

World Journal of *Clinical Cases*

World J Clin Cases 2020 July 6; 8(13): 2674-2892



Contents

Semimonthly Volume 8 Number 13 July 6, 2020

OPINION REVIEW

- 2674 Minimizing the risk of community spread of COVID-19 *via* institutional quarantine of high-risk travelers with serial viral RNA testing: A successful experience from Macao SAR, China
Lio CF, Cheong HH, Lei CI, Lo IL, Lam C, Leong IH

REVIEW

- 2679 Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: State of the art
Jin Q, Zhao ZH, Luo Q, Zhao Q, Yan L, Zhang Y, Li X, Yang T, Zeng QX, Xiong CM, Liu ZH
- 2703 Advances in para-aortic nodal dissection in gastric cancer surgery: A review of research progress over the last decade
Dong YP, Deng JY
- 2717 Relevance on the diagnosis of malignant lymphoma of the salivary gland
Zhang XY, Wang ZM

ORIGINAL ARTICLE

Clinical and Translational Research

- 2727 Role of peripheral eosinophilia in acute exacerbation of chronic obstructive pulmonary disease
Wu CW, Lan CC, Hsieh PC, Tzeng IS, Wu YK

Case Control Study

- 2738 Effects of prostaglandin E combined with continuous renal replacement therapy on septic acute kidney injury
Lei L, Wang MJ, Zhang S, Hu DJ

Retrospective Study

- 2749 Modified technique of advanced core decompression for treatment of femoral head osteonecrosis
Lin L, Jiao Y, Luo XG, Zhang JZ, Yin HL, Ma L, Chen BR, Kelly DM, Gu WK, Chen H
- 2758 Initial experience with stereotactic body radiotherapy for intrahepatic hepatocellular carcinoma recurrence after liver transplantation
Au KP, Chiang CL, Chan ACY, Cheung TT, Lo CM, Chok KSH
- 2769 Correlation between age of onset and gastrointestinal stenosis in hospitalized patients with Crohn's disease
Yang SB, Du SW, Wang JH
- 2778 Adjuvant nab-paclitaxel plus gemcitabine *vs* gemcitabine alone for resected pancreatic ductal adenocarcinoma: A single center experience in China
Yin ZZ, Zhao ZM, Tang WB, Jiang N, Zhang KD, Song YY, Wang Y, Li CG, Gao YX, Liu R

Observational Study

- 2787 Case studies in psychotherapy training using Austria as an example

Neidhart E, Löffler-Stastka H

Prospective Study

- 2802 Correlation between crowdedness in emergency departments and anxiety in Chinese patients

Wang S, Gao JY, Li X, Wu Y, Huo XX, Han CX, Kang MJ, Sun H, Ge BL, Liu Y, Liu YQ, Zhou JP, Wang Z

SCIENTOMETRICS

- 2817 Bibliometric analysis of subject trends and knowledge structures of gut microbiota

Yue YY, Fan XY, Zhang Q, Lu YP, Wu S, Wang S, Yu M, Cui CW, Sun ZR

CASE REPORT

- 2833 Acute myelomonocytic leukemia during pembrolizumab treatment for non-small cell lung cancer: A case report

Kim HB, Park SG, Hong R, Kang SH, Na YS

- 2841 Metallic ureteral stent in restoring kidney function: Nine case reports

Gao W, Ou TW, Cui X, Wu JT, Cui B

- 2849 Pheochromocytoma with delayed tumor thrombus detection in renal vein: A case report

Jia Z, Wang BJ, Li X, Zhang X

- 2855 Laparoscopic repair of uterine rupture following successful second vaginal birth after caesarean delivery: A case report

Cai YQ, Liu W, Zhang H, He XQ, Zhang J

- 2862 Missed diagnosis of femoral deep artery rupture after femoral shaft fracture: A case report

Ge J, Kong KY, Cheng XQ, Li P, Hu XX, Yang HL, Shen MJ

- 2870 Posterior reversible encephalopathy syndrome and heart failure tacrolimus-induced after liver transplantation: A case report

Liu JF, Shen T, Zhang YT

- 2876 Significant benefits of pembrolizumab in treating refractory advanced pulmonary sarcomatoid carcinoma: A case report

Chen P, Yu M, Zhang JL, Chen WY, Zhu L, Song Y, Jiang CY, Zhang S

- 2885 Two sequential surgeries in infant with multiple floor of the mouth dermoid cysts: A case report

Liu NN, Zhang XY, Tang YY, Wang ZM

ABOUT COVER

Editorial board member of *World Journal of Clinical Cases*, Dr. El Ghoch is a Full Professor in the Faculty of Health Sciences, Beirut Arab University, Lebanon. Having received his MD degree from University of Bologna, Italy in 2005, and undertook his postgraduate degree in Clinical Nutrition at the University of Modena and Reggio Emilia, Italy in 2009. In the following 10 year, he had a wide clinical and research activity in Italy in the field of obesity and eating disorders, and gained an international leadership in the study of the body composition in anorexia nervosa. In October 2018 he was appointed as Professor in the Clinical Nutrition, and Chairperson of the Department of Nutrition and Dietetics, Beirut Arab University, Lebanon. His ongoing research interests are body composition, physical activity, weight cycling, etc.

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor for *WJCC* as 1.013 (5-year impact factor: N/A), ranking *WJCC* as 120 among 165 journals in medicine, general and internal (quartile in category Q3).

RESPONSIBLE EDITORS FOR THIS ISSUE

Electronic Editor: Yan-Xia Xing, Production Department Director: Yun-Xiaojian Wu, Editorial Office Director: Jin-Lai Wang.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Semimonthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

July 6, 2020

COPYRIGHT

© 2020 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Advances in para-aortic nodal dissection in gastric cancer surgery: A review of research progress over the last decade

Yin-Ping Dong, Jing-Yu Deng

ORCID number: Yin-Ping Dong
[0000-0003-4090-340X](https://orcid.org/0000-0003-4090-340X); Jing-Yu Deng
[0000-0003-4299-1327](https://orcid.org/0000-0003-4299-1327).

Author contributions: Dong YP wrote the paper; Deng JY designed the research; all authors read and approved the final manuscript.

Supported by the Programs of National Natural Science Foundation of China, No. 81572372; National Key Research and Development Program "Major Chronic Non-infectious Disease Research", No. 2016YFC1303200; and National Key Research and Development Program "Precision Medicine Research", No. 2017YFC0908300.

Conflict-of-interest statement: The authors declare no conflicts of interest for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and

Yin-Ping Dong, Jing-Yu Deng, Department of Gastroenterology, Tianjin Medical University Cancer Hospital, City Key Laboratory of Tianjin Cancer Center and National Clinical Research Center for Cancer, Tianjin 300060, China

Corresponding author: Jing-Yu Deng, MD, PhD, Chief Doctor, Professor, Department of Gastroenterology, Tianjin Medical University Cancer Hospital, City Key Laboratory of Tianjin Cancer Center and National Clinical Research Center for Cancer, Huanhuxi Road, Hexi District, Tianjin 300060, China. dengery@126.com

Abstract

Approximately 17%-40% of para-aortic lymph node (PAN) metastasis occurs in patients with advanced gastric cancer. As the third tier of lymphatic drainage of the stomach and the final station in front of the systemic circulation, PAN infiltration is defined as distant metastasis and plays a key role in the evaluation of the prognosis of advanced gastric cancer. Many clinical factors including tumor size ≥ 5 cm, pT3 or pT4 depth of tumor invasion, pN2 and pN3 stages, the macroscopic type of Borrmann III/IV, and the diffuse/mixed Lauren classification are indicators of PAN metastasis. Whether PAN dissection (PAND) should be performed on patients with or without the macroscopic PAN invasion remains unascertained, regardless of the numerous retrospective comparative studies reported on the improved prognosis over D2 alone. Another paradoxical result from many other studies showed no significant difference in the overall survival between these two lymphadenectomies. A phase II trial launched by the Japan Clinical Oncology Group indicated that two or three courses of S-1 and cisplatin preoperatively followed by radical surgery with D2 + PAND and postoperative S-1 is the current standard strategy for the treatment of patients with extensive lymph node metastasis, and this regimen could be substituted by a promising strategy with effective combination chemotherapy or suitable chemotherapy duration. This review focuses on the advances in radical gastrectomy plus PAND with or without chemotherapy for patients with advanced gastric cancer.

