

Robotic gastrectomy for gastric cancer

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Abstract: The number of robotic gastrectomy (RG) performed per year has been increasing, particularly in East Asia where the incidence of gastric cancer is high and approximately half of the cases are diagnosed as early gastric cancer. With articulated devices of RG, surgeons are able to perform every procedure more meticulously, which can result in less bleeding and damage to organs. There are many single arm and comparative studies, and these study showed similar trends, which included relatively less estimated blood loss and longer operation time following RG than laparoscopic gastrectomy (LG), equivalent number of harvested lymph nodes and similar length of postoperative hospital stay between RG and LG. Considering the results of these retrospective comparative studies, RG seems to be as feasible as LG in terms of early surgical outcomes. However, medical expense of RG is approximately twice as much as that of LG. Lack of solid evidence in terms of long-term outcomes is another problem. Considering the higher medical expenses associated with RG, its superiority in terms of long-term survival outcomes needs to be confirmed in the future for it to be accepted more widely.

Keywords: daVinci; stomach cancer; minimal invasive surgery; laparoscopic surgery

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Introduction

Since the first case of laparoscopic gastrectomy (LG) was reported in 1994, it has been increasingly performed all over the world (1). Many potential benefits of the procedure, such as less bleeding, early recovery, and good cosmetic results, compared with conventional open gastrectomy (OG) have been reported, and the safety of the procedure was confirmed by randomized trials conducted in Asia (2-8). Equivalent long-term survival outcomes in patients with early gastric cancer were also reported in a randomized control trial (9). Consequently, LG is generally regarded as one of the standard treatments for early gastric cancer, and it is expected that the indications for LG will expand further to advanced gastric cancer (10).

However, LG has several drawbacks. Limitation in the movement range of forceps and the two-dimensional surgical view available to operating surgeons in LG, though

recent technological advancements have facilitated this to some degree, have been serious shortcomings of the procedure. Robotic gastrectomy (RG) may enable us to overcome these shortcomings.

Using the da Vinci[®] Surgical System (Intuitive Surgical, Sunnyvale, CA, USA), surgeons were able to attain a three-dimensional surgical view, instrument flexibility, tremor suppression, and improved ergonomics (11-14). The number of RG performed per year has been increasing, particularly in East Asia where the incidence of gastric cancer is high and approximately half of the cases are diagnosed as early gastric cancer. In this paper, we reviewed the literature about RG for gastric cancer to confirm the current standpoint and assess future perspectives.

Absolute benefit of RG over LG

Both RG and LG are generally classified as minimally

invasive surgeries (MIS) and the surgical procedure itself is quite similar between them. The largest and most important difference is that articulated devices are only available in RG. With articulated devices, surgeons are able to perform every procedure more meticulously, which can result in less bleeding and damage to organs. The tremor suppression function is also helpful to keep a stable surgical field and effective to reduce organ injury. Another advantage of RG is its fine three-dimensional image. Although a three-dimensional image has become available in LG with special equipment, it is not yet commonly used. Articulated devices and three-dimensional images are a potential benefit of RG and could facilitate each procedure dramatically, particularly such difficult procedures as hand suturing in deep surgical fields and extensive lymphadenectomy.

Single arm studies

There are many single arm retrospective and prospective cohort studies, mostly from Asia and Italy (*Table 1*). Among them, Park *et al.* included the largest number with 200 patients, which included their initial cases (25). The aim of most retrospective single-arm studies was to confirm the safety of RG by evaluating early surgical outcomes, such as morbidity and mortality rate, estimated intraoperative blood loss, and operation time. Although the morbidity rate ranged widely from 0% to 41.1%, probably due to the limited number of cases in each study and different indications for RG among studies, most authors concluded that RG is feasible in terms of safety. The mortality rates were quite low, with less than 1% mortality reported in most series.

