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Review

Current status of minimally invasive surgery for gastric cancer: A literature review to highlight studies limits[☆]

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HIGHLIGHTS

- Minimally invasive surgery has been developed in last years.
- Patients with gastric cancer could benefit from this approach.
- A multi-institutional study is needed.

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ABSTRACT

Background: Gastric cancer represents a great challenge for health care providers and requires a multidisciplinary approach in which surgery plays the main role.

Minimally invasive surgery has been progressively developed, first with the advent of laparoscopy and more recently with the spread of robotic surgery, but a number of issues are currently being investigate, including the limitations in performing effective extended lymph node dissections and, in this context, the real advantages of using robotic systems, the possible role for advanced Gastric Cancer, the reproducibility of completely intracorporeal techniques and the oncological results achievable during follow-up.

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Gastrectomy
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Robotic surgery
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Method: Searches of MEDLINE, Embase and Cochrane Central Register of Controlled Trials were performed to identify articles published until April 2014 which reported outcomes of surgical treatment for gastric cancer and that used minimally invasive surgical technology. Articles that deal with endoscopic technology were excluded.
Results: A total of 362 articles were evaluated. After the review process, data in 115 articles were analyzed.
Conclusion: 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.

1. Introduction

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.

2. Methods

Between February and May 2014, the preliminary phase of the study was conducted to identify relevant data. Analysis of available published studies in the literature was performed to identify papers reporting clinical experience in minimally invasive, Laparoscopic (LG)/Robotic (RG), and open (OG) gastric surgery. Searches of MEDLINE, Embase and Cochrane Central Register of Controlled Trials were performed to identify articles published until April 2014 with reported outcomes for the surgical treatment of gastric cancer and that used minimally invasive technology. The links of every search result and all of the references in the original articles identified were reviewed to identify additional literature that was not indexed. A total of 362 potentially relevant records were identified and screened. After elimination of duplicates and exclusion of non-relevant articles, 115 articles were read carefully and evaluated to perform a descriptive review.

3. Results

3.1. Lymph-node dissection

Following the first published experience of laparoscopic gastrectomy with lymph node dissection for early gastric cancer [2], several studies comparing laparoscopic vs. open gastrectomy have demonstrated the benefits of laparoscopy with regards to perioperative outcomes [3–8].

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 [9–11].

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 [12]. In addition, a more thorough lymph node dissection may improve prognosis [13].

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 [14].

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 [15–17], but some studies indicated no significant differences between the number of nodes collected in open versus laparoscopic surgery [18,19].

To clarify this and other issues, Vinuela et al. [20] 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 [21].

In a study by Woo and colleagues [22], 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. [23] 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. [24], 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 [25] 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 [26] 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 [27], 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 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 [27] found that RGS yielded significantly greater number of retrieved LNs around splenic vessels and splenic hilum compared with those obtained by a laparoscopic approach.

3.2. 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 [28] and can easily be performed by surgeons with less experience in minimally invasive surgery [25]. 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 [29]. Three-dimensional vision allows for significant improvement in performance times and reduction of error rates for both inexperienced residents and advanced laparoscopic surgeons [30].

3.3. 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 [31,32].

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. [20], 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. [33] 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. [22] 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. [34] 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. [35] who found greater blood loss after RGS compared with LGS.

In addition, Son et al. [27] 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.

3.4. 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. [36] 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. [37] 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.

3.5. Complications

The meta-analysis of Vinuela and colleagues [20] 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 ($P = 0.13$) [3].

Vinuela et al. [20] 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 [22] supported the safety of RGS, which in his study presented similar complication rates as laparoscopy.

Hyun et al. [36] 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 [27] 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 [26] 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 [37] 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 [23], 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.

3.6. 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 [38] and Woo [22]) 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. [38] 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. [22], 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 [39], 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 [33] 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 [28], 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 infraumbilical wounds create less pain, and patients were more satisfied.

Moreover, Song [40] 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 [37] 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 [25] 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 [27], 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 [26,33].

For example, Kang [33] 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).

3.7. Survival in curable gastric cancer

The 5-year survival after curative open or laparoscopic gastrectomy for locoregional gastric cancer ranges between 19 and 81% [41–45]. Obviously, survival rates depend on the proportion of EGC patients included. For a laparoscopic series, Huscher [42] reported a 59% cumulative 5-year survival but not stratified survivals for EGC and AGC. Tanimura [46] demonstrated for T2N1 pathology, there were equal survival rates for open vs. laparoscopic gastrectomy. Lee and Kim [43] 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. [21] 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 [25] 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. [27] 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.

4. Discussion

The research areas in the context of minimally invasive gastrectomy are directed to evaluate possible advantages over open surgery with regards to perioperative outcomes and quality of life while respecting the oncologic principles. Although there is growing attention concerning the role of MIS for gastric cancer, the current level of evidence on this topic is poor with only 6 RCTs on laparoscopic vs. open surgery and no RCTs for robotic surgery. In addition, the extreme heterogeneity of most studies lead to the absence of evidence-based practice guidelines. LGS is regarded as a technically feasible procedure as described in many reports which demonstrated its safety, in particular for EGC; however, several studies reported differences linked to the surgeon's experience and skill with laparoscopy, hospital and individual surgeon experience with the procedure, and the accuracy of the preoperative diagnosis. Over the past decade, robotic technology has provided a new modality for minimally invasive surgery. Potentially the robotic system may offer specific advantages in performing an extended lymphadenectomy to the level of the most complex lymph node stations and facilitate construction of an intra-corporeal anastomosis. There is little evidence to support the clinical advantages of robotic surgery at the current time.

All of the recent studies that reported results in this field emphasize the need for large randomized trials which may be difficult to perform. Costs of RCTs are high, and many surgeons may not be able to offer both approaches. In many countries, and especially those of East Asia, which have significantly higher numbers of patients with gastric cancer, the patient himself chooses whether to undergo robotic surgery because he or she must pay for the procedure.

Numerous surgical, clinical and oncological variables will need to be studied and it will be crucial that a large number of patients will be enrolled. Although a multi-centre trial is desirable at the present time, a multi-centre registry may represent the most feasible research tool to assess the outcomes of minimally invasive approaches vs. open surgery for gastric cancer [47].

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None.

Author contribution

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All authors approved the final version of the manuscript.

Conflict of interest

None.

Guarantor

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