

HOW-I-DO-IT

Surgical technique of suprapancreatic D2 lymphadenectomy focusing on the posterior hepatic plexus for advanced gastric cancer

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Short title: PHP-guided D2 lymphadenectomy

Abstract

Purpose:

Although D2 lymphadenectomy is currently considered a standard procedure for advanced gastric cancer (GC) worldwide, there is room for discussion about the appropriate range of suprapancreatic D2 lymphadenectomy. Focusing on the posterior hepatic plexus (PHP), which is not well recognized, we developed a surgical technique of suprapancreatic D2 lymphadenectomy, which we have called PHP-D2, and its short-term and long-term efficacies were evaluated in comparison with non-PHP-D2.

Methods:

GC patients who underwent distal gastrectomy with D2 lymphadenectomy between July 2006 and May 2013 were enrolled, from which patients who had peritoneal metastasis and/or were peritoneal cytology-positive during surgery were excluded. Their medical records were retrospectively reviewed.

Results:

Ninety-two patients (non-PHP-D2: 48, PHP-D2: 44) were enrolled. Shorter operation time (330 min vs 275min, $p<0.0001$) and less blood loss (290 mL vs 125 mL, $p<0.0001$) were observed in PHP-D2, and no pancreatic fistulas were observed in PHP-D2. More lymph nodes of #11p (1 vs 1.5, $p=0.0328$) and #12a lymph nodes (0 vs 1, $p=0.0034$) were retrieved in PHP-D2, with no significant differences in #8a and #9 lymph nodes. Lymphatic recurrence was significantly less in PHP-D2 ($p=0.0166$), and univariate and multivariate analyses showed that non-PHP-D2 was a significant risk factor for lymphatic recurrence ($p=0.0158$), although there were no significant differences between non-PHP-D2 and PHP-D2 in 5-year overall survival and 5-year relapse-free survival.

Conclusion:

PHP-D2 was a safe and feasible procedure that had the potential to reduce lymphatic recurrence, and it can be a standard procedure of D2 lymphadenectomy for advanced GC.

Keywords

Gastric cancer; D2 lymphadenectomy; Suprapancreatic lymphadenectomy; Posterior hepatic plexus; Distal gastrectomy.

Declarations

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Conflicts of interest: The authors had no conflicts of interest to declare.

Authors' contributions:

- Study conception and design: Shinji Kuroda
- Acquisition of data: Nobuhiko Kanaya, Shinji Kuroda
- Analysis and interpretation of data: Nobuhiko Kanaya, Shinji Kuroda, Yoshihiko Kakiuchi, Sho Takeda
- Drafting of manuscript: Nobuhiko Kanaya, Shinji Kuroda
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Introduction

Gastric cancer (GC), which has the fifth highest incidence and the fourth highest mortality among malignancies, is one of the most common and important malignancies in the world [1]. Lymph node metastasis is a main metastatic pattern alongside hematogenous metastasis and peritoneal dissemination in GC, and tumor size, depth of tumor invasion, lymphatic invasion, vascular invasion, and lymphovascular invasion are reported as risk factors for lymph node metastasis [2]. Surgery is a main treatment strategy for GC alongside endoscopic resection, chemotherapy, radiotherapy, and immunotherapy. Standard gastrectomy is described as resection of at least two-thirds of the stomach with D2 lymphadenectomy in the Japanese gastric cancer guidelines [3], and the efficacy of D2 lymphadenectomy, with lower locoregional recurrence and gastric cancer-related death rates than D1 lymphadenectomy, is currently acknowledged worldwide [4].

Loose connective tissue, called the outermost layer, exists between the autonomic nerve sheaths of the major arteries and the adipose tissue bearing lymphatic tissue, and a method of dissecting along this layer throughout the dissection process is currently established as a standard procedure in gastrectomy [5]. The hepatic plexus is the largest offshoot from the celiac plexus and is composed of the anterior hepatic plexus (AHP) and the posterior hepatic plexus (PHP) [6]. The AHP traveling along the common hepatic artery (CHA) is easy to find and widely recognized as an important landmark to find the outermost layer in suprapancreatic lymphadenectomy [7]. In contrast, the PHP traveling the posterior side of the CHA does not receive much attention in suprapancreatic lymphadenectomy. However, we focus on the PHP as an important landmark for the bottom of lymph node station No. 8a (#8a) or #12a, and we

think that transecting the continuity of #8a and #8p or #12a and #12p at this level is appropriate for D2 lymphadenectomy for advanced GC.