Some novel approaches were reported. Zhang *et al.* reported transvaginal specimen extraction after RG (31). He reported eight successful cases, and this procedure will lead to much better cosmetic results although it should be evaluated in the future with a larger number of patients. Other unique reports include RG with near-infrared fluorescence imaging, and comparison between RG with and without ultrasonic shears (29,34).

Although single arm studies are informative and very important in the early development stage of new procedures, the feasibility of RG has already been reported in a number of case series. This feasibility should be confirmed by comparative studies, ideally by prospective randomized trials, for RG to be accepted widely.

Retrospective comparative studies

Quite a few comparative studies exist, and most are from Asian countries (*Table S1*). Although the number of RGs in each study is limited, Kim *et al.* featured the largest number of cases, which included 4,542 OG, 881 LG, and 436 RG (36). As in retrospective single arm studies, authors generally evaluated early surgical outcomes between the groups, including surgical morbidity and mortality, estimated blood loss, operation time, the number of harvested lymph nodes, and postoperative hospital stay.

Although some reported a lower incidence of postoperative morbidity in RG, it was equivalent between the groups in most reports, and mortality rates were not significantly different in any of the reports. Among the studies, similar trends were observed, which included relatively less estimated blood loss and longer operation time following RG than LG, equivalent number of harvested lymph nodes and similar length of postoperative hospital stay between RG and LG. Considering the results of these retrospective comparative studies, RG seems to be as feasible as LG and OG in terms of early surgical outcomes, but the comparability of the procedures is still uncertain, and selection bias might have affected results. To eliminate probable selection biases, Han *et al.* selected patients by propensity score matching, and compared surgical outcomes between laparoscopic and robotic pylorus preserving gastrectomies (37). They found that robotic procedures took approximately one extra hour compared with the laparoscopic approach, but other parameters such as postoperative hospital stay, surgical morbidity and mortality were not significantly different.

Although equivalent surgical outcomes have been reported, superiority of the robotic approach to other approaches was rarely shown in retrospective studies. Some reported the potential benefit of RG in more complicated procedures such as total gastrectomy. Park *et al.* reported the potential benefit of RG for patients undergoing TG with D2 lymphadenectomy (38). Son *et al.* compared surgical outcomes between 58 patients undergoing laparoscopic and 51 patients undergoing robotic spleen preserving D2 total gastrectomy, and found almost equivalent surgical outcomes with higher numbers of retrieved lymph nodes along the splenic artery after robotic surgery (39). Surgery for obese patients requires a more sophisticated approach and RG could be beneficial, but the potential benefit of RG for

Table 1 Single arm studies

First author	Year	Country	No. of patients	Morbidity rate (%)	Mortality rate (%)	Blood loss (mg)	Operation time (minutes)	No. of retrieved lymph nodes	Hospital stay (days)	Follow-up period (months)	3-year OS (%)	5-year OS (%)
Anderson (15)	2007	America	7	14	0	300*	420*	24*	4*	10*	-	-
Patrioti (16)	2008	Italy	13	46	0	103**	286**	-	11**	2**	-	-
Pugliese (17)	2008	Italy	17	6	6	90**	352**	26**	10**	14*	-	-
Song (11)	2009	Korea	100	13	1	128**	231**	37**	8**	-	-	-
D'Annibale (18)	2011	Italy	24	8	0	30*	268*	28*	6*	48*	-	-
Isogaki (19)	2011	Japan	61	4	2	62; 150**	388; 520**	42; 43**	-	-	-	-
Lee (20)	2011	Korea	12	8	0	135**	253**	46**	7**	-	-	-
Patrioti (21)	2011	Italy	17	41	0	279**	327**	28**	-	20**	-	-
Park (22)	2012	Korea	60	10	0	-	247**	-	-	-	-	-
Kim (23)	2013	Korea	12	0	0	46**	235**	42**	6**	-	-	-
Liu (24)	2013	China	110	11	0	81**	271**	23**	6**	-	-	-
Park (25)	2013	Korea	200	10	1	146**	249**	38**	8**	-	-	-
Park (26)	2014	Korea	30	17	0	-	218*	34*	7*	-	-	-
Coratti (27)	2015	Italy	98	12	4	105**	296**	-	7*	47**	-	73.3
Harrison (28)	2015	America	62	11	4	-	230; 302*	19; 29*	6, 11*	-	-	-
Kakeji (29)	2015	Japan	10	20	0	63*	274*	-	11*	-	-	-
Parisi (30)	2015	Italy	22	0	0	200*	270*	19*	6*	-	-	-
Zhang (31)	2015	China	8	0	0	63**	224**	24**	4**	-	-	-
Zhou (32)	2015	China	105	5	-	120**	237**	34**	8**	-	-	-
Barchi (33)	2016	Brazil	6	-	0	-	408**	40**	-	-	-	-
Herrera-Almarino (34)	2016	America	31	5	-	88*	221*	29*	-	-	-	-
Quijano (35)	2016	Spain	17	24	0	400*	498*	21*	14*	-	-	-

