



Is D2 Lymphadenectomy Necessary in Elderly Gastric Cancer Patients? A Retrospective Study

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Objective: We retrospectively analyzed the validity of limited lymphadenectomy (D1 and D1+) in elderly gastric cancer patients.

Summary of background data: According to the aging trend in Japan, patients with gastric cancer are continuing to age. The extent of lymphadenectomy preferable for older patients is unclear.

Methods: The data of 35 and 52 patients ≥ 80 years old with cT2– or N(+) gastric cancer who underwent gastrectomy with D2 lymphadenectomy and limited lymphadenectomy, respectively, at 2 institutions between 2010 and 2019 were retrospectively reviewed.

Results: The patients who underwent limited lymphadenectomy were older and their Onodera prognostic nutritional indexes were poorer than those who underwent D2 lymphadenectomy, although the differences were not significant. After propensity score matching, 28 patients in each group were analyzed. No significant differences in postoperative complications, initial recurrence sites, or causes of death were observed between the 2 groups except for postoperative respiratory failure, which was more frequent after D2 lymphadenectomy. The median overall survival time after D2 and limited lymphadenectomy was 73.9 and 70.9 months, respectively, with a hazard ratio of 1.32 ($P = 0.53$).

Conclusions: D1+ or even D1 lymphadenectomy may be acceptable for patients ≥ 80 years old with advanced gastric cancer.

Key words: Stomach neoplasms – Aged – 80 and over – Gastrectomy – Lymph node excision

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The Japanese population is continuing to age every year. According to official Japanese statistics, 9.5% of Japan's population was estimated to be 80 years or older in 2021.¹ Therefore, patients with gastric cancer are also aging. According to Japan's nationwide registry, 15.9% of patients who underwent gastrectomy for gastric cancer were ≥ 80 years old in 2012.² However, their prognoses were not satisfactory, as the 5-year survival rate was 47.5% for patients ≥ 80 years, whereas it was 72.5% for those ≥ 60 and ≤ 79 years.

Previously, we compared the overall survival (OS) of patients ≥ 80 years old with gastric cancer who underwent surgery with those who did not and found that surgery resulted in a survival benefit.³ However, it remains unclear what type of surgery is suitable for these patients considering their condition, curability of their cancer, quality of life after surgery, and their life expectancy. Given their reduced physical capacity and ability to recover, less invasive surgery is often used. Although D2 lymph node dissection (LND) is recommended for T2- or N(+) cases according to the Japanese Gastric Cancer Treatment Guidelines 2018 (5th edition),⁴ limited LND of D1 or D1+ is often selected for these patients.

In this study, we retrospectively examined the validity of limited LND for gastric cancer patients ≥ 80 years old using propensity score matching (PSM).

Materials and Methods

Patients

The medical records of 177 consecutive patients ≥ 80 years old who underwent surgery for gastric cancer at 2 institutions between 2010 and 2019 were retrospectively reviewed. Among them, 119 patients with cT2- or N(+) disease were candidates for radical gastrectomy with D2 LND, whereas D0, D1, and D1+ LND was performed in 8, 27, and 40 patients, respectively. Those with pStage IV disease and/or noncurative resection were excluded, and thus, 35 and 52 patients with D2 LND and limited LND, respectively, were analyzed in this study. A flowchart of patient selection is shown in Fig. 1.

Information on the following preoperative clinical characteristics, cancer features, treatment, and outcomes was collected from the patients' medical records: age, sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS),⁵ American Society of Anesthesiologists physical status (ASA-

