



# D2 vs D2 Plus Para-aortic Lymph Node Dissection for Advanced Gastric Cancer

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## ABSTRACT

**Objective:** Gastric cancer is a common malignancy worldwide. Effective treatment by interdisciplinary cooperation is important and surgery still plays an important role.

**Material and Methods:** In a ten years period 355 patients were diagnosed to have gastric cancer. 162 patients with median (range) age of 58(23-83) years were eligible for study. There was 107 patients in D2 and 55 patients in D2 lymphadenectomy plus para-aortic lymph node (PALN) dissection group. Two groups were compared in terms of complications, morbidity, mortality and long-term survival.

**Results:** The duration of the stay was 12(8-34) days for D2 and 14(8-42) days for D2 plus PALN. The total number of operative mortality was 8/162 (5%) and it was not different between the groups. 20 patients (18%) had complications in D2 group and 9 (17%) patients in D2 plus PALN group. Overall survival was also similar between the groups but patients with T3-T4 tumors, patients with stage IIIA and IIIB disease and patients with higher ratio of PLN/TLN had better survival with D2 plus PALN dissection. We found that the depth of invasion, PLN, ratio (PLN/TLN), stage and LND were all independent prognostic variables.

**Conclusion:** This study has shown that D2 plus PALN dissection and for advanced gastric cancer can be performed as safely as a standard D2 dissection by experienced surgeons without increasing postoperative morbidity and mortality. D2 plus PALN dissection should be preferred in an advanced stage of the disease (IIIA-IIIB) as it increases the rate of survival.

**Keywords:** advanced gastric cancer, d2 lymphadenectomy, d2+paln lymphadenectomy, morbidity, mortality, prognosis

## INTRODUCTION

Gastric cancer is a common malignancy world-wide, and the 5-year survival rate in patients with gastric cancer is still poor despite improved survival due to early detection, rational lymphadenectomy and several therapeutic modalities (1). Effective treatment by interdisciplinary cooperation is important and surgery is currently considered the best manner to treat gastric cancer. The extensiveness of lymph node dissection is, however, unclear, and there is no world-wide consensus (2, 3, 4, 5, 6, 7, 8). Extended (D2-3) lymph node dissection has improved survival in Japan (7, 9, 10). However, the results of European studies are somewhat controversial (11, 12, 13, 14, 15, 16, 17, 18).

Japanese surgeons first introduced the extended lymphadenectomy procedure, known today as D2, in the 1960s (19). This technique requires the systematic dissection of lymph nodes in the first tier (perigastric) and the second tier (along the celiac artery and its branches) (20). Superextended lymph node dissection (D3 dissection) has been used in advanced forms gastric cancer in many Japanese centers with the aim of eliminating metastatic lymph nodes, not only in the first and second tiers, but also in the third tier (around the upper abdominal aorta) (21).

D2 dissection for gastric cancer is a standard surgical procedure in Japan and is associated with excellent early and late results (20, 22), whereas it is still controversial in the West (23). All four randomized Western trials failed to show any survival benefit for D2 dissection while finding an association between D2 dissection and increased morbidity and mortality (11, 12, 17, 18, 24), although D2 dissection is already accepted as the standard procedure for resectable gastric cancer in many countries (13, 25, 26).

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Success with D2 resection has led to the evolution of a superextended lymphadenectomy and several feasibility studies evaluating dissection of para-aortic lymph nodes have been performed (6, 21, 27, 28, 29). This procedure is performed by selected centers and D3 dissection has been practiced to improve the survival for advanced gastric cancer in this centers (21, 29, 30, 31).

Very few studies from Western centers have compared D2 and D3 dissection in surgical treatment of gastric cancer (32, 33, 34).

In the present study, we aimed to assess the value of radical surgery in gastric cancer by comparing D2 and D2 lymphadenectomy plus para-aortic lymph node (PALN) dissection.