*, median; **, mean.

these patients is still controversial (38,40).

Seo *et al.* paid special attention to the superiority of RG in terms of the incidence of postoperative pancreas fistula, and reported a lower incidence of postoperative pancreas fistula in RG than LG (41). Their multivariable analysis also identified the robotic approach as being associated with a lower incidence of POPF compared to the laparoscopic approach, indicating that meticulous procedures with articulated devices could reduce pancreas damage during lymph node dissection of the suprapancreatic area.

Okumura *et al.* compared short and long term survival outcomes of elderly patients undergoing RG and LG, and found no significant difference between the groups (42). The feasibility of RG for elderly patients is also important for future widespread adoption of this procedure, considering the increasing expected age of the general population.

Apparently, articulated devices with tremor suppression function facilitate surgeries from the surgeons' viewpoint, but it is a different question whether RG is actually beneficial for patients, and this needs to be clarified. Only marginal differences favoring RG over LG were shown in some retrospective comparative studies, and superiority needs to be confirmed by well designed comparative studies for RG to be accepted more widely.

Prospective studies

The number of prospective studies is extremely limited so far. Tokunaga *et al.* reported results of early and late phase II studies, in which 20 and 123 patients were included, respectively, and the incidence of intra-abdominal infectious complication was set as a primary endpoint (43,44). In their early phase II study, the incidence of intra-abdominal infectious complication was 0%, and it was 3.3% in their late phase II study. In both studies, the null hypothesis was rejected, and it was concluded that RG is a feasible procedure in terms of safety.

In Korea, a prospective non-randomized comparative study was conducted (45). In the study, a total of 423 patients selected either RG or LG after they received a comprehensive explanation of each procedure, and were matched according to surgeon, extent of gastric resection, and sex. Per-protocol analysis (185 patients in each group) showed similar early surgical outcomes including morbidity and mortality rate, except for longer operation time in the RG group. They also reported significantly higher total cost in the RG group (US\$13,432) than the LG group

(US\$8,090). Park *et al.* conducted a subset analyses of this study, and found that RG may be beneficial for patients undergoing D2 lymphadenectomy, although they failed to show the benefit of RG in patients undergoing total gastrectomy or those with obesity (46).

The results of a single-center prospective randomized trial were reported by Wang *et al.* (47) They randomized a total of 311 patients to either open (n=153) or robotic (n=158) gastrectomy groups by the envelope method. They showed similar complication rates between the groups, and less estimated blood loss, longer duration of surgery, and shorter postoperative hospital stay in the robotic group than open group.

Learning curve

Many surgeons have focused on the learning curve effects in RG, and hypothesized that less experience would be necessary to reach the plateau of the learning curve in RG than in LG (22,25,32,48-52). Kim *et al.* compared the learning curve effect in RG and LG, and reported that experience with LG could affect the learning process in RG (49). Provided that an experienced laparoscopic surgeon begins RG, fewer cases of RG are necessary to reach steady status, and satisfactory surgical outcomes could be obtained.