This report presents our surgical technique of suprapancreatic D2 lymphadenectomy for advanced GC focusing on the PHP as a landmark for the depth of lymphadenectomy and the results of a retrospective evaluation of its short-term and long-term efficacies compared with suprapancreatic D2 lymphadenectomy performed without attention to the PHP.

Methods

Patients

The medical records of all patients with GC who underwent distal gastrectomy (DG) with D2 lymphadenectomy between July 2006 and May 2013 at Okayama University Hospital were retrospectively assessed, and patients who were diagnosed with Stage IV after surgery due to peritoneal metastasis (P1) and/or were peritoneal cytology-positive (CY1) were excluded. Since the procedure of suprapancreatic D2 lymphadenectomy focusing on the PHP (PHP-D2) was started in our hospital in October 2010, patients were divided into two groups (non-PHP-D2 and PHP-D2) by that date to evaluate the efficacy of PHP-D2. This study was reviewed and approved by the institutional review board (IRB) of Okayama University Hospital (#2103-047).

Surgical procedure of PHP-D2

We previously reported our standard surgical procedure of laparoscopy-assisted DG with D1+ lymphadenectomy [8]. The main difference between D1+ and D2 is in the extent of suprapancreatic lymphadenectomy, and #11p and #12a are additionally

dissected in D2 lymphadenectomy. Although #8a dissection is included in both D1+ and D2, deeper dissection over the CHA is necessary for appropriate #12a dissection, and we think that the PHP can be an important landmark for setting the bottom of #8a and #12a dissection in D2 lymphadenectomy. Our surgical procedure of PHP-D2, which we recently performed by robotic surgery, is demonstrated in the Supplementary Video. Briefly, after finding the CHA in suprapancreatic lymphadenectomy, outermost layer dissection was continued over the AHP toward the posterior side along the CHA. When the portal vein (PV) was detected behind the CHA and the proper hepatic artery (PHA), the PHP was found as a bundle, attached with dissected lymph node tissue including #8a and #12a, traveling from the right celiac ganglion toward the posterior side of the PV (Fig. 1a). Then, the continuity of #8a and #8p or #12a and #12p was transected along the PHP, which was considered an appropriate depth for D2 lymphadenectomy (Fig. 1b).

Clinical data

Patients' background characteristics included age, sex, and body mass index (BMI). Histological findings such as histological type, lymphatic invasion (ly), venous invasion (v), pathological depth of tumor (pT), pathological lymph node metastasis (pN), and pathological stage (pStage) were described according to the 3rd English edition of the Japanese Classification of Gastric Carcinoma [9]. Surgical findings included approach (open, laparoscopy), operation time, blood loss, presence or absence of a concurrent procedure, reconstruction method (Billroth-I [B-I], Roux-en-Y [RY]), postoperative complications evaluated according to the Clavien-Dindo (CD) classification [10], the length of hospital stay, and the number of retrieved lymph nodes (#8a, #9, #11p, #12a).

Regarding long-term outcomes, overall and relapse-free survivals were examined, and recurrence patterns were classified into three groups: lymphatic, hematogenous, and disseminated.

Statistical analysis

Statistical analysis was conducted using JMP software (version 14; JMP Inc., Chicago, IL, USA). Student's *t*-test was used for the continuous variables of age and BMI. The Wilcoxon signed-rank test was used for the other continuous variables of operation time, blood loss, length of hospital stay, and number of retrieved lymph nodes. Pearson's χ^2 test was used for the categorical variables of sex, histological type, ly, v, pT, pN, pStage, approach, concurrent procedure, reconstruction method, postoperative complications, and recurrence patterns. Overall and relapse-free survivals were evaluated using the Kaplan-Meier method. Univariate and multivariate logistic regression analyses were performed to assess risk factors for lymphatic recurrence. A *p* < 0.05 was considered significant.