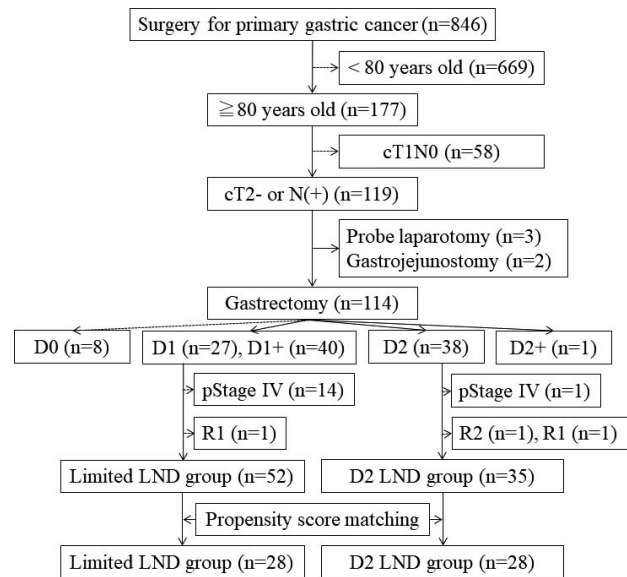


Fig. 1 The participant flow diagram. R1, microscopic residual tumor; R2, macroscopic residual tumor; LND, lymph node dissection.

PS),⁶ the physiological score of the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM),⁷ The Onodera prognostic nutritional index (PNI),⁸ clinical and pathologic cancer stage, surgical procedure including extent of gastrectomy and LND, postoperative complications during hospitalization, adjuvant chemotherapy, and the initial recurrence site. The POSSUM physiological score was calculated based on the patient's age, cardiac signs, chest radiography signs, respiratory history, systolic blood pressure, pulse rate, Glasgow Coma Scale score, hemoglobin level, white blood cell count, plasma urea level, plasma sodium level, plasma potassium level, and electrocardiography results. Each item was scored from 1 (normal) to 8 (abnormal). The sum of all scores provided a physiological score that ranged from a minimum of 12 to a maximum of 88, where a higher score indicates a higher surgical risk. The PNI was calculated according to the following formula: $10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{total lymphocyte count (/mm}^3\text{)}$. The clinicopathologic findings of gastric cancer were documented according to the Japanese classification of gastric carcinoma, 15th edition,⁹ and the surgical procedure and LND were documented according to the Japanese Gastric Cancer Treatment Guidelines.⁴ Information on prognoses, including the last date the patient was known to be alive or the date of death and cause of death, was surveyed from the medical records at our

institutions or referral institutions, in the condolences section of local newspapers, or by calling the patients or their families.

Statistical analysis

Continuous variables were compared using the Mann-Whitney *U* test. Categorical variables were compared using the χ^2 test or the Fisher exact probability test. OS was defined as the interval from the date of surgery to the date of death from any cause. Surviving patients were censored at the date that they were last known to be alive. OS is illustrated by Kaplan-Meier curves and was compared using the log-rank test. Hazard ratios (HRs) were estimated using Cox regression analysis. PSM was performed to adjust for significant differences in the characteristics between patients who underwent D2 LND and those who underwent limited LND. The propensity scores were estimated using a logistic regression model based on the following variables: age, sex, ECOG PS, ASA-PS, PNI, clinical cancer stage, and extent of gastrectomy. One-to-one pair matching was performed without replacement using a 0.20 caliper. All reported *P* values were 2-sided, and *P* values of <0.05 were considered statistically significant. Analyses were performed using JMP software (version 14.2.0 for Windows; SAS Institute Inc., Cary, NC).

Results

Full cohort analyses

The characteristics of 35 and 52 patients in the D2 and limited LND groups, respectively, are shown in Table 1. In the limited LND group, the patients were older and their PNIs were worse than those of patients in the D2 LND group, although the differences were not significant (*P* = 0.09 and 0.11). There was little difference between the 2 groups in terms of ECOG PS, pathologic stage, and adjuvant chemotherapy (*P* = 0.99, 0.74, and 0.99).

At the time of analysis, 43 patients had died. The median follow-up period of the surviving patients was 42.4 months. The OS curves of the patients in the D2 and limited LND groups are shown in Fig. 2. The median OS time of the D2 and limited LND groups was 73.9 and 40.2 months, respectively, which was nearly significantly different with an HR of 1.76 [95% confidence interval (CI), 0.92–3.39; *P* = 0.08].