Quality of life assessment

Park *et al.* assessed chronological change in health-related quality of life (HRQOL) after RG using the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire (QTC-C30) and the gastric cancer-specific module (QLQ-STO22). They compared the HRQOL of patients undergoing RG with that of the general population. Although immediate deterioration of HRQOL after RG was shown, it recovered to baseline level within 3 months and was maintained for at least 1 year (26).

Cost analysis

Because RG requires an expensive machine and devices, cost effectiveness is another intriguing issue for surgeons. In Korea and Japan, where more than half of reports have been published, the cost for RG is not reimbursed by the governments so far, and therefore patients or hospitals have to pay additional fees (53). This is a possible reason

why randomized trials have not been conducted in either country.

Although the number of reports is limited, some compared medical expenses between RG and LG, and reported that RG required approximately twice as much medical expense as LG (48,54-56). It is expected that medical expenses associated with RG will decrease in the future.

Oncological outcomes

Although most reports in the literature have focused on early surgical outcomes, some have investigated long-term oncological outcomes after RG, and compared them with those of LG. Equivalent oncological outcomes have been reported, although selection bias must be taken into account and comparability assessed carefully. Median follow-up periods in RG studies have been relatively short, except for several Korean series with 5-year or longer median follow-ups (39,40,42), and we cannot obtain any conclusive results from these retrospective studies in terms of oncological long-term outcomes of RG. The Korean prospective comparative study may shed light on this issue, although it is not a randomized trial (45). Considering the total medical expense of RG, long-term outcomes need to be better than those of LG, and should be confirmed by future prospective trials.

Discussion

So far, there has been no multicenter randomized controlled trial investigating the feasibility of RG. It seems to be safer than or as safe as LG, considering the results of studies included in this review, although its oncological safety is not confirmed and this should be clarified in the future.

Even if RG is actually safer than LG, it is an expensive procedure, and this issue should be resolved for RG to be accepted as a standard treatment in the future (45,48,54-56). Considering the extremely high cost required for RG, a marginal benefit in early surgical outcomes would not be enough. Instead, clearly better early or long-term survival outcomes would be necessary to outweigh the cost issue. The other likely scenario, which is more plausible, is that the advancement of technology will offer us a more reasonably priced robotic system. With a cost-effective system, a marginal benefit in early surgical outcomes might be enough for RG to be accepted as one of the standard treatment options.

Lack of evidence in terms of oncological safety is another problem for RG. Although some have reported feasible long-term survival after RG, the number of patients in each series is too small to obtain any conclusive results (39,40,42). In addition, because survival data is available only from retrospective studies, potential bias could not be eliminated. Surgeons should think about this issue more seriously when they operate on patients with advanced gastric cancer.

Current standard treatment for advanced gastric cancer is D2 gastrectomy followed by adjuvant chemotherapy in Asia, and perioperative chemotherapy with D2 gastrectomy in Europe (57-60). Therefore, a surgical procedure with less postoperative morbidity is very important in order to start adjuvant chemotherapy without delay. If it is true that the incidence of postoperative complication is lower after RG than LG thanks to more meticulous procedures with articulated forceps, patients receiving RG might be able to receive adjuvant chemotherapy earlier and dose intensity might be higher, possibly resulting in improved long-term survival. In addition, considering the recently reported relationship between severe intra-abdominal infectious complication and poor long-term survival, RG could improve long-term survival by reducing postoperative complications (61,62).

In summary, there are a number of reports showing the feasibility of RG by either single arm or comparative studies. However, there is no solid evidence for RG due to the lack of multicenter randomized clinical trials. Considering the higher medical expenses associated with RG, its superiority in terms of long-term survival outcomes needs to be confirmed in the future for it to be accepted more widely.