## PATIENTS AND METHODS

A prospective trial was designed to compare the two surgical techniques: the extended lymphadenectomy (D2) and the superextended lymphadenectomy (D2 plus PALN) for gastric cancer.

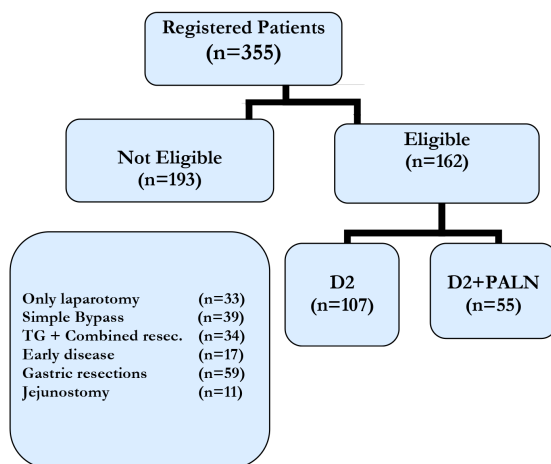
### Patients

In a ten years period, 355 patients were admitted to our unit with a diagnosis of gastric adenocarcinoma.

The inclusion criteria for this study included: 1) patients who received curative resection; and 2) patients who underwent extended (D2) lymph node dissection, or superextended (D2 plus PALN) lymph node dissection.

The exclusion criteria included: 1) patients who received a palliative operation; 2) patients with distant metastasis; 3) patients with intraperitoneal dissemination; 4) patients with previous gastrectomies; and 5) patients with poor performance status.

Based on the inclusion and exclusion criteria, 193 patients were excluded from the study and 162(107male) patients with median (range) age of 58(23-83)years were eligible for study. Due to world-wide acceptance of D2 lymph node dissection (LND) as the treatment of choice, there was 107 patients in D2 and 55 patients in D2 plus PALN dissection group (Figure 1).



**Figure 1.** Categories of the registered patients, type of surgery and type of lymph node dissection.

### Surgical methods

All operations were performed by a specialized surgical team with a standardized surgical technique.

During laparotomy, the eligibility of patients was verified by inspecting the tumor resectability, feasibility of a potentially curative resection. Depending on the tumor location in the stomach and intraoperative verification of tumor-free margins, patients were qualified for total, subtotal gastrectomy. Splenectomy was performed routinely for tumors located in the upper-third of the stomach, and resection of the tail of the pancreas was optional. In other patients, the spleen was removed according to surgeon preference. Gastrectomy was always completed by the removal of the greater omentum and parigastric lymph nodes. The type of lymphadenectomy was selected by the surgical team according to the criteria described by the Japanese Gastric Cancer Association (JGCA) (35). The D2 lymphadenectomies were performed in accordance with the fifth English edition of the JGCA (35). D2 plus PALN dissection were performed as described previously (36).

### Evaluation of operative morbidity and mortality

Resected specimens were examined carefully for accurate pathologic staging according to the JGCA rules (35). The following information was included on the case report form for prospective data collection concerning the major groups of operative morbidity: anastomotic leakage, intraabdominal abscess, pancreatic fistula, pneumonia, and others (*wound infection, wound dehiscence, pulmoner embolism, MI etc.*). Hospital mortality was defined as postoperative death any cause within 30 days, death within the same hospitalization.

A follow-up of patients was performed according to our standard protocol (every 3 months for first 2 years and then every 6 months at least 5 years), which included tumor-marker studies, endoscopic examinations, ultrasonography, computed tomography, and chest radiography.

Two groups were compared in terms of complications, morbidity, mortality and long-term survival. Effect of the type of dissection as well as the diameter of the tumor, T-stage, number of total and positive lymph nodes (TLN and PLN) and survival according to tumor stage were also analysed.