PSM analyses

Patients in the D2 and limited LND groups were matched using PSM. Consequently, 28 pairs of patients were matched. The limited LND group included 7 and 21 patients who underwent D1 and D1+ LND, respectively (Table 1).

Postoperative surgical complications of grade II or worse according to the Clavien-Dindo (CD) classification¹⁰ were detected in 3 patients each in the D2 and limited LND groups, and postoperative medical complications of CD grade II or worse were detected in 7 and 4 patients in the D2 and limited LND groups, respectively, showing no significant difference (Table 2). However, respiratory failure was more frequently encountered in the D2 LND group than in the limited LND group.

Recurrence of gastric cancer was detected in 7 and 4 patients in the D2 and limited LND groups, respectively. No significant difference was observed in the initial recurrence site between the 2 groups.

At the time of analysis, 9 and 13 patients in the D2 and limited LND groups, respectively, had died. Four (50% of known causes) and 3 (23% of known causes) patients in the D2 and limited groups, respectively, died of gastric cancer, a higher incidence of which was not observed in the limited LND group.

A comparison of OS between the 2 groups is shown in Fig. 2b. The median OS time of the patients in the D2 and limited LND groups was 73.9 and 70.9 months, respectively, with an HR of 1.32 (95% CI, 0.56–3.10; *P* = 0.53).

Discussion

This retrospective analysis showed that limited LND was performed in more than half of the patients ≥ 80 years old who underwent curative gastrectomy for cT2– or N(+) gastric cancer. The patients in the limited LND group were older and had poorer PNIs than those in the D2 LND group, although the differences were not significant. This may indicate that surgeons tend to avoid standard radical LND in those who are extremely old (especially patients aged ≥ 90 years) or in those with poor nutritional status. After PSM, patients' backgrounds appeared almost well balanced. As for postoperative complications, first recurrence sites, and causes of death, no significant difference was observed between the 2 groups, except that postoperative respiratory failure was more frequently encountered in the D2 LND group than in the limited LND group. OS curves almost overlapped

Table 1 Patients' characteristics for the D2 and limited lymph node dissection groups

| Variable | Full cohort | | | After matching | | |
|--|--------------------|-------------------------|---------|--------------------|-------------------------|---------|
| | D2 LND (n = 35) | Limited LND (n = 52) | P value | D2 LND (n = 28) | Limited LND (n = 28) | P value |
| Age, median (range), y | 83 (80–89) | 85 (80–96) | 0.09 | 83 (80–89) | 84 (80–93) | 0.79 |
| Male sex, n (%) | 28 (80) | 38 (73) | 0.46 | 23 (82) | 22 (79) | 0.74 |
| ECOG PS score, n (%) | | | | | | |
| 0 | 17 (49) | 24 (46) | 0.99 | 14 (50) | 15 (54) | 0.63 |
| 1 | 9 (26) | 16 (31) | | 8 (29) | 9 (32) | |
| 2 | 6 (17) | 9 (17) | | 5 (18) | 4 (14) | |
| 3 | 3 (9) | 3 (6) | | 1 (4) | 0 | |
| ASA-PS, n (%) | | | | | | |
| 1 | 0 | 2 (4) | 0.41 | 0 | 0 | 0.94 |
| 2 | 26 (76) | 32 (62) | | 21 (75) | 21 (75) | |
| 3 | 8 (24) | 17 (33) | | 7 (25) | 6 (21) | |
| 4 | 0 | 1 (2) | | 0 | 1 (4) | |
| POSSUM physiological score, median (range) | 28 (20–40) | 30 (21–45) | 0.23 | 28 (20–40) | 29 (22–44) | 0.58 |
| PNI, median (range) | 44.7 (32.5–63.0) | 42.7 (22.2–56.4) | 0.11 | 44.7 (32.5–63.0) | 45.0 (25.9–56.4) | 0.70 |
| cStage, n (%) | | | | | | |
| I | 8 (23) | 12 (23) | 0.34 | 8 (29) | 9 (32) | 0.65 |
| IIA | 2 (6) | 10 (19) | | 1 (4) | 1 (4) | |
| IIB | 6 (17) | 11 (21) | | 6 (21) | 7 (25) | |
| III | 18 (51) | 14 (27) | | 12 (43) | 10 (36) | |
| IVA | 1 (3) | 5 (10) | | 1 (4) | 1 (4) | |
| Surgical approach | | | | | | |
| Open | 33 (94) | 46 (88) | 0.36 | 26 (93) | 22 (79) | 0.13 |
| Laparoscopic | 2 (6) | 6 (12) | | 2 (7) | 6 (21) | |
| Extent of gastrectomy | | | | | | |
| Distal | 25 (71) | 33 (63) | 0.17 | 22 (79) | 21 (75) | 0.75 |
| Total | 10 (29) | 14 (27) | | 6 (21) | 7 (25) | |
| Proximal | 0 | 5 (10) | | 0 | 0 | |
| pStage, n (%) | | | | | | |
| IA | 4 (11) | 5 (10) | 0.74 | 4 (14) | 3 (11) | 0.72 |
| IB | 3 (9) | 4 (8) | | 3 (11) | 3 (11) | |
| IIA | 10 (29) | 15 (29) | | 7 (25) | 5 (18) | |
| IIB | 6 (17) | 10 (19) | | 5 (18) | 9 (32) | |
| IIIA | 7 (20) | 9 (17) | | 5 (18) | 4 (14) | |
| IIIB | 5 (14) | 7 (13) | | 4 (14) | 4 (14) | |
| IIIC | 0 | 2 (4) | | 0 | 0 | |
| Adjuvant chemotherapy, yes | 2 (6) | 3 (6) | 0.99 | 1 (4) | 3 (11) | 0.30 |