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Footnote

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Table S1 Comparative studies

First author	Year	Country	Approach	Number of patients	Morbidity rate (%)	Mortality rate (%)	Blood loss (mg)	Operation time (minutes)	Number of retrieved lymph nodes	Hospital stay (days)	Follow-up period (months)	5-year OS (%)	5-year DFS (%)
Song (12)	2009	Korea	LDG (early) vs. RDG	20 vs. 20	5 vs. 5	0 vs. 0	–	290 vs. 203**	32 vs. 35**	8 vs. 6**	–	–	–
			LDG (later) vs. RDG	20 vs. 20	10 vs. 5	0 vs. 0	40 vs. 94**	134 vs. 203**	43 vs. 35**	6 vs. 6**	–	–	–
Kim (63)	2010	Korea	ODG vs. LDG vs. RDG	12 vs. 11 vs. 16	17 vs. 9 vs. 13	0 vs. 0 vs. 0	79 vs. 45 vs. 30**	127 vs. 204 vs. 259**	43 vs. 37 vs. 41**	7 vs. 7 vs. 5**	–	–	–
Caruso (64)	2011	Italy	OG vs. RG	120 vs. 29	43 vs. 41	3.3 vs. 0	386 vs. 198**	222 vs. 290**	32 vs. 28**	13 vs. 10**	–	–	–
Woo (65)	2011	Korea	LG vs. RG	591 vs. 236	14 vs. 11	0.3 vs. 0.4	148 vs. 92**	171 vs. 220**	14 vs. 15**	7 vs. 8**	–	–	–
Eom (54)	2012	Korea	LDG vs. RDG	62 vs. 30	7 vs. 13	0 vs. 0	88 vs. 153**	189 vs. 229**	33 vs. 30**	8 vs. 8**	–	–	–
Huang (66)	2012	Korea	OG vs. LG vs. RG	586 vs. 64 vs. 39	15 vs. 16 vs. 15	1.4 vs. 1.6 vs. 2.6	400 vs. 100 vs. 50**	320 vs. 350 vs. 430**	26 vs. 34 vs. 32**	12 vs. 11 vs. 7**	–	–	–
Kim (36)	2012	Korea	OG vs. LG vs. RG	4542 vs. 861 vs. 436	11 vs. 9 vs. 10	0.5 vs. 0.3 vs. 0.5	192 vs. 112 vs. 85**	158 vs. 176 vs. 226**	41 vs. 38 vs. 40**	10 vs. 8 vs. 8**	–	–	–
Park (55)	2012	Korea	LDG vs. RDG	120 vs. 30	8 vs. 17	0 vs. 0	60 vs. 75*	140 vs. 218*	34 vs. 35**	7 vs. 7**	–	–	–
Uyama (50)	2012	Japan	LDG vs. RDG	25 vs. 225	11 vs. 17	0 vs. 0	81 vs. 52**	345 vs. 361**	–	17 vs. 12**	–	–	–
Yoon (67)	2012	Korea	LTG vs. RTG	65 vs. 36	15 vs. 17	0 vs. 0	–	210 vs. 306**	39 vs. 43**	10 vs. 9**	–	–	–
Hyun (68)	2013	Korea	LG vs. RG	83 vs. 38	39 vs. 47	0 vs. 0	131 vs. 131**	220 vs. 234**	33 vs. 33**	12 vs. 11**	–	–	–
Huang (48)	2014	Taiwan	LG vs. RG	73 vs. 35	8 vs. 13	1.4 vs. 1.4	116 vs. 80**	330 vs. 358**	18 vs. 31**	13 vs. 11**	–	–	–
Junfeng (69)	2014	America	LG vs. RG	394 vs. 120	4 vs. 6	–	138 vs. 118**	221 vs. 235**	33 vs. 35**	8 vs. 8**	19 vs. 15*	69.9 vs. 67.8 (3-year)	–
Kim (49)	2014	Korea	LDG vs. RDG	481 vs. 172	4 vs. 5	0.6 vs. 0	135 vs. 60**	167 vs. 206**	37 vs. 37**	7 vs. 7**	–	–	–
