Effect of lymphadenectomy extent on advanced gastric cancer located in the cardia and fundus

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INTRODUCTION

At present, surgery is the most effective treatment for gastric cancer. As the standard procedure for advanced gastric cancer, D2 radical resection has been widely accepted and practiced [1-6]. The final results of a randomized Dutch trial [7] showed that patients with N2 disease might benefit from a D2 dissection, which required removing all the lymph nodes (LNs) of Group 1 and Group 2. According to another randomized Italian trial [8], a D2 lymphadenectomy was also advised. Lymph node metastasis is considered one of the most important prognostic factors [9,7], and adequate lymphadenectomy is advocated for gastric cancer. However, the number of LNs that should be removed and examined when performing a D2 lymphadenectomy has not been determined for advanced gastric cancer located in the cardia and fundus [8]. Therefore, the aim of this retrospective study was to evaluate the relative contributions of both the number of total resected LNs and the number of negative LNs to the outcome of patients with advanced gastric cancer located in the cardia and fundus, and provide further evidence for rational lymphadenectomy.
Materials and Methods

Materials
Between January, 1996 and June, 2002, 236 patients diagnosed with primary gastric cancer located in the cardia and fundus was treated with curative resection at the Department of Oncology, Affiliated Union Hospital of Fujian Medical University, Fuzhou, China. The surgical procedure was defined as curative when no grossly visible tumor tissue (metastasis or LN involvement) remained after the resection and the resection margins were histologically normal. There were 197 male and 39 female patients whose ages ranged from 30 to 79 years (58.8 ± 9.8 years). All patients received a D2 or more extended dissection according to the Japanese Classification of Gastric Carcinoma (JCGC). Lymph nodes were meticulously dissected from the en bloc specimens, and the classification of the dissected LNs was determined by specialist surgeons who reviewed the excised specimens after surgery based on the Japanese Classification of Gastric Carcinoma[9]. The clinical and histopathologic data of each patient were collected and recorded in a specifically designed form. The tumors were histologically classified according to the WHO classification criteria and staged according to the 5th Edition of the TNM system[10], as listed in Table 1. The follow-up was carried out by trained investigators through mailings, telephone calls, visiting patients or recording the patients’ consultations at the outpatient service. The survival time was the time from diagnosis until the last contact, the date of death, or the date that the survival information was collected. All surviving patients were followed for more than five years. The median follow up for the entire cohort was 44 mo (range, 1-136 mo). The follow-up rate was 94.0%, with 222 cases involved.

Methods
Patients were stratified into five groups based on the number of total LNs removed as follows: < 15 LNs (36 cases), 15-19 LNs (43 cases), 20-24 LNs (62 cases), 25-29 LNs (40 cases) and ≥ 30 LNs (55 cases). Meanwhile, four groups were established based on the number of negative LNs as follows: 0-9 LNs (61 cases), 10-19 LNs (93 cases), 20-29 LNs (63 cases) and ≥ 30 LNs (19 cases). All calculations were performed using the SPSS 11.5 statistical package. Actuarial survival was determined using the Kaplan-Meier method, with univariate comparisons between groups through the log-rank test. Cox regression was used for multivariate analysis, with a backward elimination model for all covariates. A regression model to correlate negative LN counts with survival was obtained based on Kaplan-Meier 5-year survival estimates for each LN count interval, using the LN count interval midpoints to construct the independent variable. Significance of differences was assumed at P values less than 0.05 for all analyses.

Table 1  Clinical characteristics of the 236 patients

| Characteristics | n   | Percentage |
|-----------------|-----|------------|
| Gender          |     |            |
| Male            | 197 | 83.5       |
| Female          | 39  | 16.5       |
| Age (yr)        |     |            |
| < 60            | 103 | 43.6       |
| ≥ 60            | 133 | 56.4       |
| Tumor size (cm) |     |            |
| < 3             | 88  | 37.3       |
| 3-6             | 97  | 41.1       |
| > 6             | 51  | 21.6       |
| Borrmann’s type |     |            |
| Type I, II      | 172 | 72.9       |
| Type III, IV    | 64  | 27.1       |
| Histological classification | | |
| Papillary adenocarcinomas | 47 | 20 |
| Tubular adenocarcinomas | 101 | 42.8 |
| Mucinous adenocarcinomas | 29 | 12.3 |
| Poorly differentiated adenocarcinomas | 36 | 15.3 |
| Undifferentiated carcinomas | 8 | 3.4 |
| Others          | 15  | 6.4       |
| Depth of invasion (T category) | | |
| Muscularis (pT2) | 25 | 10.6 |
| Serosa (pT3)     | 118 | 50        |
| Invasion to adjacent organs (pT4) | 93 | 39.4 |
| Lymph node involvement (N category) | | |
| pN0             | 42  | 17.8       |
| pN1             | 97  | 41.1       |
| pN2             | 68  | 28.8       |
| pN3             | 29  | 12.3       |
| Stage           |     |            |
| II              | 48  | 20.3       |
| III             | 128 | 54.2       |
| IV              | 60  | 25.4       |
| Type of gastrectomy | | |
| TG              | 190 | 80.5       |
| PSG             | 46  | 19.5       |

Results

Analysis based on total and negative LNs examined
Overall, 82.2% of patients (194/236) had LN metastasis. The incidences of LN metastasis were 56% for T2, 78.8% for T3 and 93.5% for T4. A total of 5615 LNs were picked up for histological examination, with 4005 being negative. The median of total LN number was 23 (range, 7-74; mean 23.8 ± 8.8) per patient, and the median of negative LNs was 16 (range, 0-48; mean 16.9 ± 9.3) per patient. There were no differences between T subcategories regarding total LNs resected [median (range): T2: 22 (9-31); T3: 26 (7-47); T4: 23 (7-74); Kruskal-Wallis, P = 0.062] or negative LN counts [median (range): T2: 12 (9-28); T3: 21 (1-45); T4: 17 (1-48); Kruskal-Wallis, P = 0.502].