### Statistical Analysis

Statistical analysis was performed using SPSS version 17.0 for Windows. Comparisons of clinicopathological differences were made using a Chi-square test for discrete variables. Rate of occurrence of events were evaluated using Fisher's Exact test. Cumulative survival rate were calculated by using the Kaplan-Meier estimation and examined by the log-rank test. Survival curves compared by Chi-square test. A P-values less than 0.05 was considered to be significant.

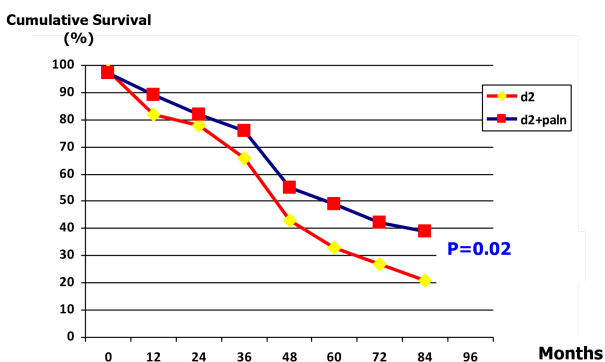
## RESULTS

Patient demographics, complications and tumor characteristics are presented in Table 1. The two groups were well balanced, as there were no significant differences in their baseline data. The age and sex distribution of the patients were comparable in both groups. The duration of the stay was 12(8-34) days for D2 and 14(10-42) days for D2 plus PALN. The total number of operative mortality was 8/162 (5%) and it was not different between the groups. 20 patients (18%) had complications in D2 group and 9 (17%) patients in D2 plus PALN group. The number of removed lymph nodes were related to dissection and it was 30(10-86) for D2 and 41(12-98) for D2 plus PALN dissection. PLN/TLN ratio was similar in both groups (Table 1).

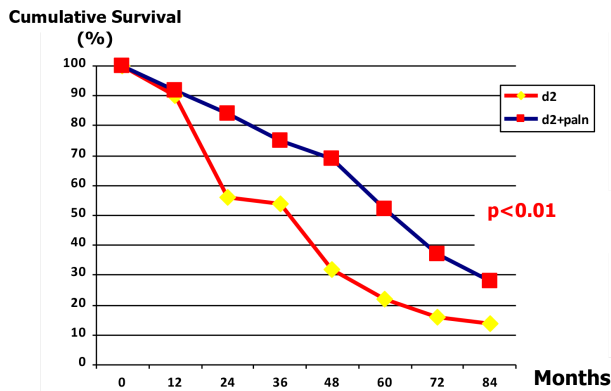
**Table 1.** Details of patients.

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Variable	D2 (n=107)	D2+PALN (n=55)	p
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Age	59.3 (23-83)	58 (32-75)	ns
Sex (M/F)	76/31	40/15	ns
Complications	20 (18%)	9 (17%)	ns
Wound infection	4	1	
Leakage	4	2	
Abscess	4	2	
Wound dehiscence	2	1	
Pancreatic fistula	0	1	
Pneumonia	4	1	
Pulmoner embolism	1	1	
MI	1	0	
Operative mortality	5 (5.2%)	3 (4.9%)	ns
Hospital stay (day)	12 (8-34)	14 (10-42)	ns
Tumor size (cm)	7.9 ± 3.4	7.1 ± 3.7	ns
TLN	30 (10-86)	41 (12-98)	0.02
PLN	4 (6)	7 (9)	ns
PLN/TLN	0.17 ± 0.3	0.17 ± 0.2	ns
Histologic type			ns
Diffuse	45	19	
Intestinal	53	29	
Unclassified	9	7	
Depth of invasion			ns
T1	0	0	
T2	28	14	
T3	60	32	
T4	19	9	
Stage grouping			ns
I	0	0	
II	29	14	
IIIA	38	18	
IIIB	35	18	
IVA	5	5	