Key words: Para-aortic lymph node; Lymphadenectomy; Stomach; Neoplasm

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Received: March 4, 2020

Peer-review started: March 4, 2020

First decision: April 12, 2020

Revised: April 30, 2020

Accepted: June 7, 2020

Article in press: June 7, 2020

Published online: July 6, 2020

P-Reviewer: Ito S, Kosugi S, Yarema RR

S-Editor: Zhang L

L-Editor: Webster JR

E-Editor: Xing YX



Core tip: Para-aortic lymph node metastasis is defined as lymph node metastasis between the aortic hiatus and the aortic bifurcation. To date, it is considered a distant metastasis and plays a crucial role in the evaluation of the prognosis of advanced gastric cancer (AGC). The necessity of para-aortic lymph node dissection (PAND) remains uncertain for patients with AGC. Preoperative S-1 and cisplatin followed by radical surgery with D2 + PAND is the current standard treatment strategy for patients with extensive lymph node metastasis. The main purpose of this review is to summarize the advances in the therapeutic effects of PAND in patients with AGC. The second purpose is to highlight the clinical significance of chemotherapy combined with radical surgery for patients with AGC.

Citation: Dong YP, Deng JY. Advances in para-aortic nodal dissection in gastric cancer surgery: A review of research progress over the last decade. *World J Clin Cases* 2020; 8(13): 2703-2716
URL: <https://www.wjgnet.com/2307-8960/full/v8/i13/2703.htm>
DOI: <https://dx.doi.org/10.12998/wjcc.v8.i13.2703>

INTRODUCTION

Gastric cancer (GC) is still the fourth most common malignancy and is the second leading cause of cancer-related deaths worldwide^[1]. Surgical resection is still the only effective treatment for localized GC. As lymph node metastasis occurs early in patients with GC, the optimal extent of regional lymph node dissection still needs further discussion, especially with the goal of radical gastrectomy. The extensive lymph-node dissection, D2 lymphadenectomy, has been recommended as the standard modality for patients with locally advanced gastric cancer (AGC) worldwide^[2,3]. However, the benefit of the super-extended lymph-node dissection, D2 plus para-aortic nodal dissection (PAND), the so-called D2+ resection, remains unclear and is still under investigation by many surgeons.

Among patients with non-early GC, the incidence of metastasis to para-aortic lymph nodes (PANs) was mainly 17%-40%^[4-11], and the 5-year survival for such subgroup reached 13% to 40% after R0 resection^[6,12,13]. Although the incidence of PAN metastasis differs between studies, PAND has been practiced to improve survival in Japan since the late 1980s for patients with AGC^[13-22]. According to the Japanese Classification of Gastric Carcinoma (JGCG)^[23] defined by the Japanese Gastric Cancer Association, PAND was defined from the upper margin of the celiac trunk to the root of the inferior mesenteric artery, with stations No. 16 a2 and No. 16 b1 routinely removed. As the final station irrespective of the tumor location within the abdominal cavity for lymphatic metastasis of GC, PANs were drained through the celiac artery from the left gastric artery nodes^[24]. PANs were termed as regional N3 nodes in past decades^[25], although have been regarded as distant metastasis (M1) and are now classified as Stage IV^[26,27]. Moreover, the incidence is deemed to be highly related to the tumor location^[28], especially in the upper third GC, along with other clinical characteristics. Whether or not to clean the PAN for curative intent has been a controversial issue for decades. The prophylactic PAND is not recommended in AGC treatment, because several trials showed no survival benefit from the D2 + PAND procedures compared with the standard D2 lymphadenectomy, and it may result in prolonged operation time, larger volume of blood loss, and longer hospital stay^[29,30]. Nevertheless, several clinical studies reported that therapeutic PAND may help improve the disease-free survival rate and prolong the survival time for patients with actual metastasis to PAN^[31]. Extensive PAND may provide precise nodal staging to inhibit stage migration, which might improve the stage-specific survival of AGC^[32]. Simultaneously, both surgery combined D2 + PAND and neoadjuvant chemotherapy, including the regimen of cisplatin (CDDP)/S-1 combined with docetaxel or other combinations of chemotherapy, could benefit the survival of patients with extensive lymph node metastasis (ELM)^[33]. Few previous large-scale trials were able to validate the optimal treatment regimen for patients with AGC. Therefore, we conducted a systematic review to summarize the therapeutic effects and clinical significance of the PAND in patients with AGC.

PARA-AORTIC LYMPH NODE

PAN metastasis has been defined as the lymph node metastasis between the aortic hiatus and the aortic bifurcation, of which the diameter exceeds 1.0 cm according to clinical imaging examination (including computed tomography scanning and ultrasonography). To our knowledge, PAND implied the complete retrieval of nodes between the upper margin of the celiac axis and the lower margin of the left renal vein (No. 16a2) and nodes between the lower margin of the left renal vein and the upper margin of the inferior mesenteric artery (No. 16b1), whereas dissection of the upper No. 16a1 and the lower No. 16b2 nodes were optional and were to be dissected if macroscopically involved or based on the tumor location. In addition, the dissection of the left upper lateral nodes ("No. 16a2-lat") was optional, and its controversy still remains even with enlarged nodes in this area^[21]. In some studies, it was supposed to be resected in upper gastric cancer^[34], while optionally resected in the distal gastrectomy^[35]. As the third-tier lymph station, patients with PAN invasion showed better survival than those with other single or multiple organ site metastases^[36]. Thus, it was defined as local lymph node metastasis by the 2nd JCGC^[25]. However, prophylactic PAND failed to improve the prognosis when compared with standard D2 alone^[30,37]. PAN involvement is thought to be a systemic disease and is currently designated as distant metastasis (M1) by the eighth edition of the American Joint Committee on Cancer tumor-node-metastasis staging system^[26] and the third JCGC^[27]. This stage IV classification, which is not indicated for intensively curative surgery, may preclude patients with PAN metastasis from undergoing surgery on the basis of the Japanese Treatment Guidelines for Gastric Cancer^[23]. In addition, PAND was proved to be effective^[6,7,9,10,13,15,16,31,38,39] and helped improve the survival of patients with AGC in past decades, nonetheless, recent studies verified that the survival rates between these two dissection techniques (D2 *vs* D2 + PAND) were almost identical^[20,30,37,40], suggesting that PAND did not benefit the survival of patients with AGC.

ANATOMICAL REGULARITY OF PARA-AORTIC LYMPH NODE METASTASIS AND THE RELATIONSHIP BETWEEN CLINICOPATHOLOGICAL FACTORS AND PARA-AORTIC LYMPH NODE METASTASIS

Lymphatic drainage from the stomach flows to the first-tier station (perigastric nodes) and then passes to the second-tier station (nodes around the celiac artery and its branches outside the perigastric region). Then, it finally enters the PANs and the systemic circulation *via* the thoracic duct. Therefore, PANs can be considered the terminal regional nodes of gastric lymphatic drainage, which can be dissected to avoid the threat of systemic metastases originating from the lymphatic system. Usually, the following several sites may exist for lymphatic flow from the stomach to PANs: (1) The left para-cardial lymph nodes (No. 2 Station); (2) The lymph nodes along the splenic artery (No. 10 Station); (3) The lymph nodes around the celiac artery (No. 9 Station); (4) The lymph nodes along the superior mesenteric artery (No. 14a Station); and (5) The lymph nodes on the posterior surface of the pancreatic head and the nodes along the posterior common hepatic artery (No. 13, No. 8p Station)^[24]. However, the route with the most frequent access to PANs remains unclear. Therefore, several studies indicated that many lymph node station metastases are related to positive PANs. For example, No. 1, 2, 3, 4d, 4sb, 5, 6, 7, 8a, 8p, 9, 11p, 12, and 14 lymph node station metastasis may be associated with positive PANs as revealed by a meta-analysis^[41], whereas No. 1, 3, 7, and 9 stations had evidently higher odd ratios than others.

Moreover, numerous studies pointed out that the lymphatics along the celiac artery^[28] and the left gastric artery^[13,24] were the most frequent routes to PANs. The most likely route of PAN metastasis is from the left gastric artery nodes through the celiac artery^[24]. The involvement of stations No. 7 (left gastric artery)^[24,28,38,41,42] and No. 9 (celiac artery)^[24,28,34,38,41,43,44] have been identified as indicators for a high incidence of PAN metastasis. Of course, No. 1, 3^[28,41], and 8^[44] are often reported to be related to the incidence of PAN metastasis. Particularly, No. 1 and 3 were regarded as the perfect factors showing the highest sensitivity with peaked negative predictive value^[28]. No exact evidence confirmed the definite relationship between the histologic status of these lower regional lymph node stations and PAN metastasis or whether an exact pathway of lymphatic drainage among all these lymph nodes exists. Thus, further

research is needed to suggest an accurate conclusion. Then, based on more accurate lymph drainage between the lower regional lymph node stations and PAN metastasis, intraoperative histological biopsy of the relevant lymph nodes may be necessary and feasible to determine whether further PAND is needed.