Results

Patients' background characteristics and histological findings (Table 1)

A total of 100 patients were first assessed for eligibility, and 92 patients were finally enrolled in this study after exclusion of 8 patients who were diagnosed with Stage IV due to P1 and/or CY1. The non-PHP-D2 and PHP-D2 groups had 48 and 44 patients, respectively (Fig. 2). Whereas there were no significant differences between non-PHP-D2 and PHP-D2 in sex, BMI, histological type, v, pT, pN, and pStage, age was significantly older in PHP-D2 (*p*=0.0174), and ly was significantly higher in PHP-D2

($p=0.0117$).

Surgical outcomes (Table 2)

In terms of surgical approach (open or laparoscopy), laparoscopic gastrectomy with D2 lymphadenectomy for advanced GC was started in our hospital at the same timing when the concept of PHP-D2 was introduced, and both open and laparoscopy were indicated for advanced GC after that. Whereas non-PHP-D2 was performed by open surgery for all 48 patients, PHP-D2 was performed by open surgery for 20 patients and by laparoscopy for 24 patients, none of whom was converted to open surgery ($p<0.0001$). Operation time was significantly longer in non-PHP-D2 than in PHP-D2 (330 min vs 275 min, $p<0.0001$), and blood loss was significantly higher in non-PHP-D2 than in PHP-D2 (290 mL vs 125 mL, $p<0.0001$). Additional procedures such as cholecystectomy and splenectomy were concurrently performed more frequently in non-PHP-D2 than in PHP-D2 (63% vs 27%, $p<0.0001$), which may have affected the results for operation time and blood loss. B-I reconstruction was more frequently selected in non-PHP-D2, and RY reconstruction was more frequently selected in PHP-D2 ($p=0.0002$). Although there was no significant difference in overall postoperative complications (CD any grade) between non-PHP-D2 and PHP-D2 (25% vs 20%, $p=0.6038$), surgery-related major complications such as anastomotic leakage, pancreatic fistula, and abdominal abscess were more common in non-PHP-D2 than in PHP-D2 (4% vs 0%, 4% vs 0%, 8% vs 2%, respectively), resulting in a longer hospital stay in non-PHP-D2 than in PHP-D2 (14.5 days vs 12 days, $p=0.0062$). One patient in PHP-D2 had neoadjuvant chemotherapy, but had no postoperative complication, although higher incidence of postoperative complications after neoadjuvant chemotherapy was reported

[11].

Effect of PHP-D2 on long-term outcomes

As for the number of retrieved lymph nodes from the suprapancreatic region, there were significant differences between non-PHP-D2 and PHP-D2 in #11p (1 vs 1.5, $p=0.0328$) and #12a (0 vs 1, $p=0.0034$), two of which were lymph nodes necessary to be dissected in D2 lymphadenectomy in addition to lymph nodes dissected in D1+

lymphadenectomy, although no significant differences were observed in #8a (2 vs 3, $p=0.2863$) and #9 (2 vs 2, $p=0.2301$) (Fig. 3a). Although there were no significant differences between non-PHP-D2 and PHP-D2 in 5-year overall survival (75% vs 84%, $p=0.5649$) (Fig. 4a) and 5-year relapse-free survival (72% vs 79%, $p=0.2813$) (Fig. 4b), interestingly, there were significant differences in recurrence patterns. A total of 23 patients had recurrence after surgery. When recurrence patterns were classified into 3 categories of lymphatic, hematogenous, and disseminated, and the correlation of the procedures of non-PHP-D2 and PHP-D2 with recurrence patterns was evaluated in 21 patients after exclusion of 2 patients whose recurrence pattern was unknown, lymphatic recurrence, which occurred all around the suprapancreatic or paraaortic regions, was significantly less in PHP-D2 ($p=0.0166$), whereas there were no significant differences in hematogenous ($p=0.3749$) and disseminated recurrence ($p=0.1301$) (Fig. 3b).

