

Robot-assisted laparoscopic gastrectomy for gastric cancer

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Abstract

Phase III evidence in the shape of a series of randomized controlled trials and meta-analyses has shown that laparoscopic gastrectomy is safe and gives better short-term results with respect to the traditional open technique for early-stage gastric cancer. In fact, in the East laparoscopic gastrectomy has become routine for early-stage gastric cancer. In contrast, the treatment of advanced gastric cancer through a minimally invasive way is still a debated issue, mostly due to worries about its oncological efficacy and the difficulty of carrying out an extended lymphadenectomy and intestinal reconstruction after total gastrectomy laparoscopically. Over the last ten years the introduction of robotic surgery has implied overcoming some intrinsic drawbacks found to be present in the conventional laparoscopic procedure. Robot-assisted gastrectomy with D2 lymphadenectomy has been shown to be safe and feasible for the treatment of gastric cancer patients. But unfortunately, most available studies investigating the robotic gastrectomy for gastric cancer compared to laparoscopic and open technique are so far retrospective and there have not been phase III trials. In the present review we looked at scientific evidence available today regarding the new high-tech surgical robotic approach, and we attempted to bring to light the real advantages of robot-assisted gastrectomy compared to the traditional laparoscopic and open technique for the treatment of gastric cancer.

Key words: Gastric cancer; Gastric resection; Minimally invasive surgery; Robot-assisted gastrectomy

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Core tip: Laparoscopic gastrectomy has been shown to be a viable option for early gastric cancer, showing survival rates comparable to those of open procedure. However, there has been criticism concerning the routine use of laparoscopy in patients with advanced gastric cancer, principally because it adapts poorly to complex maneuvers like D2 lymphadenectomy. Robotic surgery has been shown to make certain laparoscopic procedures easier and safer. Reports have recently shown the ever increasing feasibility and safety of robotic assisted laparoscopic gastrectomy for gastric cancer, in some cases even proving superior to traditional laparoscopy.

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INTRODUCTION

In 1991, Kitano *et al*^[1] performed the first laparoscopically assisted gastrectomy for gastric cancer. Subsequently, under the impulse of level III studies providing the evidence of the safety of laparoscopic assisted distal gastrectomy (LADG) for distal early-stage gastric cancer, several authors reported comparative studies with better short-term results in favor of this technique with respect to traditional open^[2]. As a consequence laparoscopic gastrectomy (LG) has progressively spread worldwide, especially in the East, for the treatment of early gastric cancer^[3,4]. On the other hand, the treatment of patients with advanced gastric cancer has always been considered difficult laparoscopically, thus techniques such as laparoscopic assisted total gastrectomy (LATG) and laparoscopic extended lymphadenectomy did not meet the same enthusiasm. As a result, the spread of laparoscopic surgery as a means of performing total gastrectomy and managing advanced gastric cancer was limited. This was mainly due to the technical difficulties and complexity of the D2 lymphadenectomy and the intestinal reconstruction after total gastrectomy^[5,6].

Robot-assisted techniques have brought about improvements to certain surgical procedures, particularly those which require precise dissection, making it possible to resolve some of the innate limitations of laparoscopy. So over the years, robot-assisted gastrectomy (RAG) has become increasingly considered as a valid, yet still debatable, alternative to executing gastrectomy for gastric cancer, in particular for total gastric resection and extended lymph node dissection in advanced tumours^[7-9].

We analyzed high-quality clinical trials by systematically reviewing the literature published so far in Pubmed comprehending robotic case series, as well as those studies that have compared RAG with LG and/or open gastrectomy for gastric cancer. Our intent is to verify if at present there is actual evidence of an advantage to robotic compared to laparoscopic and traditional open gastrectomy for gastric cancer.

Rational basis of robotic surgery as improvement of laparoscopy

Areas of surgery necessitating precise movements have employed Robotic technology. In 1994 the da Vinci[®] Surgical System (Intuitive Surgical, Sunnyvale, California, United States) gained the approval of the United States Food and Drug Administration (FDA). The da Vinci[®] Surgical Robotic has undergone constant improvement over recent years, and now includes additional features including near-infrared technology, and facilitated set-up. The latest generation, which was released in 2014 and is known as the da Vinci Xi[™] system, is less bulky and its arms are more ergonomic (Figure 1).

Robotic surgery eliminates some of the disadvantages of conventional laparoscopy. The principal drawbacks of conventional laparoscopy from a technical standpoint are: The instability of the two-dimensional (2D) camera; instruments with limited movement which augment the physiologic tremor of the surgeon's hand, therefore limiting manipulative actions and increasing ergonomic discomfort.

The robotic surgery system has the upper hand over laparoscopy when fine dissection is needed, eliminating the traces of physiologic human tremor, increasing dexterity through its typical internal articulated endoscopic wrist (EndoWrist[™] System), and providing stereoscopic vision with 3D high-resolution images^[10]. This allows surgeons to perform minimally invasive surgery with greater ease and safety, and more ergonomically. As a consequence it probably makes it possible for more surgeons to complete complex procedure in a minimally invasive fashion.

Moreover, even if laparoscopic surgery may have an effect on the robotic gastrectomy learning process, robotic surgery appears to globally need less time to master compared to a laparoscopic procedure traditionally requiring a steep learning curve^[11-14].