As found by many studies, tumor location and perigastric nodal status were significant risk factors for PAN invasion^[28,45]. As reported, the lymph flows from the upper third of the stomach (U) and directly streams into the para-aortic region. Consequently, a tumor located in the U is frequently related to PAN involvement^[11,21,28,29,34,41,43,46,47], which was considered a predictor of positive PANs. PAND was then required, especially compared with middle (M) and lower (L) third GC^[46,48,49], due to the different lymphatic path between the primary tumor locations to the PANs^[50-52]. Certainly, the above factors and other clinicopathologic characteristics were verified to have a high risk of PAN metastasis, such as tumor size ≥ 5 cm^[24,41,47]; pT3 or pT4 depth of tumor invasion that deeply invades the subserosa, serosa, or adjacent organs^[11,28,41,42,47,53,54]; pN2 and pN3 stages^[24,31,41,43,45,53]; the macroscopic-type Borrmann III/IV^[31,41,43,45,47]; and the diffuse/mixed Lauren classification^[24,28,41,47,54]. Multiple studies presented different conclusions regarding the related clinicopathologic characteristics (Table 1). Thus, several prospective clinical trials are needed to define the exact relevant factors to obtain accurate interventions.

THERAPEUTIC MEASURES FOR PARA-AORTIC LYMPH NODE METASTASIS

Currently defined as M1 metastasis, patients with metastasis to PANs have a poorer prognosis^[31] compared with metastasis to other local lymph nodes. Many studies have taken various measures including surgery plus dissection of PANs, chemotherapy or the combination of surgery and perioperative chemotherapy as a multimodality treatment to improve the survival of locally advanced GC. However, due to different eligibility criteria, interventions, and the histology of primary lesions, survival varied among studies even those in which the same treatment was administered. In addition, patients can develop different degrees of corresponding complications due to different treatments. Surgeons must try to find the most appropriate treatment modalities to balance the response benefits and decrease the toxicity.

Surgery plus extensive lymphadenectomy

Extensive PAN lymphadenectomy means the first-tier and second-tier lymph nodes plus PANs are removed, with node clearance in a wide range and in large numbers. Given the high rate of approximately 20% of PANs with micrometastasis^[7], which are not completely detectable by the current preoperative imaging examinations, prophylactic PAND measures were taken to prevent the relapse of local lymph nodes. However, many studies did not show survival benefit after prophylactic D2 + PAND^[30,40]. Among these known studies, a large Japanese prospective randomized trial (JCOG 9501) investigated the efficacy of prophylactic PAND for curable patients with AGC, which was not considered justified for patients with AGC without improved survival. The study also proved that extensive PAN dissection performed safely by specialized surgeons did not increase the incidence of major surgical complications (anastomotic leak, pancreatic fistula, abdominal abscess, and pneumonia) and acquired a low 0.8% rate of hospital mortality. However, the operation time was prolonged, and the blood loss was increased with the D2 dissection^[30]. However, some drawbacks existed in the JCOG9501 trials, in which patients with macroscopically involved metastasis were excluded. Nevertheless, whether harboring pathological micrometastasis was uncertain between the two groups, and the numbers of patients with pathological micrometastasis were not balanced.

With the exception of the JCOG9501 study on the role of prophylactic PAND, studies on therapeutic PAND have also been performed by many surgeons with varying outcomes, as shown in Table 2. The surgical results of patients with PAN metastasis were disappointing^[54], but many surgeons thought that the potential benefit of D2 plus PAND over standard D2 alone should not be ignored. For example, Hu *et al.*^[44] demonstrated that an improved survival was accomplished after extensive nodal dissection. In addition, many studies revealed that the advantages of patients who have experienced PAND with survival benefits were from related clinicopathologic factors. Roviello *et al.*^[21] showed that the high probability of survival was closely dependent on pT and pN staging. The 5-year survival rate particularly

Table 1 Analysis of clinicopathologic characteristics relevant to para-aortic lymph node metastasis

Ref.	Year	Article type	Clinicopathologic characteristics relevant to para-aortic lymph node metastasis						
			Perigastric nodal status	Tumor site (located in the U)	Tumor size ≥ 5 cm	Depth of tumor invasion	N stage of N2 and N3	Macroscopic type Borrmann III/IV	Diffuse/mixed histology
Takashima <i>et al</i> ^[11]	2005	Review	—	Yes	—	Yes	—	—	—
Lee <i>et al</i> ^[54]	2006	Article	—	—	—	Yes	—	—	Yes
Nomura <i>et al</i> ^[24]	2007	Article	No. 7	—	Yes	—	Yes	—	Yes
Chen <i>et al</i> ^[42]	2009	Meta-analysis	No. 7, 8	—	—	Yes	—	—	—
Hu <i>et al</i> ^[44]	2009	Article	No. 8a, 9	—	—	—	—	—	—
Fujimura <i>et al</i> ^[34]	2009	Article	—	Yes	—	—	—	—	—
Tokunaga <i>et al</i> ^[31]	2010	Article	—	—	—	—	Yes	Yes	—
Roviello <i>et al</i> ^[21]	2010	Article	—	Yes	—	—	—	—	—
de Manzoni <i>et al</i> ^[28]	2011	Article	No. 1, 3, 7, 8a, 9	Yes	—	Yes	—	—	Yes
Wang <i>et al</i> ^[43]	2013	Article	No. 9	Yes	—	—	Yes	Yes	—
Zhou <i>et al</i> ^[42]	2013	Meta-analysis	No. 1, 3, 7, 9	Yes	Yes	Yes	Yes	Yes	Yes
Zhang <i>et al</i> ^[53]	2014	Article	—	—	—	Yes	Yes	—	—
Liang <i>et al</i> ^[45]	2016	Review	No. 9	Yes	—	—	Yes	Yes	—
Douridas <i>et al</i> ^[47]	2018	Mini review	—	Yes	Yes	Yes	—	Yes	Yes

U: the upper third of the stomach.

worsened with the growth of pN stage under the premise of node-positive patients and worsened with increasing infiltration depth (pT staging) under the premise of node-negative patients. Better survival can be achieved by D2 + PAND for patients without node invasion (pN0) and those whose tumor was limited to subserosal invasion (pT2). However, other studies indicated that patients with tumor diameter measuring 50–100 mm and with pN2 staging might benefit from D3 dissection^[55]. A Chinese study initiated by Zhang *et al*^[53] demonstrated that D2 + PAND may be beneficial in patients with T3/T4 tumors with 1–3 PAN clinical involvement as a therapeutic method. Moreover, studies demonstrated that PAND may be beneficial in patients with a small number (< 3 or 4) of PAN^[6,56] and total lymph node (< 11) metastases^[15] or patients with < 15 total positive lymph nodes but macroscopic type, except type 4, on the basis of R0 resection^[31]. With more nodes dissected, some specialists speculated that the improved survival of PAND may benefit from accurate staging information provided by extensive surgery^[32,57,58]. Combined with these clinical factors, screening the best indications for PAND and then performing the operation by well-trained surgeons are both necessary.

Apart from this situation, for patients with proximal GC invading the esophagus, the left thoracoabdominal approach was compared with an abdominal-transhiatal (TH) approach, and TH was selected as the better method, which was recorded in the JCOG9502 trial^[59]. Overall, the TH group who underwent a total gastrectomy with D2 and additional dissection of the left upper PANs showed better survival and less morbidity than those who underwent the left thoracoabdominal approach accompanied by a thorough lower mediastinal lymphadenectomy. Thus, the fact that some western surgeons do not advocate PAND based on partial outcomes is not reasonable, because the accurate value of therapeutic PAND in PAN-positive patients with curative purpose remains undetermined. Therefore, several rigorous large-scale

Table 2 Some reported series of gastrectomy and a comparison of morbidity, mortality and survival between D2 and D2 + PAND