Univariate and multivariate analyses showed that non-PHP-D2 was a significant risk factor for lymphatic recurrence ($p=0.0158$), along with histological type (differentiated) ($p=0.0012$) and pN score (≥ 1) ($p=0.0063$) (Table 3). These findings suggested that the surgical procedure of PHP-D2 may have contributed to reduction of postoperative lymphatic recurrence.

Discussion

As the surgical approach of gastrectomy for GC has developed from open to laparoscopic and robotic, the deeper understanding of the anatomy brought by the magnifying effect of laparoscopy and robotic surgery, one example of which is lymph node dissection along the outermost layer of the autonomic nerves, seems to have progressed and improved the surgical quality, even of open surgery. In the present study, the procedure of suprapancreatic D2 lymphadenectomy was introduced, focusing on the PHP, which is not well recognized, originating from the right celiac ganglion and traveling along the posterior side of the CHA, which enables safe and sufficient lymph node dissection for GC. The procedure of PHP-D2 is considered to mainly affect the quality of #8a, #9, and #12a lymphadenectomy, and actually the number of retrieved lymph nodes of #12a was significantly higher in PHP-D2, although no significant differences were observed in #8a and #9. On the other hand, a significant difference was observed in #11p as well, which may have been brought by the improvement of overall surgical technique in suprapancreatic lymphadenectomy. No pancreatic fistulas were observed in PHP-D2, which can be evidence showing the safety and quality of this procedure.

The difference in recurrence patterns between non-PHP-D2 and PHP-D2 is interesting. Lymphatic recurrence in PHP-D2 was significantly less than that in non-PHP-D2, and non-PHP-D2 was a significant risk factor for lymphatic recurrence on univariate and multivariate analyses. Although there were no significant differences between non-PHP-D2 and PHP-D2 in overall and relapse-free survivals, relapse-free survival tended to be better in PHP-D2, which may be due to the procedure of PHP-D2.

As for other risk factors for lymphatic recurrence, differentiated type was a risk factor in this study, although undifferentiated type was often a risk factor for lymph node metastasis in previous reports [12, 13]. Lymphatic invasion is also often reported as a risk factor for lymph node metastasis [2]. Although lymphatic invasion was significantly higher in PHP-D2 in the present study, lymphatic recurrence was significantly reduced in PHP-D2, which may be evidence of the value of PHP-D2.

Though this study provided the above-mentioned interesting evidence, it has several limitations. First, this was a single-center, retrospective study with a limited number of cases. Second, this was a historical comparative study that had a lack of baseline similarities, not only in patients' background characteristics, but also in surgical quality and perioperative treatment including chemotherapy. With regard to surgical quality, there was actually more than the difference between non-PHP-D2 and PHP-D2. Since laparoscopic surgery was performed for advanced GC in addition to early GC in our hospital in the same period when the concept of PHP-D2 was introduced, laparoscopic surgery was performed only for PHP-D2 in this study. Although laparoscopic surgery generally takes more time than open surgery, PHP-D2, which was performed by laparoscopy in more than half of the patients, actually took less time than non-PHP-D2. One of the reasons was that our surgical skill was improved by the introduction of PHP-D2 although it would be another reason that prophylactic cholecystectomy during gastrectomy had not been performed routinely in the period of PHP-D2.

In the present study, our surgical technique of PHP-D2 was introduced, and this procedure was shown to be safe and feasible and, moreover, had the potential to reduce lymphatic recurrence after surgery. The quality of D2 lymphadenectomy should be the

same regardless of the surgical approach, open, laparoscopic, or even robotic. We think that PHP-D2 is a universal procedure regardless of the approach, and it can be a standard procedure of D2 lymphadenectomy for advanced GC. We expect PHP-D2 to become more commonly used worldwide and lead to improvement of short-term and long-term outcomes of GC patients.

