Revising robotic surgery for stomach, potential benefits revised II: prevention of pancreatic fistula

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Abstract: Laparoscopic gastrectomy for gastric cancer has been widely accepted especially in early stages. It reduces postoperative pain, leading to faster recovery and shorter hospital stay, however, laparoscopically enhanced anatomy and improved hemostasis via pneumoperitoneal pressure have not contributed to reduction in early postoperative complications except for wound infection or improvement in long-term outcomes. Since 2009, we have been using robotic radical gastrectomy for operable patients with resectable gastric cancer, and have demonstrated that use of the robot particularly for proximal advanced gastric cancer attenuated early local complications including postoperative pancreatic fistula (POPF), leading to even shorter hospital stay. In this article, we present the current status and future perspectives on POPF following radical gastrectomy for gastric cancer focusing on the role of robotic gastrectomy in its prevention based on our experience and review of the literature.

Keywords: Advanced gastric cancer; laparoscopic gastrectomy; postoperative pancreatic fistula (POPF); robotic gastrectomy

Submitted Oct 06, 2015. Accepted for publication Oct 21, 2015.

doi: 10.3978/j.issn.2224-4778.2015.10.05

View this article at: http://dx.doi.org/10.3978/j.issn.2224-4778.2015.10.05

Introduction

Gastric cancer is the fourth most common malignant tumor and the second leading cause of cancer-related death worldwide (1). Surgical resection remains the only curative treatment option, and regional lymphadenectomy is recommended as part of radical gastrectomy (2). According to the Japanese Classification of Gastric Cancer, D2 gastrectomy is recommended for advanced gastric cancer (AGC) (3); however, D2 lymphadenectomy, especially when combined with splenectomy or pancreaticosplenectomy, has been reported to increase morbidity and mortality (4-7). In particular, postoperative pancreatic fistula (POPF) has been one of the major complications following radical gastrectomy. It sometimes induces lethal complications such as abdominal abscesses, secondary anastomotic leakage, and intra-abdominal hemorrhage (8,9).

Laparoscopic gastrectomy has been increasingly performed mainly for the early gastric cancer (EGC) as a minimally invasive surgical approach that provides significant advantages for short-term outcomes as opposed to open surgical procedures (10-13). We previously reported that laparoscopic approach improved short-term postoperative courses in comparison with open approach even in radical gastrectomy for AGC; however, there still was no significant reduction in postoperative complications, suggesting that reduction in complications by any means, might further improve postoperative courses following minimally invasive gastrectomy (14).

The da Vinci Surgical System (Intuitive, Sunnyvale, California, USA) has been developed to overcome some of the disadvantages of standard minimally invasive surgery (15,16). This robotic system facilitates precise dissection...
in a confined surgical field with impressive dexterity (15,16). Thus, it may be postulated that use of the robot in minimally invasive radical gastrectomy attenuate postoperative complications especially related to surgical manipulation, e.g., POPF (17).

This article provides the updates on POPF following radical gastrectomy for gastric cancer and discusses effectiveness of the use of the robotic system in reducing POPF based on our experience and review of the literature.

Definition, diagnosis, and incidence of POPF following radical gastrectomy

A general definition of pancreatic fistula is an abnormal communication between the pancreatic ductal epithelium and another epithelial surface containing pancreas-derived, enzyme-rich fluid (18). Although the diagnosis of POPF is suspected when the drain amylase level is at least three times as high as the upper normal limit of the serum amylase level on the postoperative day 3, it was comprehensively diagnosed according to not only drain amylase levels, but also changes in the properties of the drain and the clinical, laboratory, and imaging findings including computed tomographic scans (8,9,17,18).

There had been no universally recognized definition of POPF following gastrectomy for gastric cancer until recently (9). Accordingly, different definitions of POPF had been applied in each clinical study, resulting in highly variable rates of POPF ranging from 5.8% to 49.7% (9). To evaluate the incidence and severity of POPF more accurately, the International Study Group on Pancreatic Fistula (ISGPF) definition and Clavien-Dindo (CD) classification have increasingly been used of late (8,9,17,18).

The ISGPF definition, graded primarily on clinical impact, was developed by an international panel of pancreatic surgeons to formulate an acceptable and objective definition of POPF that decreases interobserver variability (18). This definition has been utilized to determine the incidence, severity and treatment outcomes of POPF following gastrectomy since Obama, et al. reported the feasibility of laparoscopic gastrectomy with radical lymphadenectomy for gastric cancer (9,22). POPF is graded according to the ISGPF criteria as follows: grade A, no clinical impact requiring little change in management or deviation from the normal clinical pathway; grade B, requiring a change in management or adjustment in the clinical pathway; grade C, requiring a major change in clinical management or deviation from the normal clinical pathway (18,22).