Ref.	Year	Countries and continents	Number of patients registered	Number of patients underwent D2 + PAND or D2+	Incidence of PAN (%)	Prognosis differences between D2 vs D2 + PADN (D2+)											
						Morbidity			Mortality			Recurrence rate			5-yr survival rate		
						D2 (%)	D2 + PAND (%)	P value	D2 (%)	D2 + PAND (%)	P value	D2 (%)	D2 + PAND (%)	P value	D2 (%)	D2 + PAND (%)	P value
Günther <i>et al</i> ^[18]	2000	Turkey	459	75	—	31.5	34.2	—	6.8	1.3	—	—	—	—	—	—	—
Bostanci <i>et al</i> ^[19]	2004	Turkey	134	34	—	10	35.3	< 0.05	1	8.8	< 0.05	—	—	—	—	—	—
Sano <i>et al</i> ^[30]	2004	Japan	523	260	—	20.9	28.1	0.067	0.8	0.8	—	—	—	—	—	—	—
Marrelli <i>et al</i> ^[17]	2007	Italy	330	79	13.9	27	27	0.929	4	4	0.82	—	—	—	—	—	—
Kunisaki <i>et al</i> ^[53]	2006	Japan	580	150	—	—	—	—	—	—	—	40	50	0.3538	56.0	50.4	0.9899
Kulig <i>et al</i> ^[20]	2007	Poland	275	134	—	27.7	21.6	0.24	4.9	2.2	0.37	—	—	—	—	—	—
Sasako <i>et al</i> ^[37]	2008	Japan	523	260	8.5	—	—	—	—	—	—	—	—	—	69.2	70.3	—
Yonemura <i>et al</i> ^[40]	2008	Japan	293	134	9.0	—	—	—	—	3.7	0.12	46.7	38.8	—	52.6	55.0	0.801
Hu <i>et al</i> ^[44]	2009	China	117	62	8.1	27.3	24.2	0.703	1.8	0	0.470	—	—	—	66.1	65.8	0.946
Roviello <i>et al</i> ^[21]	2010	Italy	286	286	12.9	—	28	—	—	2.1	—	—	—	—	—	52.2	—
Tokunaga <i>et al</i> ^[31]	2010	Japan	178	178	—	—	30	—	—	2	—	—	—	—	—	13	—
de Manzoni <i>et al</i> ^[28]	2011	Italy	294	294	16	—	—	—	—	—	—	—	—	—	—	—	—
Zhang <i>et al</i> ^[53]	2014	China	157	69	40.6	—	—	—	12.5	21.7	0.122	43.2	39.1	0.628	31.8	43.7	0.044
de Manzoni <i>et al</i> ^[78]	2015	Italy	568	294	11.6	—	—	—	4	2.4	0.340	45.3	46.3	0.866	—	—	—

PAN: Para-aortic lymph node; PAND: Para-aortic lymph node dissection.

trials are needed to further verify whether differences exist in survival between these two lymphadenectomies (D2 vs D2 + PAND) performed by experienced surgeons.

Chemotherapy

Systemic chemotherapy is regarded as the standard treatment for systemic macro- or micro- metastases involving the PAN region and beyond the PAN area. Nevertheless, systemic chemotherapy alone is unlikely to have a meaningful or lasting benefit in unresectable tumors, such as those with PAN involvement. However, adjuvant chemotherapy partly helps improve surgical survival^[60].

Recently, neoadjuvant chemotherapy has gained considerable attention in the treatment of patients with distant metastasis. The following three studies, JCOG 0001, 0405, and 1002 were implemented to investigate the utility and the efficacy of neoadjuvant chemotherapy followed by gastrectomy with D2 + PAND. Among these studies, due to the same eligibility criteria but different regimens of preoperative chemotherapy followed by surgery, patients in JCOG 0001 received two or three cycles of irinotecan (70 mg/m² on days 1 and 15) and CDDP (80 mg/m² on day 1) therapy. In addition, patients in JCOG 0405 received two or three cycles of CDDP (60 mg/m² on day 8) and S-1 (40 mg/m² twice daily from day 1 to day 21 followed by a 1-week rest period) (CS) chemotherapy. JCOG 0001^[61] showed a good 3-year survival of 27.0%, but the study was terminated due to three treatment-related deaths among the 55 enrolled patients. JCOG 0405^[33] showed an excellent response rate of 64.7% and a 3-year survival of 58.8% with no treatment-related death. Since then, CS chemotherapy has been considered the current standard for patients with ELM, in which ELM was defined as PAN metastasis (no. 16a2/16b1) or bulky lymph nodes (one larger than 3 cm or two larger than 1.5 cm) along the celiac, splenic, common hepatic, or proper hepatic arteries, or both. Triplet therapy with the addition of docetaxel to CS (DCS) was then introduced as neoadjuvant chemotherapy for local patients with AGC and ELM (JCOG1002). In JCOG 1002^[62,63], with the same eligibility criteria as the above two trials, patients received two or three 28-day cycles of docetaxel (40 mg/m² on day 1), CDDP (60 mg/m² on day 1), and S-1 (40 mg/m² twice daily for 2 weeks) (DCS) therapy. However, this regimen achieved a high rate of R0 resection and a 5-year survival of 54.9% (95% confidence interval: 40.3%-67.3%), with an insufficient pathological response rate of 50.0% (26/52).

Controversy still exists regarding the best regimen of chemotherapy for patients with PAN metastasis (Table 3). Notwithstanding the JCOG 1002 study of DCS that failed to show superiority over CS^[62,63], many studies were carried out to explore its benefits. A triplet therapy of docetaxel added to CDDP and S-1 (DCS) showed longer survival of patients with PAN metastasis when compared with 5-fluorouracil. Likewise, many other studies incorporated other regimens of different chemotherapeutics. A phase II trial performed in China, which adopted capecitabine and oxaliplatin as preoperative chemotherapy delivered for a maximum of six cycles, introduced the concept of conversion therapy to treat PAN metastasis in patients with AGC. The results demonstrated a good response rate and a sufficient R0 resection rate, with acceptable toxicities^[64].

Many trials have investigated the outcome of different schemes of preoperative chemotherapy, showing different survival effects. Currently, as the tentative standard chemotherapy in Japan^[33], CS together with subsequent radical surgery is still considered the de facto standard treatment for patients with AGC and ELM. Thus, further investigations on appropriate regimens and suitable durations of perioperative chemotherapy should be used in clinical practice for better survival.

Radiotherapy

According to the fundamental role of surgery in the treatment of GC, radiotherapy is rarely used, and almost no research is available on radiotherapy alone used for AGC and is always a part of a comprehensive treatment in combination with other palliative interventions. Radiotherapy is commonly combined with chemotherapy before surgery or implemented concurrently with or subsequently to adjuvant chemotherapy after surgery in patients with GC^[65-68].

Nonetheless, treatment measures including radiotherapy aimed at curing patients with PAN involvement are rare. An individualized comprehensive treatment including neoadjuvant chemotherapy, subsequent surgery, and radiotherapy for patients with AGC and PAN metastasis with a high response rate of 76.1% for positive PANs and without treatment-related death is beneficial^[68].

Table 3 Main studies that reported clinical data including survival outcomes following chemotherapy and surgery in patients with pathological positivity of para-aortic lymph nodes

Ref.	Registration number	Types of clinical trials (Phase I/II/III)	Published year	Time of accrual	Chemotherapy regimens	Followed by surgery	Extent of lymphadenectomy	Number of patients registered	Incidence of PAN (%)	Primary endpoint	R0 resection rate	Response rate		Survival rate			
												Clinical	Pathological	Relapse-free survival	3-yr (%)	5-yr (%)	TRD
Yoshikawa <i>et al</i> ^[61]	JCOG0001	II	2009	2000-2003	CPT-11/CDDP	Yes	D2 + PAND	55	54.5	3-yr survival rate TRD rate	65 (95%CI 51-78)	56	15	—	27	NA	3/55
Oyama <i>et al</i> ^[60]	—	—	2012	1990-2008	S-1/CDDP/docetaxel	Yes	D2 + PAND	44	100	—	—	—	87.5	75 (2-yr)	—	—	0/44
Wang <i>et al</i> ^[64]	—	II	2014	2008-2013	XELOX (capecitabine and oxaliplatin)	Yes	D2	48	100	Response rate of NAC	50%	85.1	49	—	—	—	—
Tsuburaya <i>et al</i> ^[33]	JCOG0405	II	2014	2005-2007	S-1/CDDP	Yes	D2 + PAND	51	51	R0 resection rate	82(95%CI 69-92)	65	51	—	59	53	0/51
Ito <i>et al</i> ^[62]	JCOG1002	II	2017	2011-2013	S-1/CDDP/docetaxel	Yes	D2 + PAND	52	43.4	Response rate (RECISTver.1.0)	84.6	57.7	50	—	—	—	0/52
Takahari <i>et al</i> ^[63]	JCOG1002	II	2019	2011-2013	S-1/CDDP/docetaxel	Yes	D2 + PAND	52	43.4	Clinical RR	—	—	34.6	47.7 (5-yr)	62.7	54.9	0/52

PAN: Para-aortic lymph node; PAND: Para-aortic lymph node dissection; CI: Confidence interval; TRD, treatment-related death .

PROGNOSIS OF PATIENTS WITH PARA-AORTIC LYMPH NODE METASTASIS

Overall survival

The overall survival rate varies greatly between studies due to different treatments. Within the scope of an 8.1%-51% incidence of PAN metastasis, the 5-year survival of patients ranges from 43.7% to 70.3%, as listed in Tables 2 and 3.