Main drawbacks of conventional laparoscopy in gastric cancer surgery

Delicate maneuvers which necessitate excellent visualization and total precision such as intra-corporeal anastomosis and dissection of extra-perigastric lymph nodes along the major arterial structures are the principal pitfalls of conventional laparoscopic gastrectomy for gastric cancer.

The far from perfect and often shallow angulation of the traditional unergonomic laparoscopic technique render the D2 lymphadenectomy especially hard and



Figure 1 New-generation da Vinci Xi™; the system is more versatile and better manoeuvrable, the robotic arms are thinner and arranged in a more ergonomic way, enabling multi-quadrant procedures without repositioning the system.

demanding even for minimally-invasive surgeons who have been solidly trained. Areas which are quite hard to reach during laparoscopic lymphadenectomy include lymph node stations 4, 6, 9, 11p and 12a^[15]. It may be linked to the risk of important blood loss which can occur particularly during the lymph node dissection around the infra pyloric area and the inferior mesenteric vein, including stations 6 and 14, and the supra pancreatic area including stations 7, 8, and 9^[16]. Miura *et al.*^[15] indicated a far inferior amount of harvested lymph nodes obtained by laparoscopy in comparison to open surgery along the major gastric curvature (Nos. 4 and 6) and second tier nodes along the celiac and splenic arteries (Nos. 9 and 11). Similarly, Bouras *et al.*^[17] showed a greatly inferior amount of lymph nodes harvested along the common hepatic artery in a series of laparoscopic distal gastrectomy procedures compared to open distal gastrectomy (ODG).

Main technical advantages of robotics over traditional laparoscopy in gastric cancer

The majority of resectable gastric cancer patients are advised to undergo gastrectomy with D2 lymph node dissection surgical procedure^[18]. Thus, in gastric cancer treatment, in order to fit oncological criteria, minimally invasive procedures must entail proper lymphadenectomy, as in its traditional open counterpart.

It is widely accepted that D2 lymphadenectomy is one of the most difficult steps of the laparoscopic gastrectomy procedure for gastric cancer. The certain

advantage produced by the robotic system could be decisive in gastric cancer surgery, mainly ensuring an extremely precise and safe lymphadenectomy with reduced risk of vessel injury^[19], thus making this phase a principal indicator for the robot-assisted technique. The advantages of robotic surgery, such as tremor filtration and articulated function of wristed instruments, would be particularly suitable for enabling more complete dissection in demanding areas such as the dorsal part of the pancreas and behind splenic vessels at the hilum, which are not easily identified and are difficult to reach with current laparoscopic instruments and camera system^[20]. It is extremely hard to reach the back of the suprapancreatic lymphatic area laparoscopically, and the downward compression of the pancreas which is particular prominent through the laparoscopic instruments may lead to pancreatic damage and pancreatitis. In these sites especially, the EndoWrist® robotic property and a far more stable vision allow the surgeon to complete this surgical step more easily and safely in comparison to the laparoscopic counterpart.

Robotic surgery also has the advantage of making intra-corporeal anastomosis easier, and therefore overcomes one of the greatest limitations of traditional laparoscopy from a technical standpoint in carrying out digestive restoration. This is particularly true after total gastrectomy, otherwise made possible by extracorporeal anastomosis with a small mini-laparotomy. Placing a hand-sewn purse-string suture on the esophagus is made easier by using robotic assistance, and esophageal

anastomosis can subsequently be carried out by using a circular stapler, as in open surgery^[7,19]. Another option would be to carry out a full robotic hand-sewn esophagojejunal anastomosis^[21], possible because the robotic system gives surgeons the chance to suture more easily and with greater precision compared to laparoscopy, particularly in deep and narrow areas. Thus, increased know-how and confidence with the robotic system will enable the surgeon to perform high-precision and safer intra-corporeal sutures for patients undergoing digestive anastomosis.

LITERATURE EVIDENCE

Studies of feasibility and safety

The earliest reports of robot-assisted gastrectomy (RAG) were published in 2003 by Hashizume *et al*^[22] and Giulianotti *et al*^[23]. Recent reports have shown the safety and viability of robotic gastrectomy for treating gastric cancer^[24,25]. Table 1 summarizes some of the robotic case series published to date^[7-9,26-34]. Most of the experience so far derives from non-randomized retrospective studies, while only one available clinical trial to date has been prospectively conducted^[34]. The studies mainly hail from the East. In the western countries, reports on RAG are fewer and usually limited to smaller series. In 2007, in the United States Anderson *et al*^[7] reported the results of the first western series including 7 gastric cancer patients who were submitted to robot-assisted subtotal gastrectomy, demonstrating that robotic gastrectomy was viable, even if no direct comparison with laparoscopy was made^[7].

Several authors worldwide reported their experience on RAG for cancer and the largest single institution series investigating clinical and oncological outcomes so far include (Table 1): Song *et al*^[9] in 2009, Jiang *et al*^[29] in 2012, Liu *et al*^[31] and Park *et al*^[32] in 2013, Tokunaga *et al*^[34] in 2015, which included respectively 100, 120, 104, 200 and 120 patients. These studies confirmed the safety and feasibility of RAG for cancer, essentially reporting a suitable amount of lymph nodes retrieved, but they did not furnish long-term survival data. Globally, among these various studies RAG appears to be safe in terms of the incidence and severity of postoperative complications. The morbidity rate ranges between 4.9% to 13%, with a mortality rate of 0%-6%, comparable to those of conventional gastric cancer surgery. Among reported potential advantages of the robotic procedure, Tokunaga *et al*^[34] noted a very low incidence of intra-abdominal infectious complications (3.3%) in a large cohort of gastric cancer patients ($n = 120$) submitted to total or subtotal gastrectomy.

