

## Review Article

# Results and Controversial Issues Regarding a Para-Aortic Lymph Node Dissection for Advanced Gastric Cancer

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### Abstract

More than 20% of the patients with advanced gastric cancer display para-aortic lymph node (PAL) metastasis. Numerous retrospective comparative studies have reported an improved prognosis using an extensive lymph node dissection (D2) with PAL dissection, compared with D2 alone. However, many issues associated with a PAL dissection remain, such as the importance of stage migration, learning curves, and micrometastasis. This review focuses on the results and controversial issues associated with a PAL dissection. The depth of tumor invasion correlates with PAL metastasis, and whether PAL should be dissected in patients with T2 tumors remains controversial. The rate of PAL positivity is higher for cancers involving tumors of the upper third of the stomach. The most important lymphatic terminals for the stomach seem to comprise the a2 lateroaortic and b1 interaorticocaval PAL areas in tumors of the upper third and lower third, respectively. While the 5-year survival rate is about 10% after D2 plus a PAL dissection, patients with a potentially curative operation live longer. Early major complications after a PAL dissection occur in 25% of all cases, predominantly due to a pancreatectomy. A randomized clinical study evaluating a PAL dissection was launched in 1995 in Japan. Furthermore, numerous reports of patients with gastric cancer and PAL metastases responding to chemotherapy should also be considered.

**Key words** Para-aortic lymph nodes · Super-extended dissection · Gastric cancer

### Introduction

Gastric cancer is now the second most common cancer in males and the fifth most common in women worldwide, and it is one of the top three causes of death from cancer in both sexes, accounting for 646 000 deaths annually around the world.<sup>1</sup> Metastasis most commonly affects the lymph nodes, from the regional perigastric nodes to distant nodes. The lymphatic flow from the stomach and other upper abdominal organs reaches the para-aortic lymph nodes (PALs), which then join to form the thoracic duct.<sup>2,3</sup> In 1968 Yamada and Nakamura<sup>4</sup> reported, for the first time in Japan, a case of a 5-year survivor with gastric cancer and PAL metastasis who displayed simultaneous right supraclavicular lymph node metastasis. The following year, Nishi et al.<sup>5</sup> reported three 5-year survivors with gastric cancer and PAL metastasis, including the Yamada case. As of 1993, a total of 37 patients had been reported in the Japanese literature with PAL metastasis and a survival of more than 5 years following a PAL dissection.<sup>6</sup>

In Japan, an extensive lymph node dissection (D2 dissection<sup>7</sup>) for gastric cancer has become common. However, Japanese surgeons have begun to attempt more radical operations comprising a D2 plus PAL dissection, to improve the prognosis for advanced gastric cancer. Although some surgeons have reported a high frequency of PAL metastasis and a fair prognosis of patients after a PAL dissection, several problems such as higher morbidity rates have become obvious with a PAL dissection. As the efficacy of a PAL dissection remains controversial, a phase III study comparing a PAL dissection with a D2 dissection was launched by the Japan Clinical Oncology Group (JCOG) in 1995. A few more years of follow-up are needed before a final survival analysis can be made.<sup>8</sup> The present review focuses on the actual rates of metastasis to PAL, the survival benefits, the mortality and morbidity rates after a

PAL dissection, and controversial issues regarding the evaluation of this procedure.

### Frequency of Para-Aortic Lymph Node Metastasis After a Prospective Dissection

The mean number of dissected PALs was  $43 \pm 3$  in 5 autopsy cases,<sup>6</sup> compared with 14.4 in 129 surgical cases<sup>9</sup> and 15.4 in 75 surgical cases.<sup>10</sup> The median frequency of histological PAL metastasis after a prospective PAL dissection was 21.6% (range, 6.2%–33.0%; 934/4108 in total), from reports in which wall invasion of treated cancer extended as far as or beyond T2 (invading the muscularis propriae (MP) or the subserosal layer (SS)).<sup>6,9–25</sup> Differences between reports are considered to result from different indications for dissection, the extent of surgery, and/or postoperative examinations of PALs.