Morbidity and mortality

Considering the rare application of radiotherapy and other unconventional treatments, discussion on the adverse effects of chemotherapy and surgery is included. Many trials on the impact of surgery plus extensive lymphadenectomy on prognosis were carried out to explore its benefit on survival. In terms of interim/short-term outcomes, studies pointed out that extended lymphadenectomy could influence the function of adjacent abdominal organs and induce high postoperative morbidity and mortality^[30]. In

addition, reduced risk can be achieved by preserving the spleen and/or pancreas^[17,69]. For instance, Kunisaki *et al*^[13] indicated that pancreatic fistula and respiratory complications were significantly higher in patients with D2 + PAND as compared with standard D2. Conversely, no differences in surgical morbidity between D2 and D3 lymphadenectomy were found by several studies performed by experienced surgeons^[14,17,18,20,44,70,71]. In addition, several European studies also reported no association between postoperative mortality and extended lymphadenectomy^[20,57,72]. Abdominal abscess, anastomotic leakage, pancreatic fistula, abdominal abscess^[17], and pneumonia^[21,30,73,74] were reported as the most common complications after extensive surgery observed in studies. In addition, these morbidities were highly related to the American Society of Anesthesiologists' class II/III *vs* I, perioperative blood transfusions, low albumin serum levels, and age (> 75 years). The degree of radical surgery was regarded as an independent predictor of mortality by Marrelli *et al*^[17]. Other less common complications, such as diarrhea, orthostatic hypotonia, and lymphocele or lymphorrhea, were serious, and measures should be taken to reduce these complications^[30,73]. However, many studies found that PAND could increase the operation time and blood loss, required greater blood transfusion^[19,20,30,53,74], had high relaparotomy^[19,20,30,74], and could prolong hospital stay^[55] with no harmful effect on quality of life.

At the same time, the side effects of chemotherapy combined with surgery during chemotherapy were monitored by numerous trials. Furthermore, neoadjuvant chemotherapy subsequent to surgery can lead to different adverse events during chemotherapy due to the use of different chemotherapy regimens. Common adverse events but different incidences were recorded in three JCOG trials (JCOG 0001, 0405, and 1002) with similar inclusion criteria but different preoperative chemotherapy regimens^[33,61,62]. Among these adverse events, grade 3 or 4 toxicity during chemotherapy included leucopenia (31% *vs* 4% *vs* 18.9%), neutropenia (55% *vs* 19% *vs* 39.6%), anemia (24% *vs* 13% *vs* 7.5%), febrile neutropenia (16% *vs* 2% *vs* 5.7%), nausea (36% *vs* 4% *vs* 1.9%), diarrhea (5% *vs* 2% *vs* 7.5%), thrombocytopenia (4% *vs* 1.9%), anorexia (10% *vs* 9.4%) for 0405 and 1002, vomiting (13%) for 0001, anorexia (10%) for 0405, hyponatremia (15.1%), hypokalemia (5.7%), and upper respiratory tract infection (1.9%) for 1002 (Table 4). Two chemotherapy-related deaths (4%) among all 55 patients in 0001 were observed, and no chemotherapy-related deaths were noted in the other two trials. Only grade 3 adverse events without grade 4 toxicities were stated by Wang *et al*^[64], and gastrointestinal issues and leukocytopenia were the most common. These conditions were the result of preoperative capecitabine and oxaliplatin chemotherapy followed by D2 gastrectomy without PAND for AGC patients with PAN involvement^[64]. The outcomes from a retrospective study, showed that neutropenia (25.0%), leucopenia (18.8%), febrile neutropenia (6.3%), and diarrhea (6.3%) were the most common grade 3/4 toxicities, and no treatment-related deaths were observed^[60].

Recurrences

Relapse rates remain high even with extensive lymph node dissection; thus, there is a need for other adjuvant treatments^[72,75]. Lee's research^[54] concluded that more than 70% of patients with positive PANs relapsed within 11 months after surgery. Among the seven patients in the trial, two developed recurrences in local regions, and the other five patients developed distant metastases to the lung, bone, and left supraclavicular lymph node. Following D2 and neoadjuvant chemotherapy, no one had PAN recurrences. However, different to the above study, peritoneal metastasis followed by extra-regional nodal recurrence were identified as the two most frequent sites of relapse^[37,73,76]. Among these sites, more than one site including the peritoneum, lymph nodes, liver and other areas^[37] were involved at the time of first recurrence in the JCOG 9501 study. Moreover, a multi-institutional study by Kunisaki *et al*^[55] indicated that recurrences in the surgical resection nodal area was significantly lower following D3 dissection, even with a similar overall nodal recurrence rate between D2 and D3 dissection. This condition may be the result of significant differences in the distribution of recurrent lymph nodes between D2 and D3 patients due to the numbers of lymph nodes in the second and third tiers, hepatic hilar region, and mediastinal or cervical regional lymph nodes. Metastasis may also recur in other regions such as the right supraclavicular lymph node^[77,78]. However, after preoperative chemotherapy followed by surgery, the relapse-free survival rate can be as high as 70% at 2 years as shown by Oyama *et al*^[60].

Table 4 Adverse effects in three Japanese prospective randomized trials exploring neoadjuvant chemotherapy plus surgery for patients with extensive lymph node metastasis (Para-aortic lymph nodes metastasis or bulky lymph nodes)

Adverse effect	JCOG0001 ^[61]	JCOG0405 ^[63]	JCOG1002 ^[62,63]
Grade 3/4 toxicity from chemotherapy			
Leucopenia	31%	4%	18.9%
Neutropenia	55%	19%	39.6%
Anemia	24%	13%	7.5%
Febrile neutropenia	16%	2%	5.7%
Thrombocytopenia	—	4%	1.9%
Hyponatremia	—	—	15.1%
Hypokalemia	—	—	5.7%
Anorexia	—	10%	9.4%
Vomiting	13%	—	—
Chemotherapy-related mortality	2/55	0/51	0/52
Surgical complications			
Leakage	1/49	3/49	2/49
Pancreatic fistula	6/49	11/49	9/49
Abdominal abscess	2/49	8/49	—
Pneumonia	2/49	2/49	4/49
Wound infection	2/49	0/49	2/49
Anastomotic stenosis	1/49	0/49	1/49
Intestinal obstruction	0/49	0/49	2/49
Cardiac failure	1/49	—	—
Renal dysfunction	1/49	—	—
Atelectasis	—	3/49	—
Abdominal infection	—	—	5/49
Pleural effusion	—	—	6/49
Chylous ascites	—	—	3/49
Delayed gastric emptying	—	—	1/49
Thromboembolic event	—	2/49	2/49
Other	6/49	11/49	—
Postoperative mortality	1/49	0/49	0/49

CONCLUSION

The role of PAND is still worth exploring. Currently, prophylactic D2 + PAND has not shown a survival benefit, but improved survival with therapeutic PAND may benefit from related clinicopathological factors. Then, based on the survival benefit of PAND, given that many clinicopathological factors were reported to be highly related to PAN involvement, it is necessary to verify the lymphatic flow to PANs in gastric cancer and define accurate predictors for PAN metastasis and then explore indications for PAND. To date, CS chemotherapy combined with surgery plus extensive lymphadenectomy is considered the standard treatment for advanced gastric cancer in Japan. Therefore, neoadjuvant and adjuvant chemotherapy must not be ignored in the treatment of PAN metastasis. In the future, multimodal therapy including PAND combined with appropriate chemotherapy and with other therapies, such as conversion surgery or radiotherapy, remains to be evaluated in the form of a clinical trial to obtain improved prognosis and as few complications as possible.