Comparative studies

Despite the existence of numerous reports regarding the safety and feasibility of RAG, only few robotic comparative analysis investigated RAG vs laparoscopic and/or open gastrectomy (Table 2)^[11,12,24,25,35-50]. Most

studies comparing robotic gastrectomy with open and laparoscopic surgery are retrospective case-control studies, almost all of these with sample sizes of fewer than 100 cases. Only one multi-centre comparative study was prospectively conducted: Kim *et al*^[50], compared a total of 434 gastric cancer patients submitted to robotic and laparoscopic gastrectomy (223 vs 211 respectively), and showed similar overall complications rate with no operative mortality in either group, at the expense of significantly higher operative time and higher costs of the robotic group.

However, initial outcome demonstrated comparable or superior short-term results of RAG than the results achieved by open and laparoscopic procedures, at the price of generally longer operation time, as well as higher cost. The prolonged operation time is attributable also to the additional time docking the robotic system, however that time decreases gradually as the expertise of the team increases, and robotic devices are upgraded^[9]. Multiple series have reported various ranges in morbidity (5%-17%) after RAG (Table 2). Essentially, outcomes shown in these studies are satisfactory and similar to those of traditional surgical procedures (Table 2). Aforementioned outcomes demonstrate the clinical feasibility in using robotic radical gastrectomy for gastric adenocarcinoma in comparison with the conventional open and traditional minimally invasive laparoscopic approach, in some cases with potential clinical advantages also. For example, Kim *et al*^[44] and Suda *et al*^[49] showed a statistically significant improvement of the postoperative morbidity rate in gastric cancer patients submitted to RAG compared to LAG. In particular, Suda *et al*^[49] noted that local (particularly pancreatic fistula, robotic 0% vs conventional laparoscopy 4.3%, $P = 0.029$) rather than systemic complication rates were attenuated using the surgical robot. Also Seo *et al*^[47] reported an advantages of RAG in comparison to LAG in terms of a reduction of the incidence of postoperative pancreatitis or pancreatic fistula, which has been attributed to what is assumed to be a more gentle and steady pancreatic compression through the robotic system compared to laparoscopy during the suprapancreatic lymph nodes dissection.

For the first time Kim *et al*^[36] reported the results achieved with robotic surgery with respect to laparoscopic and open gastrectomy for the treatment of early gastric cancer. They compared 16 patients who underwent robotic procedure with 11 and 12 laparoscopic and open gastrectomy respectively, revealing longer operative times of the robotic group, but less bleeding and reduced length of hospital stay. With regards to number of harvested lymph nodes and post-operative outcomes amongst the groups no difference was demonstrated.

The biggest (not meta-analyzed) comparative study so far was carried out by Kim *et al*^[41]. They retrospectively looked at data on surgical complications of 5839 gastric cancer patients (4542 open, 861 laparoscopic and 436 robotic gastrectomies), and found no

Table 1 Robot-assisted laparoscopic gastrectomy series for treatment of gastric cancer

Ref.	Country	Patients (n)	Stage disease	Resection type		Operative time ¹ (min ± SD)	Blood loss ¹ (mL ± SD)	Open conversion (%)	Harvested nodes ¹ (n ± SD)	Morbidity (%)	Mortality (%)	Hospital stay ¹ (d ± SD)
				Total	Subtotal							
Anderson <i>et al</i> ^[7]	United States	7	0- I -II	-	7	420 ± NR	300 ± NR	0	24 ± NR	11.1	0	4 ± NR
Patriti <i>et al</i> ^[8]	Italy	13	I - II -III	4	9	286 ± 32.6	103 ± 87.5	0	28.1 ± 8.3	7.7	0	11.2 ± 4.3
Song <i>et al</i> ^[9]	South Korea	100	I - II - III	33	67	231.3 ± 43.2	128.2 ± 217.5	0	36.7 ± NR	13	1	7.8 ± 17.1
Pugliese <i>et al</i> ^[26]	Italy	18	All stages	-	18	344 ± 62	90 ± 48	12	25 ± 4.5	6	6	10 ± 3
Lee <i>et al</i> ^[27]	South Korea	12	I	-	12	253.7 ± 53.0	135.8 ± 133.9	0	46.0 ± 25.5	8.3	0	6.6 ± 1.6
D'Annibale <i>et al</i> ^[28]	Italy	24	I - II - III	11	13	267.5 ± NR	30 ± NR	0	28 ± NR	8.3	0	6 ± NR
Jiang <i>et al</i> ^[29]	China	120	I - II - III	35	85	245 ± 50	70 ± 45	0.9	22.5 ± 10.7	5	0	6.3 ± 2.6
Isogaki <i>et al</i> ^[30]	Japan	61	Not reported	14	47	520 ± 177 TG 388 ± 85 SDG	150 ± 234 TG 61.8 ± 46.5 SDG	0	43 ± 14 TG 42 ± 18 SDG	4.9	1.6	13.3 ± NR
Liu <i>et al</i> ^[31]	China	104	I - II - III	54	50	272.52 ± 53.91	80.78 ± 32.37	2	23.1 ± 5.3	11.5	0	6.2 ± 2.5
Park <i>et al</i> ^[32]	South Korea	200	All stages	46	154	248.8 ± 55.6	146.1 ± 130.3	7	37.9 ± NR	10	0.5	8.0 ± 3.7
Coratti <i>et al</i> ^[33]	Italy	98	All stages	38	60	296.1 ± NR	105.4 ± NR	7.1	30.6 ± NR	12.1	4.1	8.7 ± NR
Tokunaga <i>et al</i> ^[34]	Japan	120	I	12	108	348.5 ± NR	19 ± NR	2.5	44 ± NR	14.2	0	9 ± NR