### Relationship Between Clinicopathological Factors and PAL Metastasis

#### Depth of Tumor Invasion

Para-aortic lymph node metastasis in patients with early gastric cancer is very rare. The median frequency of PAL metastasis was 8.6% (range, 0%–27.3%) for tumors with a histological depth of pT2,<sup>7</sup> 28.0% (range, 14.9%–32.2%) for pT3, and 33.0% (range, 19.4%–50%) for pT4 (Table 1). The rate of metastasis correlates with the depth of tumor invasion. Regarding macroscopic serosal cancer invasion, 10.1%–11.5% of all patients without serosal invasion display positive PALs.<sup>13,14,20</sup> These results indicate that even patients without macroscopic serosal invasion may require a PAL dissection for the effective treatment of gastric cancer.

**Table 1.** Correlation between the histological depth of invasion and the metastatic rate to the para-aortic lymph nodes (PAL) in patients with gastric cancer

First author <sup>Ref.</sup>	Year	T1	T2	T3	T4
Sasaki <sup>11</sup>	1989	4.8%	15.1%	25.7%	26.7%
Yonemura <sup>26</sup>	1989	—	5.4%	19.7%	19.4%
Kouji <sup>27</sup>	1994	—	0%	14.9%	41.2%
Kitamura <sup>19</sup>	1996	—	7.9%	32.2%	30.2%
Yamamura <sup>20</sup>	1996	0%	20.4%	32.0%	37.5%
Nakane <sup>22</sup>	1998	0%	8.6%	30.2%	50.0%
Baba <sup>10</sup>	2000	—	27.3%	28.0%	33.0%

Data are defined according to rules of the Japanese Gastric Cancer Association (JGCA), 1999<sup>7</sup>

T1, mucosa and submucosa; T2, muscularis propria and subserosa; T3, serosa exposed; T4, invasive into adjacent organs

### Macroscopic Lymph Node Metastasis

In the PAL metastasis group, accuracy was high, probably because frozen-section procedures were used during surgery. Conversely, the median frequency of PAL metastasis did not seem to correlate with the N category in other cases (Table 2).<sup>11,14,19,20,23</sup> Clinicians need to be more aware that the accuracy of the operative diagnosis for lymph node metastasis remains poor.

#### Location of Stomach Tumor

According to the tumor site, the median frequency of PAL metastasis is relatively low in patients with cancer of the middle third (M) or lower third of the stomach (L), at 16.7% (range, 13%–25%) and 17.6% (range, 10.7%–26%), respectively. In comparison, the frequency is 27.0% (range, 15.7%–38.9%) with cancer of the upper third of the stomach (U) and 42.1% (range, 27.3%–46.9%) with tumors of the whole stomach.<sup>6,9,10,12,22</sup> The frequency is high in tumors of the whole stomach because these tumors are larger and more advanced than those in other categories. Furthermore, the lymphatic system flows from the upper part of the stomach directly down to the para-aortic region, thus leading to an increased frequency of PAL metastasis in patients with U.