REFERENCES

- 1 **Ferlay J**, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359-E386 [PMID: [25220842](#) DOI: [10.1002/ijc.29210](#)]
- 2 **Maruyama K**, Okabayashi K, Kinoshita T. Progress in gastric cancer surgery in Japan and its limits of radicality. *World J Surg* 1987; **11**: 418-425 [PMID: [3630186](#) DOI: [10.1007/bf01655804](#)]
- 3 **Sasako M**, McCulloch P, Kinoshita T, Maruyama K. New method to evaluate the therapeutic value of lymph node dissection for gastric cancer. *Br J Surg* 1995; **82**: 346-351 [PMID: [7796005](#) DOI: [10.1002/bjs.1800820321](#)]
- 4 **Takahashi S**. [Study of para-aortic lymph node metastasis of gastric cancer subjected to superextensive lymph node dissection]. *Nihon Geka Gakkai Zasshi* 1990; **91**: 29-35 [PMID: [2314380](#)]
- 5 **Kitamura M**, Arai K, Iwasaki Y. [Clinico-pathological studies and problems on para-aortic lymph node dissection--D4 dissection]. *Nihon Geka Gakkai Zasshi* 1996; **97**: 302-307 [PMID: [8692148](#)]
- 6 **Isozaki H**, Okajima K, Fujii K, Nomura E, Izumi N, Mabuchi H, Nakamura M, Hara H. Effectiveness of paraaortic lymph node dissection for advanced gastric cancer. *Hepatogastroenterology* 1999; **46**: 549-554 [PMID: [10228860](#)]
- 7 **Baba M**, Hokita S, Natsugoe S, Miyazono T, Shimada M, Nakano S, Takao S, Aikou T. Para-aortic lymphadenectomy in patients with advanced carcinoma of the upper-third of the stomach. *Hepatogastroenterology* 2000; **47**: 893-896 [PMID: [10919056](#)]
- 8 **Takeda J**, Koufujii K, Kodama I, Tsuji Y, Maruiwa M, Kawabata S, Suematsu T, Kakegawa T. Para-aortic lymph node dissection for the treatment of advanced gastric cancer. *Kurume Med J* 1993; **40**: 101-106 [PMID: [8139208](#) DOI: [10.2739/kurumemedj.40.101](#)]
- 9 **Yonemura Y**, Katayama K, Kamata T, Fushida S, Segawa M, Ooyama S, Miwa K, Miyazaki I. Surgical treatment of advanced gastric cancer with metastasis in para-aortic lymph node. *Int Surg* 1991; **76**: 222-225 [PMID: [1778720](#)]
- 10 **Nakane Y**, Okamura S, Masuya Y, Okumura S, Akehira K, Hioki K. Incidence and prognosis of para-aortic lymph node metastasis in gastric cancer. *Hepatogastroenterology* 1998; **45**: 1901-1906 [PMID: [9840173](#)]
- 11 **Takashima S**, Kosaka T. Results and controversial issues regarding a para-aortic lymph node dissection for advanced gastric cancer. *Surg Today* 2005; **35**: 425-431 [PMID: [15912287](#) DOI: [10.1007/s00595-004-2976-1](#)]
- 12 **Yonemura Y**. Lymphatic systems of the stomach and the patterns of lymph node metastases. *Contemporary approaches toward cure of gastric cancer* 1996; 3-14
- 13 **Kunisaki C**, Shimada H, Yamaoka H, Wakasugi J, Takahashi M, Akiyama H, Nomura M, Moriwaki Y. Significance of para-aortic lymph node dissection in advanced gastric cancer. *Hepatogastroenterology* 1999; **46**: 2635-2642 [PMID: [10522056](#)]
- 14 **Maeta M**, Yamashiro H, Saito H, Katano K, Kondo A, Tsujitani S, Ikeguchi M, Kaibara N. A prospective pilot study of extended (D3) and superextended para-aortic lymphadenectomy (D4) in patients with T3 or T4 gastric cancer managed by total gastrectomy. *Surgery* 1999; **125**: 325-331 [PMID: [10076618](#)]
- 15 **Kunisaki C**, Shimada H, Yamaoka H, Takahashi M, Ookubo K, Akiyama H, Nomura M, Moriwaki Y. Indications for paraaortic lymph node dissection in gastric cancer patients with paraaortic lymph node involvement. *Hepatogastroenterology* 2000; **47**: 586-589 [PMID: [10791244](#)]
- 16 **Gunji Y**, Suzuki T, Kobayashi S, Hori S, Hayashi H, Shimada H, Matsubara H, Nabeya Y, Ochiai T. Evaluation of D3/D4 lymph node dissection for patients with grossly N2 positive advanced gastric cancer. *Hepatogastroenterology* 2003; **50**: 1178-1182 [PMID: [12846009](#)]
- 17 **Marrelli D**, Pedrazzani C, Neri A, Corso G, DeStefano A, Pinto E, Roviello F. Complications after extended (D2) and superextended (D3) lymphadenectomy for gastric cancer: analysis of potential risk factors. *Ann Surg Oncol* 2007; **14**: 25-33 [PMID: [17024558](#) DOI: [10.1245/s10434-006-9063-3](#)]
- 18 **Günther K**, Horbach T, Merkel S, Meyer M, Schnell U, Klein P, Hohenberger W. D3 lymph node dissection in gastric cancer: evaluation of postoperative mortality and complications. *Surg Today* 2000; **30**: 700-705 [PMID: [10955732](#) DOI: [10.1007/s005950070080](#)]
- 19 **Bostanci EB**, Kayaalp C, Ozogul Y, Aydin C, Atalay F, Akoglu M. Comparison of complications after D2 and D3 dissection for gastric cancer. *Eur J Surg Oncol* 2004; **30**: 20-25 [PMID: [14736518](#) DOI: [10.1016/j.ejso.2003.10.008](#)]
- 20 **Kulig J**, Popiela T, Kolodziejczyk P, Sierzega M, Szczepanik A; Polish Gastric Cancer Study Group. Standard D2 versus extended D2 (D2+) lymphadenectomy for gastric cancer: an interim safety analysis of a multicenter, randomized, clinical trial. *Am J Surg* 2007; **193**: 10-15 [PMID: [17188080](#) DOI: [10.1016/j.amjsurg.2006.04.018](#)]
- 21 **Roviello F**, Pedrazzani C, Marrelli D, Di Leo A, Caruso S, Giacomuzzi S, Corso G, de Manzoni G. Super-extended (D3) lymphadenectomy in advanced gastric cancer. *Eur J Surg Oncol* 2010; **36**: 439-446 [PMID: [20392590](#) DOI: [10.1016/j.ejso.2010.03.008](#)]
- 22 **Kodera Y**. Para-aortic lymph node dissection revisited: have we been neglecting a promising treatment option for gastric carcinoma? *Eur J Surg Oncol* 2010; **36**: 447-448 [PMID: [20385470](#) DOI: [10.1016/j.ejso.2010.03.012](#)]
- 23 **Sano T**, Aiko T. New Japanese classifications and treatment guidelines for gastric cancer: revision concepts and major revised points. *Gastric Cancer* 2011; **14**: 97-100 [PMID: [21573921](#) DOI: [10.1007/s10120-011-0040-6](#)]
- 24 **Nomura E**, Sasako M, Yamamoto S, Sano T, Tsujinaka T, Kinoshita T, Furukawa H, Shimizu T, Hiratsuka M, Kobayashi O, Kurokawa Y, Tanigawa N; Gastric Cancer Surgical Study Group of the Japan Clinical Oncology Group. Risk factors for para-aortic lymph node metastasis of gastric cancer from a randomized controlled trial of JCOG9501. *Jpn J Clin Oncol* 2007; **37**: 429-433 [PMID: [17656480](#) DOI: [10.1093/jjco/hym067](#)]
- 25 **Japanese Gastric Cancer Association**. Japanese Classification of Gastric Carcinoma - 2nd English Edition -. *Gastric Cancer* 1998; **1**: 10-24 [PMID: [11957040](#) DOI: [10.1007/s101209800016](#)]