Clavien-Dindo classification was developed by Clavien and Dindo in 2004 with the aim of presenting an objective, simple, reliable, and reproducible way of reporting negative events after surgery (19,20,23). According to this classification, surgical complications are classified as follows based on the intensity of therapeutic interventions required to treat the complication: grade I, any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions; grade II, requiring pharmacological treatment; grade III, requiring surgical, endoscopic or radiological intervention; grade IV, life-threatening complication requiring IC/ICU management; grade V, death of a patient (19,20). The CD classification may be more advantageous than the ISGPF in terms of the fact that, using CD classification, not only POPF but also any other kind of postoperative complications could be quantitatively determined on the same scale, although the principle of these grading systems are quite similar.

Incidences of POPF following radical gastrectomy determined based on these grading systems are summarized in Table 1.

Therapeutic strategy for POPF following radical gastrectomy in correspondence with its severity

Patients with high drain amylase level and no abnormal physical and laboratory findings are observed without any treatment (ISGPF Grade A, CD Grade I) (17). The abdominal drainage tube is removed basically after the drain amylase level was sufficiently recovered. Patients with high drain amylase level accompanied by abnormal findings such as fever, abdominal pain and high inflammatory markers, are intensively treated with antibiotics, octreotide acetate and parenteral nutrition while the drainage tube position is urgently confirmed using computed tomographic scans and radiographic contrast study (ISGPF Grade B, CD Grade II) (17). When the drainage tube position is not appropriate, an additional or alternative drainage tube is placed into the fluid cavity using percutaneous computed tomography or ultrasonography-guided technique (ISGPF Grade C, CD Grade IIIa), and irrigation and drainage with saline is performed (17). Parenteral nutrition is gradually switched to enteral nutrition without delay, once pancreatic fistula is confined to a certain space and inflammatory response is settled. To be noted, patients requiring only repositioning but not replacement of their drainage tubes
Table 1 Rates of postoperative pancreatic fistula following radical gastrectomy

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Study design</th>
<th>Definition of POPF</th>
<th>Rates of POPF (%)</th>
<th>Total number of enrolled patients</th>
<th>Type of operation (TG or others vs. DG)</th>
<th>Extent of lymph node dissection (D2 vs. non-D2)</th>
<th>Type of approach (open vs. laparoscopic vs. robotic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obama et al. (2011) (22)</td>
<td>Retrospective</td>
<td>ISGPF Grade ≥ B</td>
<td>5.1</td>
<td>233</td>
<td>73:160</td>
<td>141:92</td>
<td>95:138:0</td>
</tr>
<tr>
<td>Tomimaru et al. (2011) (24)</td>
<td>Retrospective</td>
<td>ISGPF Grade ≥ B</td>
<td>9.2</td>
<td>173</td>
<td>173:0</td>
<td>126:47</td>
<td>173:0:0</td>
</tr>
<tr>
<td>Jiang et al. (2012) (25)</td>
<td>Retrospective</td>
<td>ISGPF Grade ≥ B</td>
<td>4.3</td>
<td>798</td>
<td>0:798</td>
<td>90:708</td>
<td>0:798:0</td>
</tr>
<tr>
<td>Komatsu et al. (2013) (9)</td>
<td>Retrospective</td>
<td>ISGPF Grade ≥ B</td>
<td>2.6</td>
<td>1,341</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Yu et al. (2013) (8)</td>
<td>Retrospective</td>
<td>ISGPF Grade ≥ B</td>
<td>3.3</td>
<td>900</td>
<td>197:703</td>
<td>518:382</td>
<td>306:594:0</td>
</tr>
<tr>
<td>Miyai et al. (2013) (26)</td>
<td>Retrospective</td>
<td>ISGPF Grade ≥ B</td>
<td>4.0</td>
<td>277</td>
<td>69:208</td>
<td>132:145</td>
<td>0:277:0</td>
</tr>
<tr>
<td>Kung et al. (2014) (27)</td>
<td>Retrospective</td>
<td>ISGPF Grade ≥ B</td>
<td>11.9</td>
<td>92</td>
<td>64:28</td>
<td>92:0</td>
<td>92:0:0</td>
</tr>
<tr>
<td>Seo et al. (2015) (28)</td>
<td>Retrospective</td>
<td>ISGPF Grade ≥ B</td>
<td>5.0</td>
<td>80</td>
<td>0:80</td>
<td>35:45</td>
<td>0:40:40</td>
</tr>
<tr>
<td>Katai et al. (2010) (29)</td>
<td>Prospective</td>
<td>CTCAE v3.0 Grade ≥ II</td>
<td>1.1</td>
<td>176</td>
<td>34:142</td>
<td>30:146</td>
<td>0:176:0</td>
</tr>
<tr>
<td>Inaki et al. (2015) (30)</td>
<td>Prospective</td>
<td>CTCAE v4.0 Grade ≥ II</td>
<td>3.5</td>
<td>86</td>
<td>0:86</td>
<td>86:0</td>
<td>0:86:0</td>
</tr>
</tbody>
</table>