### Extent of PAL Dissection

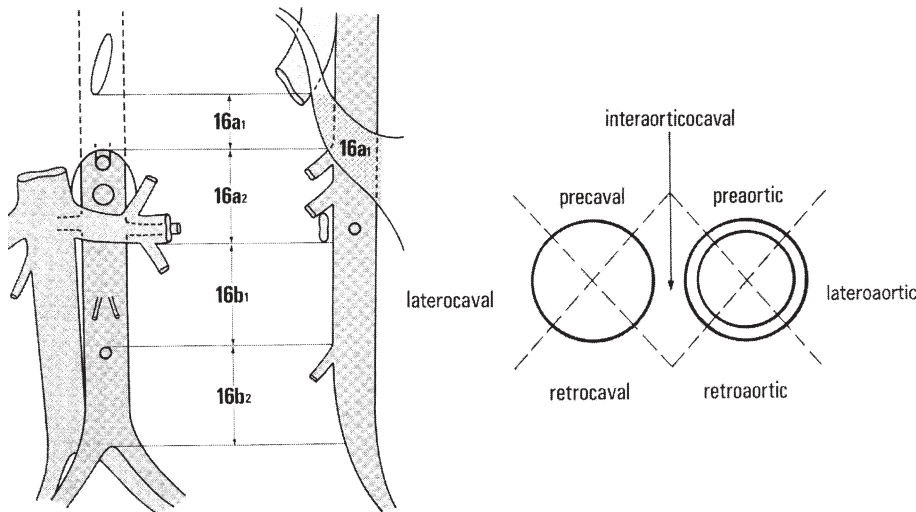
#### Classification of PALs in Japan

The Committee on the Classification of Regional Lymph Nodes of Japan Society of Clinical Oncology proposed a revised classification of the regional nodes in 2003.<sup>29</sup> Abdominal PALs are classified into the following four groups, from cranial to caudal: a1, a2, b1, and b2 (Fig. 1). The nodes between a2 and b1 are classified into compartment 3 groups in the latest rules of gastric cancer in Japan. Conversely, the nodes in a1 and b2 are considered to represent stage M1 distant metastases.<sup>7</sup> The lymph nodes in the cross-sectional circumference

**Table 2.** Correlation between the macroscopic degree of lymph node metastasis and the metastatic rate to the PAL in patients with gastric cancer

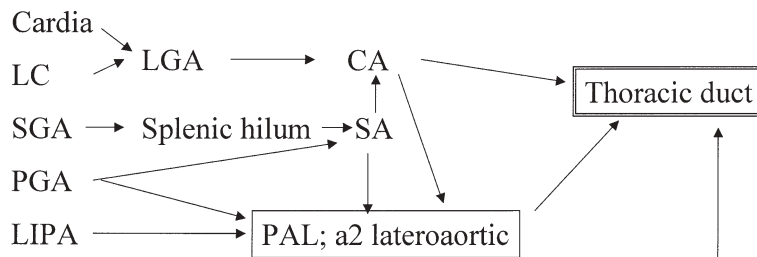
First author <sup>Ref.</sup>	Year	N0	N1	N2	N3	N4
Yonemura <sup>26</sup>	1989	0.9%	0.9%	0%	6.7%	58.3%
Nashimoto <sup>14</sup>	1991	0%	3.6%	8.7%	15.0%	84.4%
Kitamura <sup>19</sup>	1996	7.5%	7.1%	23.2%	41.7%	76.9%
Yamamura <sup>20</sup>	1996	1.9%	—	17.6%	—	71.4%
Sasaki <sup>11</sup>	1999	—	10.1%	10.1%	26.7%	26.7%

N stage defined according to rules of the JGCA, 1995<sup>28</sup>  
N4, positive PAL metastasis

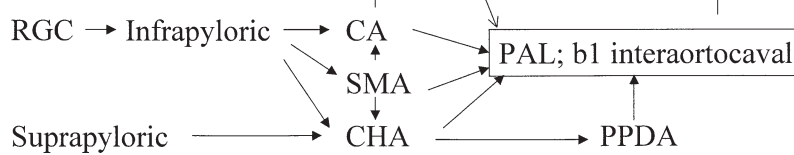


**Fig. 1.** Classification of the lymph nodes around the abdominal aorta according to the Japanese Gastric Cancer Association, 1999<sup>7</sup>

a. Upper third of the stomach



b. Lower third of the stomach



**Fig. 2.** Lymphatic flow from the stomach. *LC*, lesser curvature; *LGA*, left gastric artery; *CA*, celiac artery; *SGA*, short gastric artery; *SA*, splenic artery; *PGA*, posterior gastric artery; *LIPA*, left inferior phrenic artery; *RGC*, right greater curvature; *SMA*, superior mesenteric artery; *CHA*, common hepatic artery; *PPDA*, posterior pancreaticoduodenal artery

of the abdominal aorta and inferior vena cava can be classified as follows: preaortic, lateroaortic, retroaortic, interaortocaval, precaval, laterocaval, and retrocaval (Fig. 1).<sup>29</sup>