¹Mean value. SD: Standard deviation; NR: Not reported; TG: Total gastrectomy; SDG: Subtotal distal gastrectomy.

significant differences between the three groups with regards to post-operative complication and morbidity.

In another large single institute comparative study^[25] the authors made a comparison between 236 patients who had undergone robotic curative resection of gastric cancer and 591 laparoscopic surgery patients (Table 2). The authors revealed a statistical significance difference, the mean duration of surgery was 49 min longer in the robotic group, whereas blood loss was 56.3 mL less. Morbidity, mortality and number of lymph nodes retrieved per level were comparable.

In yet another large comparative study (39 patients with gastric cancer undergoing robotic, 586 open and 64 laparoscopic gastrectomies)^[39], RAG was linked to diminished bleeding and reduced hospital stay, but with longer operative time than was necessary for both open and laparoscopic gastrectomy. The amount of harvested lymph nodes was also similar between the open and robotic groups, but less in the laparoscopic group (Table 2). The authors especially underlined that robotic instruments made it a great deal more simple to carry out the lymph node dissection, rather than the conventional laparoscopic approach, more so in the infra-pyloric and supra-pancreatic stations.

Junfeng *et al*^[24] retrospectively compared 120 vs 394 gastric cancer patients who had undergone RAG and laparoscopic assisted gastrectomy (LAG) respectively, revealing similar results. However, it is interesting to note that the authors showed, in addition to once more less intra operative bleeding and longer RAG operative time compared to the laparoscopic counterpart, that the numbers of harvested lymph nodes were notably

superior in the RAG group at tier 2. In the same way, Kim *et al*^[44] commented that, with regard to their experience achieved on 87 gastric cancer patients who had undergone robot-assisted distal gastrectomy (RADG) compared to 288 submitted to LADG, RADG seemed to be advantageous over LADG in performing the dissection of the second level lymph nodes, in particular those located in the suprapancreatic space and those around the splenic artery. Also Son's *et al*^[45] showed that robotic gastric surgery gave a much larger amount of harvested lymph nodes around splenic vessels in comparison to lymph nodes retrieved during laparoscopic procedure. This current medical research evidence, albeit initial, seems to consolidate the advantage of robotic surgery over LAG in its ability to perform a more complete D2 lymphadenectomy, probably making it possible to overcome one of the greatest surgical drawbacks of the laparoscopy in the treatment of gastric cancer.

An advantage of RAG compared to LAG has been reported in terms of a reduction of the incidence of postoperative pancreatitis or pancreatic fistula. This has been attributed to what is assumed to be a more gentle and constant pancreatic compression obtained using the robotic system compared to laparoscopy during the suprapancreatic lymph nodes dissection, *i.e.*, at station 9 and 11^[47].

Review and meta-analysis studies

To date, several review articles^[10,19,51-55] have been published which provide a critical appraisal of the effectiveness of RAG for gastric cancer, but they are not systematic research and do not actually supply any statistical

Table 2 Comparative case-control studies of robot-assisted gastrectomy *vs* laparoscopic assisted gastrectomy and/or open gastrectomy

