitis requiring conservative treatment will be included in grade II.

All mechanical interventions after surgery will be classified as grade III, including endoscopic stenting or clipping, reoperation, and radiologic-assisted peripheral abdominal drainage insertion. ICU care or hemodialysis will indicate grade IV.

If a patient has more than one type of complication, the complication with the highest grade will be recorded for statistical analysis.

Description of the pathological features

Macroscopic features:

- Early Gastric Cancer (EGC) is considered to be a malignant epithelial tumor confined to the mucosa of the stomach or even infiltrating the submucosa; it will be classified according to its superficial appearance, as defined by a macroscopic endoscopic classification proposed by the Japanese Gastroenterological Endoscopic Society.[62]
- EGC classification according to growth: the Kodama classification will be considered.[71] It distinguishes small mucosal carcinomas that superficially spread, the invasion of which is limited to the mucosa or superficial portion of the submucosa and forms penetrating (Pen A and B) in which the neoplastic invasion affects the deeper layers of the submucosa.
- Advanced Gastric Cancer (AGC) will be defined according to the classification of Borrmann[72]: polypoid neoplasms (type I), exophytic / fungiform (type II), ulcerated (type III) and diffusely infiltrating (type IV).

Microscopic features:

- The WHO classification will be considered.[66] It is based on the recognition of the predominant histologic type. It includes the 4 most frequent histological types (tubular carcinoma, papillary, mucinous and signet-ring cell) and some rare variants (epatoid carcinoma, carcinoma with lymphoid stroma, choriocarcinoma, adenosquamous carcinoma, squamous, and undifferentiated small cell)
- The classification of Lauren[67] will also be used because of its widespread application and simplicity. It distinguishes two main types of cancer, that of "intestinal type" and the "spread." The cases that do not fit in the characteristics of the two main forms, such as the undifferentiated carcinoma sec. WHO, are defined as "unclassifiable". The tumors that carry both aspects are classified as "mixed".

STUDY PERIOD AND SITES

The study takes into account data of patients treated from January 1, 2000, to the official opening of the registry (May 14, 2015).

The maintenance of the registry is currently guaranteed until January 1, 2018. At the end of this period the system could continue to be active and in any case, even after this period, the collected data will be made safe and available to all involved Centers.

The study has been shared by the members of the international study group on minimally invasive surgery for gastric cancer (IMIGASTRIC)[14]. The group involves some of the most important researchers and institutes around the world (see the attached affiliation list) for the treatment of gastric cancer and began working in 2014 to reach the definitive agreement on the principles, objectives, data to be collected and software tools of the study.

During the study period other interested institutions can join the registry, thus increasing the size of the samples and allowing new statistical analysis.

Also, it would be possible the opening of a prospective trial after sharing a specific protocol.

STATISTICAL ANALYSIS

Based on the data of the registry every investigator can perform all the statistical analysis he needs for his researches purposes, while a basic analysis for monitoring the study will be performed as follows.

SPSS version 22 will be used to carry out this statistical analysis. The dichotomous variables will be expressed as numbers and percentages, while continuous variables will be expressed as mean and standard deviation (SD) or median and interquartile range (minimum and maximum values).

Continuous variables, will be compared using one-way ANOVA with post hoc multiple comparison by Tukey's procedure. Pearson's χ^2 test or Fisher's exact test, as appropriate, will be used for analysis of categorical data. For each of these tests a value of alpha (α) < 0.05 will be considered statistically significant.

POTENTIAL RISKS AND SAFETY MANAGEMENT

Participation in the research registry involves the potential risks of a breach of confidentiality of the medical record information and associated privacy of the participants.

Such risks will be minimized by the use and the establishment of appropriate tailor-made systems, as specified in the sections above, developed by experts in web security.

In particular, confidentiality and data security will be ensured by:

- 1) removing direct participant identifiers (i.e., names, social security numbers, and medical record numbers) from the information stored in the research registry;
- 2) securing in a separate location and limiting access to information linking codes assigned to the registry information with direct participant identifiers;
- 3) limiting access to information contained within the research registry to center investigators.

The data and safety monitoring plan for the research registry will involve routine (i.e., quarterly) monitoring by the organizing committee of 1) the removal of direct identifiers from information contained within the research registry, 2) the documentation of investigator access to the research registry, 3) the security of the database linking the research registry linkage codes with participant identifiers and the documentation of investigator access to this database, and 4) any conditions that may negatively impact the confidentiality of information contained within the research registry.

In addition, any unauthorized access to medical record information contained within the research registry or to the database linking the registry information to participant direct identifiers shall be reported to a data and safety monitoring board.

The organizing committee will ensure that confidential information will be secured and that Protected Health Information (PHI) will not be revealed. Access to subject information will be limited to the study personnel and PHI will be kept in a separate secure storage.

ETHICAL ASPECTS

All Investigators agree the study is conducted in compliance with ethical principles originating from the Helsinki Declaration, with the guidelines of Good Clinical Practice (GCP) and with applicable laws.

Investigators shall undertake to act according to the rules of their Institutional Review Board (IRB) and Ethics Committee (EC) regarding the retrospective collection of data.

PUBLICATIONS

The organizing committee will have no prerogative on publications. Each participating center, with equal right, will be able to access the data of the registry, perform statistical analysis, discuss the results, and freely write scientific manuscripts. However, each study that is generated based on the registry must be known by all Centers before final publication.

FINANCING OF THE STUDY

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