- 26 **Amin MB**, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, Meyer L, Gress DM, Byrd DR, Winchester DP. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin* 2017; **67**: 93-99 [PMID: 28094848 DOI: 10.3322/caac.21388]
- 27 **Japanese Gastric Cancer Association**. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**: 101-112 [PMID: 21573743 DOI: 10.1007/s10120-011-0041-5]
- 28 **de Manzoni G**, Di Leo A, Roviello F, Marrelli D, Giacomuzzi S, Minicozzi AM, Verlato G. Tumor site and perigastric nodal status are the most important predictors of para-aortic nodal involvement in advanced gastric cancer. *Ann Surg Oncol* 2011; **18**: 2273-2280 [PMID: 21286941]
- 29 **Wang Z**, Chen JQ, Cao YF. Systematic review of D2 lymphadenectomy versus D2 with para-aortic nodal dissection for advanced gastric cancer. *World J Gastroenterol* 2010; **16**: 1138-1149 [PMID: 20205287 DOI: 10.3748/wjg.v16.i9.1138]
- 30 **Sano T**, Sasako M, Yamamoto S, Nashimoto A, Kurita A, Hiratsuka M, Tsujinaka T, Kinoshita T, Arai K, Yamamura Y, Okajima K. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy--Japan Clinical Oncology Group study 9501. *J Clin Oncol* 2004; **22**: 2767-2773 [PMID: 15199090 DOI: 10.1200/jco.2004.10.184]
- 31 **Tokunaga M**, Ohyama S, Hiki N, Fukunaga T, Aikou S, Yamaguchi T. Can superextended lymph node dissection be justified for gastric cancer with pathologically positive para-aortic lymph nodes? *Ann Surg Oncol* 2010; **17**: 2031-2036 [PMID: 20182811 DOI: 10.1245/s10434-010-0969-4]
- 32 **Yoshikawa T**, Sasako M, Sano T, Nashimoto A, Kurita A, Tsujinaka T, Tanigawa N, Yamamoto S. Stage migration caused by D2 dissection with para-aortic lymphadenectomy for gastric cancer from the results of a prospective randomized controlled trial. *Br J Surg* 2006; **93**: 1526-1529 [PMID: 17051601 DOI: 10.1002/bjs.5487]
- 33 **Tsuburaya A**, Mizusawa J, Tanaka Y, Fukushima N, Nashimoto A, Sasako M; Stomach Cancer Study Group of the Japan Clinical Oncology Group. Neoadjuvant chemotherapy with S-1 and cisplatin followed by D2 gastrectomy with para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis. *Br J Surg* 2014; **101**: 653-660 [PMID: 24668391 DOI: 10.1002/bjs.9484]
- 34 **Fujimura T**, Nakamura K, Oyama K, Funaki H, Fujita H, Kinami S, Ninomiya I, Fushida S, Nishimura G, Kayahara M, Ohta T. Selective lymphadenectomy of para-aortic lymph nodes for advanced gastric cancer. *Oncol Rep* 2009; **22**: 509-514 [PMID: 19639196 DOI: 10.3892/or.00000464]
- 35 **Morita S**, Fukagawa T, Fujiwara H, Katai H. Questionnaire survey regarding the current status of super-extended lymph node dissection in Japan. *World J Gastrointest Oncol* 2016; **8**: 707-714 [PMID: 27672429 DOI: 10.4251/wjgo.v8.i9.707]
- 36 **Park IH**, Kim SY, Kim YW, Ryu KW, Lee JH, Lee JS, Park YI, Kim NK, Park SR. Clinical characteristics and treatment outcomes of gastric cancer patients with isolated para-aortic lymph node involvement. *Cancer Chemother Pharmacol* 2011; **67**: 127-136 [PMID: 20221601 DOI: 10.1007/s00280-010-1296-y]
- 37 **Sasako M**, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A, Hiratsuka M, Tsujinaka T, Kinoshita T, Arai K, Yamamura Y, Okajima K; Japan Clinical Oncology Group. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med* 2008; **359**: 453-462 [PMID: 18669424 DOI: 10.1056/NEJMoa0707035]
- 38 **Yonemura Y**, Wu CC, Fukushima N, Honda I, Bandou E, Kawamura T, Kamata S, Yamamoto H, Kim BS, Matsuki N, Sawa T, Noh SH; East Asia Surgical Oncology Group. Metastasis in para-aortic lymph nodes in patients with advanced gastric cancer, treated with extended lymphadenectomy. *Hepatogastroenterology* 2007; **54**: 634-638 [PMID: 17523339]
- 39 **Shimoyama S**, Mafune K, Kaminishi M. Safety of a paraaortic node dissection for selected advanced gastric cancer patients. *Hepatogastroenterology* 2005; **52**: 1631-1635 [PMID: 16201131]
- 40 **Yonemura Y**, Wu CC, Fukushima N, Honda I, Bandou E, Kawamura T, Kamata T, Kim BS, Matsuki N, Sawa T, Noh SH; East Asia Surgical Oncology Group. Randomized clinical trial of D2 and extended paraaortic lymphadenectomy in patients with gastric cancer. *Int J Clin Oncol* 2008; **13**: 132-137 [PMID: 18463957 DOI: 10.1007/s10147-007-0727-1]
- 41 **Junfeng Z**, Yingxue H, Peiwu Y. Systematic review of risk factors for metastasis to para-aortic lymph nodes in gastric cancer. *Surg Oncol* 2013; **22**: 210-216 [PMID: 24269310 DOI: 10.1016/j.suronc.2013.10.003]
- 42 **Chen XZ**, Hu JK, Zhou ZG, Rui YY, Yang K, Wang L, Zhang B, Chen ZX, Chen JP. Meta-analysis of effectiveness and safety of D2 plus para-aortic lymphadenectomy for resectable gastric cancer. *J Am Coll Surg* 2010; **210**: 100-105 [PMID: 20123339 DOI: 10.1016/j.jamcollsurg.2009.09.033]
- 43 **Wang L**, Liang H, Wang X, Li F, Ding X, Deng J. Risk factors for metastasis to para-aortic lymph nodes in gastric cancer: a single institution study in China. *J Surg Res* 2013; **179**: 54-59 [PMID: 23040213 DOI: 10.1016/j.jss.2012.08.037]
- 44 **Hu JK**, Yang K, Zhang B, Chen XZ, Chen ZX, Chen JP. D2 plus para-aortic lymphadenectomy versus standardized D2 lymphadenectomy in gastric cancer surgery. *Surg Today* 2009; **39**: 207-213 [PMID: 19280279 DOI: 10.1007/s00595-008-3856-x]
- 45 **Liang H**, Deng J. Evaluation of rational extent lymphadenectomy for local advanced gastric cancer. *Chin J Cancer Res* 2016; **28**: 397-403 [PMID: 27647967 DOI: 10.21147/j.issn.1000-9604.2016.04.02]
- 46 **Ohno S**, Tomisaki S, Oiwa H, Sakaguchi Y, Ichiyoshi Y, Maehara Y, Sugimachi K. Clinicopathologic characteristics and outcome of adenocarcinoma of the human gastric cardia in comparison with carcinoma of other regions of the stomach. *J Am Coll Surg* 1995; **180**: 577-582 [PMID: 7749534]
- 47 **Douridas GN**, Pierrakakis SK. Is There Any Role for D3 Lymphadenectomy in Gastric Cancer? *Front Surg* 2017; **5**: 27 [PMID: 29740588 DOI: 10.3389/fsurg.2018.00027]
- 48 **Craanen ME**, Dekker W, Blok P, Ferwerda J, Tytgat GN. Time trends in gastric carcinoma: changing patterns of type and location. *Am J Gastroenterol* 1992; **87**: 572-579 [PMID: 1306644]
- 49 **Blot WJ**, Devesa SS, Kneller RW, Fraumeni JF Jr. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA* 1991; **265**: 1287-1289 [PMID: 1995976]