Compliance with Ethical Standards

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent: The IRB waived the requirement to obtain informed consent from the patients for this study because of the retrospective nature of the study.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 71(3):209-249
2. Hatta W, Gotoda T, Kanno T, Yuan Y, Koike T, Moayyedi P, Masamune A (2020) Prevalence and risk factors for lymph node metastasis after noncurative endoscopic resection for early gastric cancer: a systematic review and meta-analysis. *J Gastroenterol* 55(8):742-753
3. Japanese Gastric Cancer A (2020) Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer*
4. Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ (2010) Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol* 11(5):439-449
5. Suda K, Nakauchi M, Inaba K, Ishida Y, Uyama I (2016) Minimally invasive surgery for upper gastrointestinal cancer: Our experience and review of the literature. *World J Gastroenterol* 22(19):4626-4637
6. Ren K, Yi SQ, Dai Y, Kurosawa K, Miwa Y, Sato I (2020) Clinical anatomy of the anterior and posterior hepatic plexuses, including relations with the pancreatic plexus: A cadaver study. *Clin Anat* 33(5):630-636
7. Lee SW, Kawai M, Tashiro K, Bouras G, Kawashima S, Tanaka R, Nomura E, Uchiyama K (2017) Laparoscopic distal gastrectomy with D2 lymphadenectomy followed by intracorporeal gastroduodenostomy for advanced gastric cancer: technical guide and tips. *Transl Gastroenterol Hepatol* 2:84

8. Kuroda S, Kikuchi S, Hori N, Sakamoto S, Kagawa T, Watanabe M, Kubota T, Kuwada K, Ishida M, Kishimoto H, Uno F, Nishizaki M, Kagawa S, Fujiwara T (2017) Training system for laparoscopy-assisted distal gastrectomy. *Surg Today* 47(7):802-809
9. Japanese Gastric Cancer A (2011) Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 14(2):101-112
10. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 240(2):205-213
11. Bracale U, Corcione F, Pignata G, Andreuccetti J, Dolce P, Boni L, Cassinotti E, Olmi S, Uccelli M, Gualtierotti M, Ferrari G, De Martini P, Bjelovic M, Gunjic D, Cuccurullo D, Sciuto A, Pirozzi F, Peltrini R (2021) Impact of neoadjuvant therapy followed by laparoscopic radical gastrectomy with D2 lymph node dissection in Western population: A multi-institutional propensity score-matched study. *J Surg Oncol* 124(8):1338-1346
12. Toyokawa T, Ohira M, Tanaka H, Minamino H, Sakurai K, Nagami Y, Kubo N, Yamamoto A, Sano K, Muguruma K, Tominaga K, Nebiki H, Yamashita Y, Arakawa T, Hirakawa K (2016) Optimal management for patients not meeting the inclusion criteria after endoscopic submucosal dissection for gastric cancer. *Surg Endosc* 30(6):2404-2414
13. Choi KK, Bae JM, Kim SM, Sohn TS, Noh JH, Lee JH, Choi MG, Kim S (2016) The risk of lymph node metastases in 3951 surgically resected mucosal gastric cancers: implications for endoscopic resection. *Gastrointest Endosc* 83(5):896-901

Figure Legends

Fig 1. Suprapancreatic D2 lymphadenectomy focusing on the PHP (PHP-D2)

- a. Note that the yellow dashed line is a recommended dissection line.
- b. Completion of suprapancreatic D2 lymphadenectomy.

* posterior hepatic plexus (PHP).

CHA, common hepatic artery; PHA, proper hepatic artery; LGV, left gastric vein; PV, portal vein.

Fig 2. CONSORT diagram

GC, gastric cancer; P1, peritoneal metastasis; CY1, peritoneal cytology-positive.

Fig 3. PHP-D2 and lymphatic recurrence

- a. The number of retrieved lymph nodes of #8a, #9, #11p, and #12a. The median number (range) of lymph nodes in each lymph node station is described under the procedure.
- b. The correlation of surgical procedures (non-PHP-D2, PHP-D2) with recurrence patterns (lymphatic, hematogenous, disseminated).

Fig 4. Survival analysis

- a. Kaplan-Meier survival curves of non-PHP-D2 and PHP-D2 for overall survival.
- b. Kaplan-Meier survival curves of non-PHP-D2 and PHP-D2 for relapse-free survival.