Ref.	Subject	Stage disease	Patients (n)			Operation time (min) ¹	Blood loss (mL) ¹	Harvested nodes (n) ¹	Morbidity (%)	Mortality (%)	Hospital stay (d) ¹
			RAG	LAG	OG						
Song <i>et al</i> ^[35]	RAG <i>vs</i> iLAG2 <i>vs</i> rLAG2	I - II	20 ²	20 ²	-	230 <i>vs</i> 289.5 <i>vs</i> 134.1 (RAG < iLAG > rLAG) ³	94.8 RAG <i>vs</i> 39.5 rLAG (NS)	35.3 <i>vs</i> 31.5 <i>vs</i> 42.7 (NS)	5 <i>vs</i> 5 <i>vs</i> 10 (NS)	0 <i>vs</i> 0 <i>vs</i> 0	5.7 <i>vs</i> 7.7 <i>vs</i> 6.2 (RAG < iLAG) ³ (RAG~rLAG, NS)
Kim <i>et al</i> ^[36]	RAG <i>vs</i> LAG <i>vs</i> OG	I - II - III	16	11	12	259.2 <i>vs</i> 203.9 <i>vs</i> 126.7 (RAG > LAG > OG) ³	30.3 <i>vs</i> 44.7 <i>vs</i> 78.8 (RAG < LAG < OG) ³	41.1 <i>vs</i> 37.4 <i>vs</i> 43.3 (NS)	0 <i>vs</i> 10 <i>vs</i> 20 (NS)	0 <i>vs</i> 0 <i>vs</i> 0	5.1 <i>vs</i> 6.5 <i>vs</i> 6.7 (RAG < LAG < OG) ³
Eom <i>et al</i> ^[37]	RAG <i>vs</i> LAG	I - II - III	30	62	-	229.1 <i>vs</i> 189.4 (RAG > LAG) ³	152.8 <i>vs</i> 88.3 (NS)	30.2 <i>vs</i> 33.4 (NS)	13.3 <i>vs</i> 6.6 (NS)	0 <i>vs</i> 0	7.9 <i>vs</i> 7.8 (NS)
Woo <i>et al</i> ^[25]	RAG <i>vs</i> LAG	I - II - III	236	591	-	219.5 <i>vs</i> 170.7 (RAG > LAG) ³	91.6 <i>vs</i> 147.9 (RAG < LAG) ³	39.0 <i>vs</i> 37.4 (NS)	11 <i>vs</i> 13.7 (NS)	0.4 <i>vs</i> 0.3 (NS)	7.7 <i>vs</i> 7.0 (RAG > LAG) ³
Caruso <i>et al</i> ^[38]	RAG <i>vs</i> OG	All stages	29	-	120	290 <i>vs</i> 222 (RAG > OG) ³	197.6 <i>vs</i> 386.1 (RAG < OG) ³	28.0 <i>vs</i> 31.7 (RAG~OG)	10.34 <i>vs</i> 10.0 ⁴ (NS)	0 <i>vs</i> 3.3 (NS)	9.6 <i>vs</i> 13.4 (RAG < OG) ³
Huang <i>et al</i> ^[39]	RAG <i>vs</i> LAG <i>vs</i> OG	I - II - III	39	64	586	430 <i>vs</i> 350 <i>vs</i> 320 (RAG > LAG > OG) ³	50 <i>vs</i> 100 <i>vs</i> 400 (RAG < OG) ³	32 <i>vs</i> 26 <i>vs</i> 34 (RAG = OG > LAG) ³	15.4 <i>vs</i> 15.6 <i>vs</i> 14.7 (NS)	1.4 <i>vs</i> 1.6 <i>vs</i> 2.6 (NS)	7 <i>vs</i> 11 <i>vs</i> 12 (RAG < LAG < OG) ³
Uyama <i>et al</i> ^[40]	RAG <i>vs</i> LAG	All stages	25	225	-	361 <i>vs</i> 345 (NS)	51.8 <i>vs</i> 81.0 (RAG < LAG) ³	44.3 <i>vs</i> 43.2 (NS)	11.2 <i>vs</i> 16.9 (NS)	0 <i>vs</i> 0	12.1 <i>vs</i> 17.3 (RAG < LAG) ³
Kang <i>et al</i> ^[12]	RAG <i>vs</i> LAG	I - II - III	100	282	-	202.05 <i>vs</i> 173.45 (RAG > LAG) ³	93.25 <i>vs</i> 173.45 (RAG < LAG) ³	NR	14.0 <i>vs</i> 10.3 (NS)	0 <i>vs</i> 0	9.81 <i>vs</i> 8.11 (RAG > LAG) ³
Kim <i>et al</i> ^[41]	RAG <i>vs</i> LAG <i>vs</i> OG	0 - I - II - III	436	861	4542	226 <i>vs</i> 176 <i>vs</i> 158 (RAG > LAG > OG) ³	85 <i>vs</i> 112 <i>vs</i> 192 (RAG = LAG < OG) ³	40.2 <i>vs</i> 37.6 <i>vs</i> 40.5 (RAG = OG > LAG) ³	10.1 <i>vs</i> 10.4 <i>vs</i> 10.7 (NS)	0.5 <i>vs</i> 0.3 <i>vs</i> 0.5 (NS)	7.5 <i>vs</i> 7.8 <i>vs</i> 10.2 (RAG = LAG < OG) ³
Yoon <i>et al</i> ^[42]	RAG <i>vs</i> LAG	I - II - III	36	65	-	305.8 <i>vs</i> 210.2 (RAG > LAG) ³	NR	42.8 <i>vs</i> 39.4 (NS)	16.7 <i>vs</i> 15.4 (NS)	0 <i>vs</i> 0	8.8 <i>vs</i> 10.3 (NS)
Hyun <i>et al</i> ^[43]	RAG <i>vs</i> LAG	I - II - III	38	83	-	234.4 <i>vs</i> 220.0 (NS)	131.3 <i>vs</i> 130.48 (NS)	32.8 <i>vs</i> 32.8 (NS)	13.1 ⁴ <i>vs</i> 16.8 ⁴ (NS)	0 <i>vs</i> 0	10.5 <i>vs</i> 11.9 (NS)
Kim <i>et al</i> ^[11]	RAG <i>vs</i> LAG	I - II - III	172	481	-	206.4 <i>vs</i> 167.1 (RAG > LAG) ³	59.8 <i>vs</i> 134.9 (RAG < OG) ³	37.3 <i>vs</i> 36.8 (NS)	5.2 <i>vs</i> 4.2 (NS)	0 <i>vs</i> 0.6 (NS)	7.1 <i>vs</i> 6.7 (NS)
Kim <i>et al</i> ^[44]	RAG <i>vs</i> LAG	I - II - III	87	288	-	248.4 <i>vs</i> 230.0 (RAG > LAG) ³	NR	37.1 <i>vs</i> 34.1 (RAG > LAG) ³	5.7 <i>vs</i> 9.0 (RAG < LAG) ³	1.1 <i>vs</i> 0.3 (NS)	6.7 <i>vs</i> 7.4 (RAG < LAG) ³
Son <i>et al</i> ^[45]	RAG <i>vs</i> LAG	I - II - III	51	58	-	264.1 <i>vs</i> 210.3 (RAG > LAG) ³	163.4 <i>vs</i> 210.7 (NS)	47.2 <i>vs</i> 42.8 (NS)	16 <i>vs</i> 22 (NS)	1.9 <i>vs</i> 0 (NS)	8.6 <i>vs</i> 7.9 (NS)
Park <i>et al</i> ^[46]	RAG <i>vs</i> LAG	I - II - III	30	120	-	218 <i>vs</i> 140 (RAG > LAG) ³	75 <i>vs</i> 60 (NS)	34 <i>vs</i> 35 (NS)	17 <i>vs</i> 7.5 (NS)	0 <i>vs</i> 0	7.0 <i>vs</i> 7.0 (NS)
Junfeng <i>et al</i> ^[24]	RAG <i>vs</i> LAG	I - II - III	120	394	-	234.8 <i>vs</i> 221.3 (RAG > LAG) ³	118.3 <i>vs</i> 137.6 (RAG < LAG) ³	34.6 <i>vs</i> 32.7 (RAG > LAG) ³	5.8 <i>vs</i> 4.3 (NS)	NR	7.8 <i>vs</i> 7.9 (NS)
Seo <i>et al</i> ^[47]	RAG <i>vs</i> LAG	I - II - III	40	40	-	243 <i>vs</i> 224 (NS)	76 <i>vs</i> 227 (RAG < LAG) ³	40.4 <i>vs</i> 35.4 (NS)	NR	NR	6.75 <i>vs</i> 7.37 (RAG < LAG) ³
Shen <i>et al</i> ^[48]	RAG <i>vs</i> LAG	I - II - III	93	330	-	257.1 <i>vs</i> 226.2 (RAG > LAG) ³	176.6 <i>vs</i> 212.5 (RAG < LAG) ³	33.0 <i>vs</i> 31.3 (RAG > LAG) ³	9.8 <i>vs</i> 10.0 (NS)	NR	9.4 <i>vs</i> 10.6 (NS)
Suda <i>et al</i> ^[49]	RAG <i>vs</i> LAG	All stages	88	438	-	381 <i>vs</i> 361 (RAG > LAG) ³	46 <i>vs</i> 34 (RAG > LAG) ³	40 <i>vs</i> 38 (NS)	2.3 <i>vs</i> 11.4 (RAG < LAG) ³	1.1 <i>vs</i> 0.2 (NS)	14 <i>vs</i> 15 (RAG < LAG) ³
Kim <i>et al</i> ^[50]	RAG <i>vs</i> LAG	I - II - III	223	211	-	226 <i>vs</i> 180 (RAG > LAG) ³	50 <i>vs</i> 60 (NS)	33 <i>vs</i> 32 (NS)	13.5 <i>vs</i> 14.2 (NS)	0 <i>vs</i> 0	7.8 <i>vs</i> 7.9 (NS)