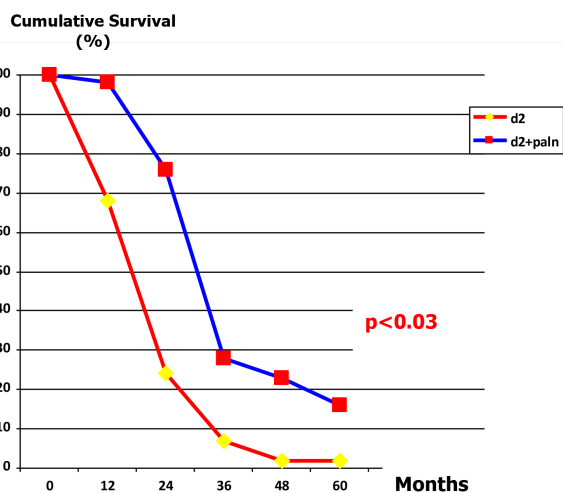


**Figure 2.** Overall survival curves in patients with D2 and D2 +PALN dissection.



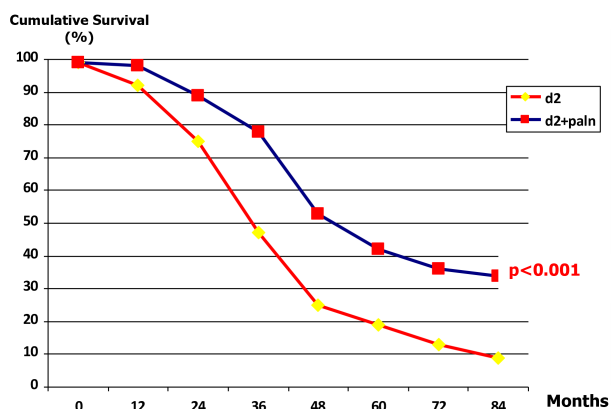
**Figure 3.** Survival curves in patients with T3 tumors.

Patients were followed up for a period of 75(22-130) months. We observed that better overall survival with D2 plus PALN than D2 (Figure 2). Patients with T3-T4 tumors (Figure 3-4) had better survival with D2 plus PALN dissection than D2 alone. Patients with Stage IIIA also had better survival with D2 plus PALN than D2.



**Figure 4.** Survival curves in patients with T4 tumors .

Although the survival rates were similar in patients with Stage I-III and IV, it was significantly better after D2 plus PALN dissection in patients with Stage IIIA (Figure 5) and IIIB disease (Figure 6).



**Figure 5.** Survival curves in patients with stage IIIA.

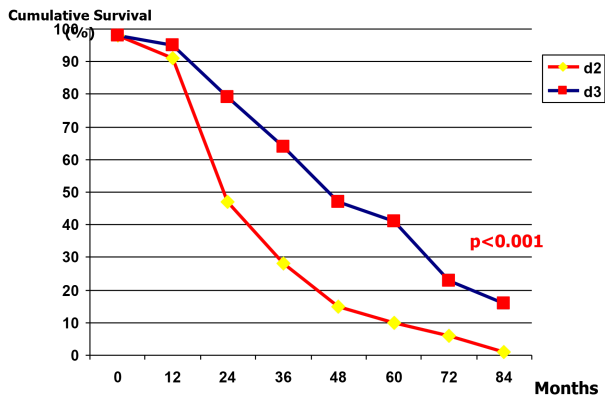


Figure 6. Survival curves in patients with stage IIIB.

We found that depth of invasion (T) (T small number 1,2 is better than 3,4), positive lymph node (LN(-) is better), lymph node ratio (PLN/TLN  $< 0.2$  is better than  $> 0.3$ ), stage (lower the stage better the survival) and lymph node dissection (D2+ PALN is better than D2) were all prognostic variables (Table 2).

Table 2. Prognostic variables after surgery.