Noshiro (70)	2014	Japan	LDG vs. RDG	460 vs. 21	10 vs. 10	0 vs. 0	115 vs. 96**	315 vs. 439**	40 vs. 44**	13 vs. 8**	–	–	–
Son (39)	2014	Korea	LTG vs. RTG	58 vs. 51	22 vs. 16	0 vs. 2.0	211 vs. 153**	210 vs. 264**	43 vs. 47**	8 vs. 9**	70*	91.1 vs. 89.5	90.2 vs. 91.2
Han (37)	2015	Korea	LPPG vs. RPPG	69 vs. 68	22 vs. 19	0 vs. 0	–	194 vs. 258**	37 vs. 33**	9 vs. 9**	19 vs. 23*	–	–
Lee (40)	2015	Korea	LDG vs. RDG	267 vs. 133	13 vs. 11	–	87 vs. 47**	171 vs. 218**	40 vs. 41**	7 vs. 6**	75*	N.S.	–
Seo (41)	2015	Korea	LDG vs. RDG	40 vs. 40	30 vs. 28	–	227 vs. 76**	224 vs. 243**	–	7 vs. 7**	–	–	–
Park (38)	2015	Korea	LG vs. RG	622 vs. 148	8 vs. 8	0.5 vs. 0	146 vs. 171**	189 vs. 255**	–	–	–	–	–
Suda (71)	2015	Japan	LG vs. RG	438 vs. 88	11 vs. 2	0.2 vs. 1.1	34 vs. 48*	361 vs. 381*	38 vs. 40*	15 vs. 14*	–	–	–
Cianchi (72)	2016	Italy	LDG vs. RDG	41 vs. 30	12 vs. 13	4.9 vs. 3.3	119 vs. 100**	262 vs. 323**	30 vs. 39**	8 vs. 10**	–	–	–
Kim (73)	2016	Korea	LDG vs. RDG	288 vs. 87	9 vs. 6	0.3 vs. 1.1	–	230 vs. 248**	34 vs. 37**	7 vs. 7**	–	–	–
Nakauchi (53)	2016	Japan	LG vs. RG	437 vs. 84	12 vs. 2	–	33 vs. 44*	361 vs. 378*	38 vs. 40*	15 vs. 14*	42 vs. 41*	88.8 vs. 86.9 (3-year)	86.3 vs. 86.9 (3-year)
Okumura (42)	2016	Korea	OG vs. RG	132 vs. 49	18 vs. 14	0 vs. 0	157 vs. 85**	174 vs. 227**	33 vs. 37**	6 vs. 5*	58*	N.S.	–
Procopiuc (74)	2016	Romania	OG vs. RG	29 vs. 18	28 vs. 22	0 vs. 0	564 vs. 208**	243 vs. 320**	25 vs. 22**	11 vs. 8**	32 vs. 25*	N.S.	–
Shen (75)	2016	China	LG vs. RG	330 vs. 93	10 vs. 10	–	213 vs. 177**	226 vs. 257**	31 vs. 33**	11 vs. 9**	–	–	–
Yang (76)	2017	Korea	OG vs. LG vs. RG	241 vs. 511 vs. 173	25 vs. 12 vs. 5	0.8 vs. 0.4 vs. 0	149 vs. 66 vs. 53**	193 vs. 174 vs. 202**	45 vs. 36 vs. 41**	11 vs. 8 vs. 6**	–	–	–

*, median; **, mean. Bold font with underline indicates P<0.05. LDG, laparoscopic distal gastrectomy; LG, laparoscopic gastrectomy; LTG, laparoscopic total gastrectomy; LPPG, laparoscopic pylorus preserving gastrectomy; RDG, robotic distal gastrectomy; RG, robotic gastrectomy; RTG, robotic total gastrectomy; RPPG, robotic pylorus preserving gastrectomy; ODG, open distal gastrectomy; OG, open gastrectomy.

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