*Relationship Between the Tumor Location in the Stomach and the Localization of Lymph Node Metastasis in the Para-Aortic Region*

In patients with U, some surgeons<sup>11,14</sup> have reported a high frequency of metastasis in the lateroaortic area of the a2 region, while metastases commonly occur in the lateroaortic area of the a2 and b1 regions in patients with M, and in the interaortocaval and lateroaortic areas of the b1 region in patients with L. However, other authors have reported that patients with U display a high frequency of metastasis in the lateroaortic area of

the a2 and b1 regions, whereas M is associated with metastases in the interaortocaval and lateroaortic areas, and L with metastases of the interaortocaval area of the a2 and b1 regions.<sup>16,22</sup> Furthermore, some reports<sup>19,23</sup> have noted that the rates of lymph node metastasis at each PAL site do not differ with the tumor location. Such discrepancies may result from differing indications for a PAL dissection, the extent of procedures, and definitions of PAL subclassification. Although the relationships between the tumor location in the stomach and the localization of lymph node metastasis in the para-aortic region remain controversial, these results indicate that the major and important PAL sites are the lateroaortic area of a2 in U, the interaortocaval area of b1 in L, and both areas in M or tumors of the entire stomach, as these display the characteristics of both U and L (Fig. 2).<sup>30</sup>

**Table 3.** Gastric cancer patients with PAL metastasis surviving more than 5 years at Kanazawa Medical University Hospital

Age (years)	Sex	Surgery	pT	P	PAL	Outcome	Metastasis
64	M	DG	SS	0	1/4	5y 0mo, alive	
64	F	DG	SS	0	2/29	5y 4mo, alive	
67	M	DG	SS	0	3/13	5y 10mo, alive	
64	M	DG	SE	0	2/7	5y 10mo, dead	Lung
39	M	TG	SE	1	1/33	7y 4mo, alive	
67	M	TG	MP	0	6/23	7y 5mo, alive	
56	M	DG	SI	0	1/5	7y 7mo, dead	Bone
74	M	TG	SE	0	8/27	8y 4mo, alive	

PAL, number of positive nodes/total number of nodes. Data are defined according to the rules of the JGCA, 1999<sup>7</sup>

DG, distal gastrectomy; TG, total gastrectomy; pT, histological depth of tumor invasion; MP, muscularis propria; SS, subserosa; SE, serosa exposed; SI, serosa exposed and invasive into adjacent organs; y, years; mo, months

### Survival of Patients with Positive PALs

The median 5-year survival rate of gastric cancer patients with PAL metastasis was 9% (range, 0%–20%) in all dissected cases.<sup>6,9,10,12,13,16,20,22,23</sup> Furthermore, the median 5-year survival rate went up to 16.5% (range, 12.1%–23%) in the potentially curative resection cases (Curability B of Japanese Gastric Cancer Association rules 1999<sup>7</sup>),<sup>11,13,14,19,20,21</sup> and much higher in cases with smaller numbers of PAL metastases (Table 3).<sup>9,10,14,16,21</sup> The criteria for a PAL dissection in advanced gastric cancer for reported studies comprised no distant metastasis other than PALs, and a small number of PAL metastases.

### Morbidity and Mortality After a PAL Dissection

The median rate of early major complications after a PAL dissection was 26.1% (range, 21.8%–33.7%) and the median operative mortality was 1.3% (range, 0.7%–6.2%). Of all complications, pancreatic fistulae and abscesses (range, 12.2%–28.0%) are the most common and critical complications, and result not from the removal of PALs, but from the combined resection of adjacent organs, such as the pancreas.<sup>12,13,16,17,19,20,23,25,31</sup> Several surgeons have reported an organ-preserving gastrectomy with a super-extended lymphadenectomy, including a PAL dissection.<sup>32,33</sup> The reported operative morbidity and mortality rates have decreased in recent cases compared with those for the initial cases. Surgical subspecialization has thus reduced the operative mortality due to the learning curve.<sup>34</sup>