Variable	5 year survival (%)	p
<b>Age</b>		
< 60	41.2	ns
> 60	39.4	
<b>Sex</b>		
M	49.2	ns
F	51.4	
<b>T</b>		
T2	52.5	0.001
T3	37.4	
T4	19.8	
<b>Historical type</b>		
Intestinal	50.2	ns
Diffuse	48.5	
Unclassified	45.8	
<b>Location</b>		
Upper	37.7	0.003
Middle	50.2	
Lower	61.7	
<b>Stage</b>		
II	47.4	0.001
IIIA	28.5	
IIIB	25.3	
IV	15.1	
<b>LN</b>		
+	31.3	0.0001
-	64.5	
<b>LN ratio (PLN/TLN)</b>		
< 0.2	46.3	0.001
> 0.3	24.1	
<b>LND</b>		
D2	33.1	0.02
D2 plus PALN	49.4	

## DISCUSSION

Gastric cancer still remains a major health problem, numerous aspects of surgical treatment still remain unresolved. Despite improvements in local control and empirical chemotherapy, prognosis particularly for advanced stage patients remains poor worldwide. New therapeutic strategies are needed.

Treatment of advanced gastric cancer has become much more sophisticated and complicated than ever. New directions in cancer biology research and new randomized trials promise to reach the goal of an individualized approach (37, 38). Recently, the decision was reached that the only possibility for curative treatment of gastric cancer remains surgical resection. For many years it has been debated whether an extended lymph node dissection for gastric cancer is beneficial. Theoretically, removal of a wider range of lymph nodes by extended lymph node dissection increases the chances for cure (17, 39). Such resection, however, may be irrelevant if there are no lymph nodes affected, if the cancer has developed into a systemic disease, or if resection increases morbidity and mortality substantially (17, 39, 40). From this point of view, several studies have compared generally D1 dissection with D2 dissection (11, 12, 13, 24). However, only a few study have compared D2 dissection with D3 dissection (20, 27, 32, 33, 34, 36, 41, 42, 43). Therefore, in this study, we prospectively compared D2 dissection morbidity, mortality and outcome with those of D2 plus PALN dissection.

There is a wide variation in operative morbidity and mortality following gastric cancer surgery among countries and institutions (20). The presence of comorbid disease that affects patient fitness for surgery, surgical experience of the operator, and the workload volume seem to be important factors (20).

D2 dissection is a safe procedure in specialized centers, where it is associated with a low risk of postoperative complications and mortality (13, 25, 26, 44). The risk of complications can be reduced by avoiding resection of the pancreatic tail and spleen (14, 27). These associated procedures were strongest factors influencing morbidity and mortality in the two European randomized trials, without any offering any potential improvement in long-term survival (17, 18, 45). Recently, based on the results of British (12) and Dutch (11) trials, D1 gastrectomy has been routinely used for the treatment of gastric cancer in Western countries (43). These trials suggested that a high incidence of postoperative complications after D2 gastrectomy offset the more beneficial surgical results obtained with D2 surgery. However, in Japan, D2 gastrectomy is accepted as the gold standard on the basis of abundant data (43). For gastric cancer, only potentially curative resection (R0) achieves good outcomes, and, in view of the distribution of lymph node metastases, D1 gastrectomy is insufficient for advanced gastric cancer (41). On the other hand, safety outcomes after more extended lymph node dissection (ie, D1 vs. D3, or D2 vs. D3) were analyzed in a few study (20, 27, 32, 33, 34, 36, 41, 42, 43, 46).

In JCOG9501 study (36) a total of 523 patients were assigned to compare the treatment of D2 versus D3 (D2 + PAN) lymph node dissection. The results showed that the surgical mortality rate was very low in both groups (0.8%). No significant difference was found between the two treatment groups in terms of 5-year recurrence-free survival (62.6% vs. 61.7%, respectively), but the overall perioperative complication rate in the D3 group was higher than that in the D2 group (28.1% vs. 20.9%, respectively) (36). These trials showed that there were no significant survival rate benefit for performing PAN dissection in curable gastric cancer patients and simultaneously revealed its association to a higher surgical morbidity. They reported that gastrectomy with D2

lymphadenectomy has been considered as the standard routine lymphadenectomy for locally advanced gastric cancer (36).