¹Mean value; ²The authors compared 20 gastric cancer patients who underwent robotic gastrectomy with 20 initial patients who underwent laparoscopic subtotal gastrectomy (iLAG) and 20 recent laparoscopic subtotal gastrectomy performed during the same period as the 20 robotic gastrectomy (rLAG); ³Difference statistically significant, *P* < 0.05; ⁴Major complications rate base on Clavien-Dindo classification ≥ 3, such as anastomotic and duodenal leakage. RAG: Robot-assisted laparoscopic gastrectomy; LAG: Laparoscopic assisted gastrectomy; OG: Open gastrectomy; NR: Not reported; NS: Not statistically significant difference.

comparative analysis. Thus, the usefulness of these articles is essentially of scientific expounding and debating, they do not add any new knowledge to that so far evidenced by clinical studies.

On the other hand, 9 meta-analyses^[20,56-63] conducted using a systematic method have been published to date in literature trying to focus on RAG utility in treating

gastric cancer (Table 3). One meta-analysis included certain reports which compared RAG to OG^[57]; 5 meta-analyses utilized high quality studies which compared RAG and LG^[56,59-61,63], and the remaining 3 meta-analyses contained a systematic review and meta-analysis of studies investigating short-term results of RAG vs LG and OG^[20,58,62]. Exclusively prospective and retrospective

Table 3 Meta-analysis comparing robot-assisted gastrectomy with laparoscopic assisted gastrectomy and/or open gastrectomy in the treatment gastric cancer