POPF, postoperative pancreatic fistula; TG, total gastrectomy; DG, distal gastrectomy; ISGPF, International Study Group on Pancreatic Fistula; CD, Clavien-Dindo.
are classified as ISGPF Grade B or CD Grade II (9,31). If these series of conservative treatments were not effective, open drainage and debridement for POPF abscess by laparotomy would be performed and the irrigation type drainage tube and an enteral feeding tube would be placed (ISGPF Grade C, CD Grade ≥ IIIb) (9).

**Etiology and prevention of POPF following radical gastrectomy: use of the robot?**

**Causes and risk factors**

The incidence of POPF has reportedly been associated with greater extent of resection and lymph node dissection, i.e. total gastrectomy, splenectomy, pancreaticosplenectomy, and D2 lymphadenectomy, suggesting that surgical manipulation of the suprapancreatic area and splenic hilum with excessive retraction of pancreatic body may cause pancreatic injury leading to POPF (8,9,17,27). Open gastrectomy, age, male gender, and obesity were also reported as significant risk factors in relation to POPF, however, the cause-effect relationship between these factors and POPF has been unclear (8,25,32).

**Prevention**

It is needless to say that excessive resection and lymph node dissection should be avoided to prevent POPF. Particularly, the practical importance of station ten lymph node dissection and splenectomy in D2 total gastrectomy has been controversial (5-7,10). At present, according to the latest Japanese gastric cancer treatment guidelines 2014 (ver. 4), complete clearance of station 10 nodes by splenectomy should still be considered for potentially curable T2-T4 tumors invading the greater curvature of the upper stomach (3). However, in patients with T2-4/N0-2/M0 gastric cancer not invading the greater curvature, the Japan Clinical Oncology Group (JCOG) 0110 trial demonstrated that prophylactic splenectomy should be avoided to improve operative safety and survival (2,33). In addition to this, no one would argue against the possibility that combination of pancreas-protective operative maneuver and the use of surgical devices which may attenuate tissue damage and make the surgical procedures easier might lower the risk of POPF. The following strategies have been tested so far.

**Evolution of surgical energy devices**

In open and conventional laparoscopic gastrectomy, ultrasonically activated scalpel and/or vessel sealing system have been used over a decade. The tip temperature and the degree of lateral thermal spread of these devices were lower than those of monopolar diathermy (34); however, the incidence of POPF has still been reported as 1.7-22.1% (laparoscopic gastrectomy for EGC, 1.7-7%; open total gastrectomy, 13.0-22.1%) (8). So far there has been no report that clearly determined the effectiveness of these devices in reducing POPF.

**The outermost layer-oriented medial approach**

To improve the safety, efficacy, and reproducibility of suprapancreatic nodal dissection, we developed our original methodology called outermost layer-oriented medial approach (35,36). In this approach, the layer between the autonomic nerve sheaths of the major arteries and the adipose tissue bearing lymphatic tissue is dissected (35,36). Although the chance of intraoperative pancreatic injury could undoubtedly decrease just by keeping the appropriate layer while performing suprapancreatic dissection, POPF occurred in as high as 4.3% of the patients who underwent conventional laparoscopic radical gastrectomy at our institute (17). This might be at least partly because retraction of pancreas, which could potentially traumatize pancreas, was required to create sufficient operative field for conventional laparoscopic approach (8,9,17,22).