However, the effect of the D3 dissection on gastric cancer patients with PAN metastasis is still debatable (47). D3 lymphadenectomy may be beneficial in some patients with PAN metastasis, but more research is needed for appropriate patient selection.

Some studies have shown that incidence of metastasis to para-aortic lymph node could be around 20% (48), and the 5-year survival rate for patients with para-aortic node metastasis who had undergone para-aortic node dissection could be up to about 20%. Therefore, the rationale of therapeutic para-aortic lymphadenectomy for advanced gastric cancer is suggested for further evaluations (48). D2 plus para-aortic lymphadenectomy after neo-adjuvant or conversion chemotherapy could be considered as a promising treatment for patients with para-aortic lymph nodes involved (48).

Bencivenga et al. (49) reported that, the debate concerning the role of "prophylactic" super-extended lymphadenectomy apparently came to an end after the publication of the JCOG 9501 trial that found no survival advantage when D2 lymphadenectomy was extended to PANs in patients with T2b, T3, and T4 gastric cancer (36). Consequently, prophylactic D2 plus PAN dissection is no longer recommended as a first-choice treatment for patients with curable gastric cancer in the Japanese guidelines. However, it should be remembered that the baseline prevalence of 16 metastases in that trial was rather low (8.5%), probably because it only enrolled patients without macroscopic metastases to PANs, and the control group underwent D2 lymphadenectomy extended to the posterior nodal stations (12p, 13, and 14v), which are not usually resected in the case of a conventional D2 (19).

Liang and Deng reported that (50), the following are indications for D2+PAND candidates: 1) patients in good condition with no serious organ dysfunction; 2) patients without peritoneal dissemination or liver metastases; 3) patients with pathologic N2, N3a and N3b stage disease or positive No.9 LN; 4) patients with Borrmann type III/IV disease; and 5) patients with upper-middle third or occupied more than one-third. However, they recommend that D2+PAND should be carried out only in cancer centers equipped with surgeons with extensive experience for extended LN dissections, because there are some risks in some rare situations, such as complications like formation of chylous fistula. In addition, multiple methods should be used in selecting the suitable cases for further study.

Dong and Deng also reported that (51), 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 (51).

A recent studies clearly showed that standard D2 and extended D3 dissection can be performed safely without any increase in

postoperative morbidity and mortality (20, 41). Both the morbidity and mortality rates and the percentage of individual complications in our trial have shown no significant differences between the D2 and D2 plus PALN groups. Hospital stay was also similar both groups in our study. In the light of these results, we confirm that D2 plus PALN dissection may be performed in specialized centers with an acceptable operative risk.

In this study, we observed a positive linear correlation between removed lymph node and more extensive lymph node dissection (Table 1). Some authors have suggested that better disease control could be achieved through "inducing a reduction of metastatic nodes ratio" just by extending the number of dissected nodes (13, 52, 53, 54). Schwarz et al. (55) believe that their results for a therapeutic benefit as a result of extended lymph node dissection, even in patients with more advanced yet resectable gastric cancer. They showed that stage-based survival prediction of advanced gastric cancer without distant metastases depends on total lymph node number and number of negative lymph nodes (55). Kunisaki et al. (43) also showed that the incidence of lymph node recurrence in the surgically dissected area was significantly lower in D3 patients. They suggest that D3 gastrectomy might be effective for metastatic lymph nodes in the para-aortic regions (43).

In our study, we also observed a positive relation between more lymph node positivity and T-stage. Shen et al. (56) showed that greater numbers of dissected lymph nodes could lead to a better prognosis in patients with pT3N2 disease and even in patients with pT3N3 disease. This findings indicates the important impact of thorough lymph node dissection on survival, even in patients with pT3N3 gastric cancer, who many believed had incurable disease (56).