Ref.	Subject	Patients (n)			Operation time (min) ¹	Blood loss (mL) ¹	Harvested nodes (n) ¹	Morbidity (%)	Mortality (%)	Hospital stay (d) ¹
		RAG	LAG	OG						
Xiong <i>et al</i> ^[56]	RAG vs LAG	268	650	-	68.77 ² (RAG > LAG) ³	-41.88 ² (RAG < LAG) ³	-0.71 ² (NS)	0.74 ⁴ (NS)	1.80 ⁴ (NS)	-0.54 ² (NS)
Liao <i>et al</i> ^[57]	RAG vs OG	520	-	5260	65.73 ² (RAG > LAG) ³	-126.08 ² (RAG < LAG) ³	-0.78 ² (NS)	0.98 ⁴ (NS)	0.98 ⁴ (NS)	-2.87 ² (RAG < LAG) ³
Hyun <i>et al</i> ^[58]	RAG vs LAG	634	1236	-	61.99 ² (RAG > LAG) ³	-6.08 ² (NS)	-0.25 ² (NS)	1.12 ⁴ (NS)	NR	-0.60 ² (NS)
	RAG vs OG	558	-	5301	65.73 ² (RAG > OG) ³	-154.18 ² (RAG < OG) ³	-1.13 ² (NS)	1.37 ⁴ (NS)	NR	-2.18 ² (RAG < OG) ³
Marano <i>et al</i> ^[20]	RAG vs OG	404	-	718	95.83 ² (RAG > OG) ³	-225.58 ² (NS)	-2.68 ² (NS)	0.93 ⁴ (NS)	NR	-2.92 ² (RAG < OG) ³
	RAG vs LAG	404	845	-	63.70 ² (RAG > LAG) ³	-35.53 ² (RAG < LAG) ³	0.50 ² (NS)	0.87 ⁴ (NS)	NR	-0.60 ² (NS)
Xiong <i>et al</i> ^[59]	RAG vs LAG	736	1759	-	48.64 ² (RAG > LAG) ³	-33.56 ² (RAG < LAG) ³	1.28 ² (NS)	1.13 ⁴ (NS)	1.66 ⁴ (NS)	-1.16 ² (NS)
Liao <i>et al</i> ^[60]	RAG vs LAG	762	1473	-	50.0 ² (RAG > LAG) ³	-46.97 ² (RAG < LAG) ³	1.61 ² (NS)	0.88 ⁴ (NS)	0.45 ⁴ (NS)	-0.5 ² (NS)
Shen <i>et al</i> ^[61]	RAG vs LAG	506	1369	-	48.46 ² (RAG > LAG) ³	-38.43 ² (RAG < LAG) ³	1.06 ² (NS)	0.95 ⁴ (NS)	NR	-1.0 ² (NS)
Zong <i>et al</i> ^[62]	RAG vs OG	481	-	4674	68.47 ² (RAG > OG) ³	-106.63 ² (RAG < OG) ³	-0.78 ² (NS)	0.92 ⁴ (NS)	0.72 ⁴ (NS)	-2.49 ² (RAG < OG) ³
	RAG vs LAG	997	2207	-	57.15 ² (RAG > LAG) ³	-28.59 ² (NS)	-0.63 ² (NS)	1.06 ⁴ (NS)	1.05 ⁴ (NS)	-0.16 ² (NS)
Chuan <i>et al</i> ^[63]	RAG vs LAG	551	1245	-	42.9 ² (RAG > LAG) ³	-16.07 ² (RAG < LAG) ³	2.45 ² (NS)	1.05 ⁴ (NS)	NR	-1.98 ² (RAG < LAG) ³

¹Mean value; ²Weighted mean difference; ³Difference statistically significant, $P < 0.05$; ⁴Odds ratio. RAG: Robot-assisted laparoscopic gastrectomy; LAG: Laparoscopic assisted gastrectomy; OG: Open gastrectomy; NR: Not reported; NS: Not statistically significant difference.

studies were included in these meta-analysis, while no randomized controlled trials (RCTs) were found. The aforementioned meta-analysis showed that the RAG short-term clinical results were basically to be compared to LG and OG results. In terms of bleeding in particular, RAG was superior to both LG and OG, in spite of longer operation time. In addition RAG and LG groups did not show differences with regards to the number of harvested lymph nodes and conversion to open rates; RAG comported slightly inferior hospital stay or similar to that for LAG, but much less than OG; complications occurring after the operation were similar for all three operating methods.

Robotic surgery lasts longer mainly because of the additional set-up and docking-time necessary for the robotic system. However, it must be said that operating time noticeably diminished as surgical experience in robotic gastrectomy increased^[9,32,46]. Moreover, there are major limits to how these meta-analysis are interpreted. All data came from non-randomized controlled trials, and the included studies are essentially limited in number and with small sample sizes. Moreover, significant heterogeneity exists among the included studies deriving from several factors, such as different surgeon skill levels, different types of gastrectomy, different extent of lymph node dissection, different tumour stage, different rate of adjuvant treatment, and different protocols of post-operative management and discharge of patients. Thus, the overall level of clinical evidence of this pooled data was low and, since there have been no randomized comparative studies, even if a meta-analysis is

performed, it seems difficult to reach a clear conclusion.

Long term outcome

At the present time, long-term benefits of RAG for the treatment of gastric cancer are under reported in literature. Pugliese *et al*^[26] are among the few who have reported long term results in their minimally invasive surgical experience in gastric cancer patients. Among a cohort-case study of 70 patients who underwent minimally invasive subtotal gastrectomy with D2 lymphadenectomy, the authors included also 18 patients submitted to the robotic procedure. The authors did not provide data specifically referred to the robotic group only, however, always on the basis of analogous short-term results between groups undergoing laparoscopic and robotic procedures, the reported 5-year survival was 81% for the whole cohort. Coratti *et al*^[33] were the first to report long-term survival data specifically referring to gastric cancer patients submitted to robot-assisted gastrectomies. They analyzed survival results in a group of 98 patients with either early and advanced gastric cancer submitted to RAG. In a mean follow-up of 46.9 mo, they registered a cumulative 5-year survival rate of 73.3%. Son *et al*^[45] carried out the longest follow-up study till now available. They evaluated the survival rates in a cohort-study group of 51 gastric cancer patients submitted to robotic total gastrectomy with D2 lymph nodes dissection and compared it to 58 patients who underwent analogous surgery but through the laparoscopic approach. In a median long-term follow-up of 70 mo, the authors did not find significant differences

in overall survival and disease-free survival between the two groups. Specifically, the authors reported a 5-year overall survival rate of 89.5% for the robotic group, which was not statistically significant different with respect to the rate revealed in the laparoscopic group (91.1%).