**Table 4.** Retrospective comparative studies between D2 + PAL and D2, showing a better prognosis in the former group

First author <sup>Ref.</sup>	Year	Categories in which the prognosis of the D2 + PAL group was better than in the D2 group
Suzuki <sup>12</sup>	1990	Stage III
Yonemura <sup>13</sup>	1991	PAL positive
Kitamura <sup>17</sup>	1995	Various stages
Kosaka <sup>18</sup>	1995	PAL positive
Sawai <sup>21</sup>	1997	Histological SE–SI and N0–N2
Isozaki <sup>23</sup>	1999	PAL positive
Kunisaki <sup>24</sup>	2000	N2 and SE
Gunji <sup>25</sup>	2003	Stage IIIB

Data are defined according to the rules of the JGCA, 1999<sup>7</sup>

SE, serosa exposed; SI, serosa exposed and invasive into adjacent organs

### Comparison of a D2 Dissection Plus PAL and D2 Alone

Retrospective comparative studies between a conventional D2 dissection and D2 + PAL have shown the benefits of the latter procedure regarding the survival rates. The completeness of a D2 dissection, stage migration,<sup>35,36</sup> micrometastasis, and the learning curve following PAL can all improve the survival rates for D2 with a PAL dissection (Table 4).

An immunohistological (IHC) analysis demonstrated microinvolvement in 22.9% (736/3208) of the removed lymph nodes from pN0 cases, and the presence of cancer cells in the lymph nodes was of significant prognostic value.<sup>37</sup> Several recent studies have reported 3.0%–17.6% of the lymph nodes to be negative for metastasis based on hematoxylin–eosin (H&E) staining, but positive based on an IHC analysis, and 14.5%–45.5% of the patients are staged as histologically negative based on H&E staining, but display positive results for metastasis based on an IHC analysis. The size, depth of tumor

invasion, and histological type also reportedly correlate with the frequency of lymph node micrometastasis, and the presence of micrometastasis correlates with a worse prognosis for patients with histological node-negative gastric cancer.<sup>38-42</sup>

### Randomized Clinical Trial

A comparative phase III study of a PAL dissection with conventional D2 was launched by JCOG in 1995. During surgery, they registered patients with advanced cancer invading as far as or beyond the subserosa, with no evidence of distant metastasis, negative findings on peritoneal washing cytology, and a potential for a curative resection.<sup>8</sup> Although we must await the final analysis, some problems may exist in this protocol, particularly regarding the fact that eligibility criteria are based on the operative findings and the preoperative diagnosis. The operative diagnosis of serosal invasion and PAL metastasis can be very challenging and it also has a high probability of differing among surgeons.

### Responders to Antitumor Drugs with PAL Metastasis

Some surgeons have reported responders to postoperative adjuvant chemotherapy among advanced gastric cancer patients with PAL metastasis.<sup>43,44</sup> Recently, neoadjuvant chemotherapy has received increasing attention for the treatment of patients with distant metastasis. Drugs such as 5-fluorouracil, cisplatin, TS-1, and irinotecan have shown high response rates and thus positively contribute to subsequent curative surgery even with a preoperative diagnosis of PAL metastasis.<sup>45-50</sup>

### Conclusions

More than 20% of the patients with advanced gastric cancer display PAL metastasis. The 5-year survival rate is about 10% after a D2 + PAL dissection. Patients with a potentially curative tumor display a better prognosis among all dissected cases. Early major complications after a PAL dissection occur in 25% of all cases, and are mainly related to the resection of adjacent organs, such as the pancreas. The depth of gastric cancer invasion correlates with PAL metastasis. The dissection of PAL for patients with T2 cancer remains controversial. Surgeons need to be more aware of the importance of making an accurate diagnosis of the cancer depth. A better understanding of the lymphatic flow will result in fewer complications and an improved patient survival. Appropriate chemotherapy combined with a D2 plus a

PAL dissection also appears to be a promising approach in the near future.

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