Clinicopathologic findings are provided according the Japanese classification of gastric carcinoma (15th edition). ASA-PS, American Society of Anesthesiologists physical status; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LND, lymph node dissection; PNI, Onodera prognostic nutritional index; POSSUM, Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity.

between the 2 groups. The current results may indicate that D1+ or even D1 LND is acceptable for elderly patients with advanced gastric cancer.

The Japanese Gastric Cancer Treatment Guidelines⁴ recommend that patients with cT2– or cN+ can be treated with gastrectomy and D2 LND with curative intent. Globally, the consensus on D2 LND is accepted because of improved survival among D2 patients and improvements in skill and experience with D2 LND, as shown in some randomized

controlled trials conducted in the Netherlands,¹¹ Taiwan,¹² and Italy.¹³ However, the feasibility of D2 LND for elderly patients remains unclear. The Dutch trial included patients <85 years, but the Taiwanese and Italian trials excluded those >75 and ≥80 years, respectively. In the OS analysis of the Dutch trial,¹¹ in which the median age was 65 and 67 years for D2 and D1 LND, respectively, the Kaplan-Meier survival curve of patients who underwent D2 LND exceeded that of patients who underwent D1 LND

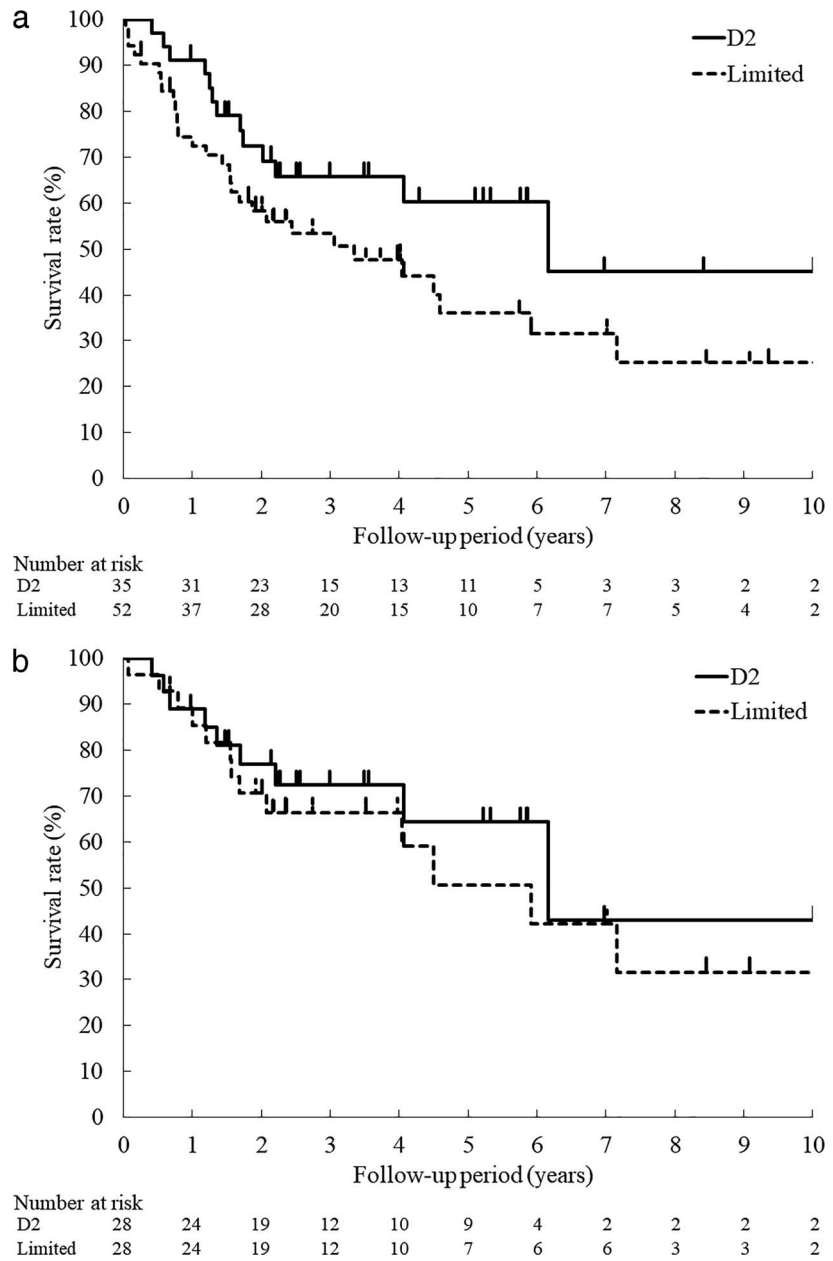


Fig. 2 Kaplan-Meier curves of the D2 and limited (D1, D1+) lymph node dissection groups for the full cohort (a) and the propensity score-matched cohort (b).

after 4.5 years, but until then, D1 LND resulted in a better prognosis because of a lower complication rate than D2 LND. This result suggests that D2 LND results in fewer survival benefits in elderly patients whose life expectancies are relatively short.