**Use of the robot**

According to our previous retrospective cohort study, the use of the robot reduced surgery-related complications including POPF, leading to further improvement in short-term postoperative courses following minimally invasive radical gastrectomy (17). Moreover, the greater the extent of gastric resection and lymphadenectomy, the more effective the use of the robot to reduce postoperative complications and to improve short-term outcomes, suggesting that the best indication for the use of the robot should be radical gastrectomy for AGC accompanied by D2 dissection (17). Strikingly, no POPF took place in the robotic group (17). This might be brought about not only because of the integrity of the robot-specific functions including articulating forceps, natural three-dimensional magnified view with high definition, tremor filtering, and motion scaling, which enables us to conduct suprapancreatic lymph node dissection with little touch on the pancreas, but also because of the outermost layer-oriented medial approach to the suprapancreatic area, and our original setup using da Vinci’s plane and the monitor-quadrisection theories.
In addition, the “double bipolar” method characterized by simultaneous use of Maryland bipolar forceps (bipolar forced coagulation, 420172, Intuitive) with the right hand and Fenestrated bipolar forceps (bipolar soft coagulation, 420205, Intuitive) with the left hand might also facilitate pancreas-protective dissection in robotic gastrectomy (15,17,35). Actually, heat production in bipolar devices was demonstrated to be lower than ultrasonic cutting devices (37).

According to the latest meta-analysis and multi-institutional RCT on the short-term outcomes of robotic vs. conventional laparoscopic gastrectomy, use of the robot significantly increased operative time and cost, whereas there were no significant differences in other short-term outcomes including POPF (21,38). Contribution of robotic gastrectomy to long-term outcomes has yet to be demonstrated (17,21). These results suggested that use of the robot might even deteriorate the cost-effectiveness (38). In other words, the greatest issue around robotic surgery is that clear benefits of the robotic system which justify the longer operative time and higher cost have never been clarified (21). However, apart from our aforementioned previous study in which 43% of the robotic group had pStage II or III diseases (17), most of the patients enrolled in these previous studies had pStage I diseases (21,38). Moreover, Harmonic Scalpel (420275, Intuitive) or monopolar cautery but not the Fenestrated bipolar forceps was used as the principal energy device in these studies. Thus, multi-institutional prospective studies in which considerable number of patients with AGC are enrolled should be required to determine whether use of the robotic system for AGC, notably combined with the double bipolar method, truly attenuates POPF, possibly leading to improvement in long-term outcomes.

In reality, since the beginning of October, 2014, we have been conducting a multi-institutional single-arm prospective study, which Japanese Ministry of Health, Labor, and Welfare has recently approved for Advanced Medical Technology (“senshiniryo”) (Figure 1). This study was designed to determine the impact of the use of the robot, for minimally invasive radical gastrectomy to treat resectable gastric cancer, on short-term outcomes, mainly focusing on postoperative complications, as well as long-term outcomes and cost. The specific hypothesis of the present study was that the use of the robot in patients with cStage I or II diseases reduces the morbidity (CD ≥ III) of 6.4% in conventional laparoscopic gastrectomy down to 3.2%. All the patients will be registered in 2 years and followed up for 3 years, thus the expected study period should be 5 years in total. Interim analyses will be done once the initial 220 cases are registered.

Are there any solutions for longer operative time and higher cost in robotic gastrectomy? To shorten the...
operative time, not only reduction in time for docking, undocking, and exchanging forceps but also prevention of conflict of the robotic arms and forceps are supposed to be essential (17). Use of da Vinci Xi Surgical System may be of some help in this regard. To reduce the cost, competition between rival robots such as Telelap AlF-X (39) as well as efforts of the Intuitive Surgical Inc. to lower the price are desirable.

Conclusions

The use of the robot is assumed to provide a technically superior operative environment for minimally invasive surgery (21). The greatest advantage of the robotic procedure may be the potential that the use of the robot helps lots of surgeons perform technically demanding operations more easily in a less invasive manner (17). As long as POPF has still been an important issue on radical gastrectomy for gastric cancer, further investigation would be warranted to clarify the association between the use of the robot and reduction in POPF.

Acknowledgements

The authors thank Dr. Seiichiro Kanaya for his wonderful contribution to establishing our original method of robotic gastrectomy.

Footnote

Conflicts of Interest: K. Suda and I. Uyama are funded by Intuitive Surgical, Inc. in relation to the aforementioned “senshiniyiro” study. M. Nakauchi, K. Inaba and Y. Ishida have no commercial association with or financial involvement that might pose a conflict of interest in connection with the submitted article.

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