The aforementioned results are comforting, but it must be said that the case studies were limited, and selection bias is a real worry as it was a non-randomized study design. Follow-up periods longer than 5 years are needed to show oncological results, and so further RCTs are required in order to validate definitive conclusions.

DISCUSSION

The relative new technological advance in surgery through the introduction of minimally invasive technique can be accepted as an alternative to open surgery, which usually confers better short-term post-operative results, only if the oncologic parameters are as sufficiently respected as for the traditional open approach. Obviously, at the same time the long-term survival rates should not be adversely affected either.

With specific reference to gastric cancer one of the most important oncological criterion is the quality of lymphadenectomy, thus in order for laparoscopic or robot-assisted laparoscopic gastric surgery to be considered adequate, at least the same extent of lymph node dissection as in traditional surgery should be achieved, and moreover favorable postoperative results should also be evident.

Over the last two decades LG with lymph node dissection has developed as minimally invasive surgery for gastric cancer and it has been principally applied to early gastric cancer. Certain RCTs and meta-analysis showed that laparoscopic gastrectomy did not have inferior oncologic results compared to open surgery for early-stage gastric cancer, with instead improved results in the short term^[3,64,65]. In fact, laparoscopic extended D1 lymphadenectomy may be seen as sufficient for almost all early gastric cancer in which lymph node metastases rarely occur, and is today the recommended approach in the East. On the other hand, only few high quality reports investigating the oncological adequacy of laparoscopic minimally invasive techniques for advanced gastric cancer are available to date. Recently, some meta-analyses related to this have been published, but there have been contrasting outcomes, particularly regarding complications after total gastrectomy and the actual adequacy of D2 lymphadenectomy in patients affected by advanced-stage of gastric cancer^[4,64,66-69]. Even though a complete LG and extended lymph nodes dissection has been demonstrated by several experts to be feasible laparoscopically^[5,6,26,70], due to some intrinsic limiting drawbacks of the laparoscopic technique, important oncologic preoccupations have been raised. When in the meta-analysis studies data not restricted to LADG solely for early gastric cancer was considered, but instead included advanced-stage tumour too, it was not possible to guarantee the same amount of lymph node dissection

as in conventional surgical procedures^[71,72]. Thus, the laparoscopic techniques cannot be considered a standard validated procedure for all gastric cancer sufferers.

Certain inherent drawbacks of conventional laparoscopy may be eliminated by robotics by increasing the use of minimally invasive procedures, especially when more extended lymph nodes dissection and complicated reconstruction are required. In light of this, the introduction of robotic technologies could lead to the improvement of health care and final results. Particularly during typical difficult maneuvers in laparoscopy, such as the dissection of the lymphatic tissue around major abdominal vessels (gastric, gastroepiploic, common hepatic, and celiac artery lymph nodes), robotics offers some indisputable advantages, which make it possible to perform the dissection more safely and easily. Consequently, robotic techniques should be viewed more as a technical advancement and auxiliary tool of the traditional minimally invasive laparoscopic approach, rather than an independent device system.

Most surgeons who are experts in robotics reported in their experience amounts of retrieved lymph nodes during RAG similar to those obtainable by the classic open counterpart procedure and sometimes more than those achieved by laparoscopy^[8,20,38,56-63]. However, it must be said that the explanation of available comparable data among RAG, LG and OG has notable limitations. The principal issue that could affect the interpretation of these data is essentially the lack of a comprehensive comparative RCT. However, we have also to consider that the number of published high quality observational and retrospective studies is limited, and globally the sample sizes in each singular trial is poor. Ultimately, but not less importantly from the point of view of oncological adequacy, the duration of follow up is almost always limited.

CONCLUSION

RAG appears to be a safe and feasible alternative to conventional open or laparoscopic gastrectomy for the treatment of early stage gastric carcinoma, having demonstrated satisfactory perioperative outcomes and oncological adequacy. The number of collected lymph nodes when comparing RAG to open and laparoscopic gastrectomy are essentially similar when considering early-stage gastric cancer only, while an advantageous lower blood loss estimation was revealed in comparison with the other two approaches.

Basically the robotic system simplifies certain hard conventional laparoscopy techniques and renders them safer, in addition simultaneously possessing a learning curve and reproducibility that appear to be briefer than conventional laparoscopy^[11-14]. These results, albeit initial, are promising, but the superiority of robotic gastric surgery over the traditional laparoscopic approach has not yet been solidly proved and its validation is still a long way off for all gastric cancer patients. The main controversial issue regards the possibility of

demonstrating that the supposed superiority of RAG with respect to laparoscopy in carrying out a more adequate extended lymphadenectomy could lead to potential oncological benefit, probably true in gastric cancer of a more advanced stage.

Unfortunately, due to inadequate long-term follow-up results and a limited number of studies to date available, larger and randomized prospective trials are required to draw definitive conclusion.

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