Some reports have recommended limited LND for elderly patients with gastric cancer. Shinozuka *et al*¹⁴ reported that the OS rates of the D2 group tended to be poorer than those of the non-D2 group (HR 1.49, $P = 0.104$) after PSM and concluded that D2 LND for patients ≥ 80 years old with gastric

cancer conferred little benefit in OS despite increased complication rates. Silva *et al*¹⁵ found that D2 LND was an independent factor for worse OS and concluded that D1 LND should be the standard of care in patients ≥ 80 years.

Postoperative complications in elderly patients who are frail, are malnourished, have comorbidities, or have low physiological capacity may be critical and can shorten their lives. Our data showed that postoperative respiratory failures, such as pneumonia, atelectasis, and CO₂ narcosis, were more common in

Table 2 Postoperative complications according to Clavien-Dindo classification \geq II

| Variable | D2 LND, n (%), n = 28 | Limited LND, n (%), n = 28 | P value |
|--------------------------|-----------------------------|----------------------------------|---------|
| Surgical complications | 3 (11) | 3 (11) | 1.00 |
| Pancreatic fistula | 2 (7) | 1 (4) | 0.55 |
| Abscess | 1 (4) | 2 (7) | 0.55 |
| Medical complications | 7 (25) | 4 (14) | 0.31 |
| Respiratory failure | 4 (14) | 0 | 0.04 |
| Arrhythmia | 1 (4) | 1 (4) | 1.00 |
| Pseudomembranous colitis | 1 (4) | 0 | 0.31 |
| Urinary tract infection | 1 (4) | 0 | 0.31 |
| Hepatic dysfunction | 0 | 2 (7) | 0.55 |
| Cerebral infarction | 0 | 1 (4) | 0.31 |