Several papers have reported a correlation between survival benefits and D3 lymph node dissection (20, 32, 41, 43, 57, 58). Kunisaki et al. (43) suggest that D3 dissection may confer a survival advantage with respect to D2 dissection in patients with tumor diameters measuring 50-100 mm and pN2 disease.

In our survival analyses, we observed four three results: First, better overall survival with D2 plus PALN than D2. Second, better survival with D2 plus PALN in T3-T4 tumors. Third, better mean survival and 5-year survival in stage IIIA – IIIB. This might imply that D2 plus PALN dissection does contribute to improved survival at advanced stage of gastric cancer.

In early stages of the disease D2 is safer and better, D2 plus PALN dissection be preferred in an advanced stage of the disease as it increases the rate of survival. Although D2 plus PALN patients had slightly longer hospital stay, extended lymph node dissection performed without any increase on morbidity and mortality.

We observed that depth of invasion (T), positive lymph nodes (PLN), lymph node ratio (PLN/TLN), stage and lymph node dissection are prognostic variables. From the all prognostic variables, only lymph node dissection influenced by the surgeon. Our results were in agreement with those of Japanese and support the efficacy of extended lymph node dissection in surgical management of gastric cancer for the Western patients as well.

In conclusion, this study has shown that D2 plus PALN dissection and for advanced gastric cancer can be performed as safely as a standard D2 dissection by experienced surgeons without increasing postoperative morbidity and mortality. D2 plus PALN dissection should be preferred in an advanced stage of the disease (IIIA-IIIB) as it increases the rate of survival.

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## ORJİNAL ARAŞTIRMA

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## İleri Evre Mide Kanserlerinde D2 ve D2+ Para-aortik Lenf Nodu Diseksiyonu Sonuçlarının Karşılaştırılması

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### ÖZET

**Amaç:** Mide kanseri dünya çapında yaygın bir malignitedir. Disiplinler arası işbirliği ile etkili tedavi önemlidir ve cerrahi hala önemli bir rol oynamaktadır.

**Gereç ve Yöntemler:** Kliniğimizde on yıl içinde 355 hastaya mide kanseri teşhisi kondu. Medyan yaşı 58 (23-83) olan 162 hasta çalışmaya uygundu. D2'de 107 hasta ve D2 lenfadenektomi artı para-aortik lenf nodu (PALN) diseksiyon grubunda 55 hasta vardı. İki grup komplikasyon, morbidite, mortalite ve uzun süreli sağkalım açısından karşılaştırıldı.

**Bulgular:** Hastanede kalış süresi D2 için 12(8-34) gün ve D2+ PALN için 14(8-42) gündü. Toplam operatif mortalite sayısı 8/162 (%5) idi ve gruplar arasında farklı değildi. 20 hastada (%18) D2 grubunda komplikasyon, 9 hastada (%17) D2+ PALN grubunda komplikasyon vardı. Genel sağkalım gruplar arasında da benzerdi, ancak T3-T4 tümörleri olan hastalar, evre IIIA ve IIIB hastalığı olan hastalar ve daha yüksek PLN/TLN oranı olan hastalar D2+ PALN diseksiyonu ile daha iyi sağkalım gösterdi. İnvazyon derinliği, PLN, PLN/TLN oranı, evre ve LND'nun bağımsız prognostik değişkenler olduğunu bulduk.

**Sonuç:** Bu çalışma, D2+ PALN diseksiyonunun ileri evre mide kanseri için, postoperatif morbidite ve mortaliteyi arttırmadan deneyimli cerrahlar tarafından standart bir D2 diseksiyonu kadar güvenli bir şekilde yapılabileceğini göstermiştir. D2+ PALN diseksiyonu, sağkalım oranını arttırdığı için hastalığın ileri evresinde (IIIA-IIIB) tercih edilmelidir.

**Anahtar Kelimeler:** ileri evre mide kanseri, d2 lenf nodu diseksiyonu, d2+paln lenf nodu diseksiyonu, prognoz

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