- 50 **Kodama I**, Kofuji K, Yano S, Shinozaki K, Murakami N, Hori H, Takeda J, Shirouzu K. Lymph node metastasis and lymphadenectomy for carcinoma in the gastric cardia: clinical experience. *Int Surg* 1998; **83**: 205-209 [PMID: [9870775](#)]
- 51 **Ota K**, Nishi M, Nakajima T. Significance of dissecting lateroaortic lymph node (around left renal vein) in cardiac cancer. *Jpn J Gastroenterol Surg (in Japanese)* 1990; **23**: 1204-1207
- 52 **Sarrazin R**, Pissas A, Dyon J, Bouchet Y. Lymphatic Drainage of Stomach. *Anatomia Clinica* 1979; **2**: 95-110
- 53 **Zhang C**, He Y, Schwarz RE, Smith DD, Wang L, Liu F, Zhan W. Evaluation of para-aortic nodal dissection for locoregionally advanced gastric cancer with 1-3 involved para-aortic nodes. *Chin Med J (Engl)* 2014; **127**: 435-441 [PMID: [24451947](#)]
- 54 **Lee JH**, Paik YH, Lee JS, Song HJ, Ryu KW, Kim CG, Park SR, Kook MC, Kim YW, Bae JM. Candidates for curative resection in advanced gastric cancer patients who had equivocal para-aortic lymph node metastasis on computed tomographic scan. *Ann Surg Oncol* 2006; **13**: 1163-1167 [PMID: [16952027](#) DOI: [10.1245/s10434-006-9002-3](#)]
- 55 **Kunisaki C**, Akiyama H, Nomura M, Matsuda G, Otsuka Y, Ono H, Nagahori Y, Hosoi H, Takahashi M, Kito F, Shimada H. Comparison of surgical results of D2 versus D3 gastrectomy (para-aortic lymph node dissection) for advanced gastric carcinoma: a multi-institutional study. *Ann Surg Oncol* 2006; **13**: 659-667 [PMID: [16538414](#) DOI: [10.1245/ASO.2006.07.015](#)]
- 56 **Nomura M**, Kunisaki C, Akiyama H, Matsuda G, Otsuka Y, Ono H, Takahashi M, Shimada H. Surgical outcome of para-aortic lymph node dissection preserving neural tissue based on anatomical evaluations. *J Gastrointest Surg* 2005; **9**: 781-788 [PMID: [15985233](#) DOI: [10.1016/j.gassur.2005.03.004](#)]
- 57 **de Manzoni G**, Verlato G, Guglielmi A, Laterza E, Genna M, Cordiano C. Prognostic significance of lymph node dissection in gastric cancer. *Br J Surg* 1996; **83**: 1604-1607 [PMID: [9014687](#) DOI: [10.1002/bjs.1800831137](#)]
- 58 **Bunt AM**, Hermans J, Smit VT, van de Velde CJ, Fleuren GJ, Bruijn JA. Surgical/pathologic-stage migration confounds comparisons of gastric cancer survival rates between Japan and Western countries. *J Clin Oncol* 1995; **13**: 19-25 [PMID: [7799019](#) DOI: [10.1200/JCO.1995.13.1.19](#)]
- 59 **Sasako M**, Sano T, Yamamoto S, Sairenji M, Arai K, Kinoshita T, Nashimoto A, Hiratsuka M; Japan Clinical Oncology Group (JCOG9502). Left thoracoabdominal approach versus abdominal-transhiatal approach for gastric cancer of the cardia or subcardia: a randomised controlled trial. *Lancet Oncol* 2006; **7**: 644-651 [PMID: [16887481](#) DOI: [10.1016/S1470-2045\(06\)70766-5](#)]
- 60 **Oyama K**, Fushida S, Kinoshita J, Makino I, Nakamura K, Hayashi H, Nakagawara H, Tajima H, Fujita H, Takamura H, Ninomiya I, Kitagawa H, Tani T, Fujimura T, Ohta T. Efficacy of pre-operative chemotherapy with docetaxel, cisplatin, and S-1 (DCS therapy) and curative resection for gastric cancer with pathologically positive para-aortic lymph nodes. *J Surg Oncol* 2012; **105**: 535-541 [PMID: [22006649](#) DOI: [10.1002/jso.22125](#)]
- 61 **Yoshikawa T**, Sasako M, Yamamoto S, Sano T, Imamura H, Fujitani K, Oshita H, Ito S, Kawashima Y, Fukushima N. Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer. *Br J Surg* 2009; **96**: 1015-1022 [PMID: [19644974](#) DOI: [10.1002/bjs.6665](#)]
- 62 **Ito S**, Sano T, Mizusawa J, Takahari D, Katayama H, Katai H, Kawashima Y, Kinoshita T, Terashima M, Nashimoto A, Nakamori M, Onaya H, Sasako M. A phase II study of preoperative chemotherapy with docetaxel, cisplatin, and S-1 followed by gastrectomy with D2 plus para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis: JCOG1002. *Gastric Cancer* 2017; **20**: 322-331 [PMID: [27299887](#) DOI: [10.1007/s10120-016-0619-z](#)]
- 63 **Takahari D**, Ito S, Mizusawa J, Katayama H, Terashima M, Sasako M, Morita S, Nomura T, Yamada M, Fujiwara Y, Kimura Y, Ikeda A, Kadokawa Y, Sano T; Stomach Cancer Study Group of the Japan Clinical Oncology Group. Long-term outcomes of preoperative docetaxel with cisplatin plus S-1 therapy for gastric cancer with extensive nodal metastasis (JCOG1002). *Gastric Cancer* 2020; **23**: 293-299 [PMID: [31515693](#) DOI: [10.1007/s10120-019-01007-w](#)]
- 64 **Wang Y**, Yu YY, Li W, Feng Y, Hou J, Ji Y, Sun YH, Shen KT, Shen ZB, Qin XY, Liu TS. A phase II trial of Xeloda and oxaliplatin (XELOX) neo-adjuvant chemotherapy followed by surgery for advanced gastric cancer patients with para-aortic lymph node metastasis. *Cancer Chemother Pharmacol* 2014; **73**: 1155-1161 [PMID: [24748418](#) DOI: [10.1007/s00280-014-2449-1](#)]
- 65 **Macdonald JS**, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; **345**: 725-730 [PMID: [11547741](#) DOI: [10.1056/NEJMoa010187](#)]
- 66 **Inoue T**, Yachida S, Usuki H, Kimura T, Hagiike M, Okano K, Suzuki Y. Pilot feasibility study of neoadjuvant chemoradiotherapy with S-1 in patients with locally advanced gastric cancer featuring adjacent tissue invasion or JGCA bulky N2 lymph node metastases. *Ann Surg Oncol* 2012; **19**: 2937-2945 [PMID: [22466666](#) DOI: [10.1245/s10434-012-2332-4](#)]
- 67 **Sun J**, Sun YH, Zeng ZC, Qin XY, Zeng MS, Chen B, Liu TS, Zhang JY. Consideration of the role of radiotherapy for abdominal lymph node metastases in patients with recurrent gastric cancer. *Int J Radiat Oncol Biol Phys* 2010; **77**: 384-391 [PMID: [19577861](#) DOI: [10.1016/j.ijrobp.2009.05.019](#)]
- 68 **He Q**, Ma L, Li Y, Li G. A pilot study of an individualized comprehensive treatment for advanced gastric cancer with para-aortic lymph node metastasis. *BMC Gastroenterol* 2016; **16**: 8 [PMID: [26782354](#) DOI: [10.1186/s12876-016-0422-7](#)]
- 69 **Kodera Y**, Sasako M, Yamamoto S, Sano T, Nashimoto A, Kurita A; Gastric Cancer Surgery Study Group of Japan Clinical Oncology Group. Identification of risk factors for the development of complications following extended and superextended lymphadenectomies for gastric cancer. *Br J Surg* 2005; **92**: 1103-1109 [PMID: [16106493](#) DOI: [10.1002/bjs.4979](#)]
- 70 **Zhan WH**, Han FH, He YL, Li YM, Zheng ZQ, Peng JS, Cai SR, Ma JP. [Disciplinarian of lymph node metastasis and effect of paraaortic lymph nodes dissection on clinical outcomes in advanced gastric carcinoma]. *Zhonghua Wei Chang Wai Ke Za Zhi* 2006; **9**: 17-22 [PMID: [16437364](#)]

- 71 **Jiang B**, Gao Y, Sun R, Shen H, Lu M, Tu C. Clinical study on the dissection of lymph nodes around abdominal aortic artery in advanced gastric cancer. *Zhongguo Putong Waiké Zazhi* 2000; **9**: 292-295
- 72 **Marrelli D**, De Stefano A, de Manzoni G, Morgagni P, Di Leo A, Roviello F. Prediction of recurrence after radical surgery for gastric cancer: a scoring system obtained from a prospective multicenter study. *Ann Surg* 2005; **241**: 247-255 [PMID: [15650634](#) DOI: [10.1097/01.sla.0000152019.14741.97](#)]
- 73 **Morita S**, Fukagawa T, Fujiwara H, Katai H. The clinical significance of para-aortic nodal dissection for advanced gastric cancer. *Eur J Surg Oncol* 2016; **42**: 1448-1454 [PMID: [26876636](#) DOI: [10.1016/j.ejso.2016.01.002](#)]
- 74 **Yonemura Y**, Wu CC, Fukushima N, Honda I, Bandou E, Kawamura T, Kamata S, Yamamoto H, Kim BS, Matsuki N, Sawa T, Noh SH; East Asia Surgical Oncology Group. Operative morbidity and mortality after D2 and D4 extended dissection for advanced gastric cancer: a prospective randomized trial conducted by Asian surgeons. *Hepatogastroenterology* 2006; **53**: 389-394 [PMID: [16795979](#)]
- 75 **Cunningham D**, Allum W, Stenning S, Weeden S. Perioperative chemotherapy in operable gastric and lower oesophageal cancer: final results of a randomised, controlled trial (the MAGIC trial, ISRCTN 93793971). *J Clin Oncol* 2005; **23**: 4001 [DOI: [10.1200/jco.2005.23.16_suppl.4001](#)]
- 76 **Wu CW**, Lo SS, Shen KH, Hsieh MC, Chen JH, Chiang JH, Lin HJ, Li AF, Lui WY. Incidence and factors associated with recurrence patterns after intended curative surgery for gastric cancer. *World J Surg* 2003; **27**: 153-158 [PMID: [12616428](#) DOI: [10.1007/s00268-002-6279-7](#)]
- 77 **Yamada S**. A five-year survivor of gastric cancer with para-aortic and right supra-clavicular lymph node metastasis. *Nippon Rinsho (Jpn J Clin Med)* 1968; **26**: 2052-2053
- 78 **de Manzoni G**, Verlato G, Bencivenga M, Marrelli D, Di Leo A, Giacomuzzi S, Cipollari C, Roviello F. Impact of super-extended lymphadenectomy on relapse in advanced gastric cancer. *Eur J Surg Oncol* 2015; **41**: 534-540 [PMID: [25707350](#) DOI: [10.1016/j.ejso.2015.01.023](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