LND, lymph node dissection.

the D2 LND group than in the limited LND group and that 3 patients required mechanical ventilation (CD grade IVa). A previous study also showed that D2 LND was a significant risk factor for the development of postoperative pneumonia in patients \geq 75 years and concluded that the extent of LND during curative resection should be limited to prevent postoperative pneumonia and should be based on the patient's frailty.¹⁶ It has been reported that pneumonia deaths occur so often after gastrectomy in elderly patients that efforts to reduce pneumonia are necessary with less invasive intervention, as well as oral care, breathing exercises, and early ambulation.^{17–20}

The Dutch trial¹¹ showed that D2 LND was associated with significantly lower regional, local, and liver recurrence than D1 LND (13% versus 19%, 12% versus 22%, and 11% versus 17%). Shinozuka *et al*¹⁴ showed that frequencies of initial lymph node recurrence in patients \geq 80 years were lower after D2 LND than after non-D2 LND (16% versus 29%), although the difference was not significant. Our data showed that initial lymph node recurrence was detected in only 1 (4%) and 2 patients (7%) in the D2 and limited LND groups, respectively, with no significant difference. Initial local recurrence was also detected in 1 and 2 patients, respectively, and initial liver recurrence was detected in 1 patient in each group. Routine computed tomography checkup was often omitted in the elderly in our series, which may have contributed to the low recurrence rates.

In the current series, gastric cancer death was not more frequently encountered in the limited LND group than in the D2 LND group, while the Dutch trial¹¹ showed that its rate was significantly higher in the D1 group than in the D2 group. Elderly

patients were likely to die of other diseases, such as pneumonia (15% and 25% in the limited and D2 LND groups, respectively) and senility (13% in the limited LND group), after gastrectomy. Therefore, the effect of radical LND on prognosis can be ignored even if the possibility of cancer recurrence is higher in the limited LND group.

In PSM, the choice of covariates is important. In our previous report, patients \geq 80 years old with ECOG PS \geq 3 did not exhibit a survival benefit after surgery.³ Furthermore, our multivariate analysis indicated that ASA-PS was an independent risk factor for mortality in patients \geq 80 years who underwent gastrectomy (data not shown). In addition, PNI is a well-known prognostic factor after surgery.²¹ Therefore, we included ECOG PS, ASA-PS, and PNI in addition to age, sex, clinical cancer stage, and extent of gastrectomy as covariates for estimating propensity scores.

This study has several limitations. First, this study is limited by its retrospective nature. Confounding biases may have also affected the survival differences between the groups even after PSM. Second, this study was conducted at only 2 institutions with a relatively small number of patients. Third, some patients were not followed for a sufficient time because it was difficult for them to visit regular outpatient clinics or because they transitioned to other institutions after surgery.

In conclusion, we retrospectively compared the prognoses of patients \geq 80 years old with advanced gastric cancer after D2 and limited LND and found that D1+ or even D1 LND was acceptable.

Acknowledgments

This study was approved by the Institutional Review Board of Kawasaki Medical School (approval No. 5083-01) and conformed to the principles of the Declaration of Helsinki. The requirement for informed consent was waived by the Institutional Review Board of Kawasaki Medical School due to the retrospective nature of the study. Shunji Endo and Ken Sugimoto wrote the protocol. Shunji Endo gathered and analyzed the data, and wrote the manuscript. Yoshinori Fujiwara, Masaharu Higashida, Hisako Kubota, Hideo Matsumoto, Hironori Tanaka, Toshimasa Okada, Kazuhiko Yoshimatsu, Ken Sugimoto, and Tomio Ueno reviewed and edited the manuscript. All authors read and approved the final manuscript. All authors declare that they have no competing interests.

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