Multivariate survival analysis
The five-year overall survival rate of the entire cohort was 37.5%. The backwards elimination model yielded the following independent prognostic variables: total LN count (or number of negative LNs examined; P < 0.0001), number of positive LNs (P < 0.0001), T category (P < 0.0001) and tumor size (P = 0.015). The covariates gender (P = 0.052), age (P = 0.329),...
Borrmann type ($P = 0.373$), histological grade ($P = 0.132$), and type of gastrectomy ($P = 0.093$) all failed to retain significance levels in this model. The risk ratios and 95% confidence intervals are listed in Table 2. The number of negative LNs and the total number of LNs examined behaved interchangeably and maintained a similar significance level when substituted for each other. This suggests that the number of negative LN can reflect the extent of lymphadenectomy, as can the total number of LNs.

**Impact of total LN counts by univariate survival analysis**

When five-year overall survival was compared by increasing total LN count, higher LN counts were generally associated with better survival (Figure 1A). Of the entire cohort, for the T4, N2 and N3 categories, the best survival outcomes were observed with total LN counts no less than 30. For the N1 category, the best survival outcomes were observed with total LN counts between 25 and 29, as shown in Table 3. When adjusted for the T category, the survival rate of the 25-29 LNs group was higher than that of the < 15 ($\chi^2 = 13.41$, $P = 0.0002$), 15-19 ($\chi^2 = 7.06$, $P = 0.008$) and 20-24 LNs groups ($\chi^2 = 5.69$, $P = 0.017$). The survival rate of the $\geq 30$ LNs group was higher than that of the < 15 ($\chi^2 = 7.03$, $P = 0.008$) and the 15-19 LNs groups ($\chi^2 = 4.91$, $P = 0.03$). When adjusted for the N category, the survival rate of the 25-29 LNs group was higher than that of the 15-19 ($\chi^2 = 9.67$, $P = 0.002$) and 20-24 LNs groups ($\chi^2 = 5.68$, $P = 0.02$); the survival rate of the $\geq 30$ LNs group was higher than that of the 15-19 ($\chi^2 = 6.56$, $P = 0.01$) and 20-24 LNs groups ($\chi^2 = 4.56$, $P = 0.03$).

**Cut point analysis of survival differences relating to total LNs dissected**

In an attempt to identify the optimal total LN count cutoff, survival comparisons were made for all stage groups at increasing total LN counts between 7 and 35. The greatest discrepancies, as measured by the chi-square test, were stage dependent, and varied from the cutoff levels of 20 (stage II), 25 (stage III), and 30 (stage IV) to the cutoff level of 15 (entire cohort), as listed in Table 4.

**Impact of negative LN counts by univariate survival analysis**

The five-year survival, based on categories, showed considerable variations with increasing counts of negative LNs. An obvious trend toward better survival results for higher negative LN counts was observed (Table 5). Figure 1B shows the overall survival curve for all patients according to different negative LN strata.

**Projected impact of negative LN counts on overall survival**

Based on the statistical linearity regression, the impact of negative LN counts on overall survival was analyzed. For the stage II subgroup, the hypothetical baseline five-year survival (based on the y-intercept, i.e. no negative
LNs) was 39.6%. Similarly, for the stage III subgroup, the baseline five-year survival (with an assumed zero negative LNs) was 15.4%. For the stage IV subgroup, the baseline five-year survival (also with an assumed zero negative LNs) was 2.5%. For all patients, the calculated five-year survival rate at baseline was 11.2%. For every ten extra LNs added to the negative LN count, the calculated overall survival increased by 5.77% (stage II), 6.09% (stage III), 7.65% (stage IV) or 6.24% (the entire cohort). In this setting, the regression showed a statistically significant survival improvement based on increasing negative LN number only for patients with stages III (P = 0.013) and stages IV (P = 0.035). The results for stage II had no statistical significance (P = 0.195).

**DISCUSSION**

Over the last few decades, an increase in the incidence of upper third gastric cancer has been reported by many investigators around the world [14-15]. It is generally accepted that the prognosis of patients with this type of carcinoma is worse than for tumors in other parts of the stomach [15-16]. The only potentially curative treatment for this disease is complete surgical resection, with an en bloc LN dissection. The D2 radical resection has been regarded as the standard surgical procedure for advanced gastric cancer [16]. Lymph node dissection during the D2 radical resection is not confined to the anatomical extent, but also to the number of LNs dissected. The current edition of the UICC staging manual recommends examining at least 15 LNs for adequate gastric cancer staging. However, is that adequate for advanced gastric cancer located in the cardia and fundus? It was reported that patients with advanced gastric cancer located in the cardia and fundus often showed a higher frequency of perigastric LNs and higher proportion of overall LN metastasis than for tumors in other parts of the stomach [17-18]. Koubuji et al. [18] investigated 49 cases with an upper gastric cancer invading the esophagus who underwent surgical treatment. The incidences of LN metastasis were 0% for T1, 67% for T2, 81% for T3 and 80% for T4. Ichikura et al. [19] retrospectively analyzed 65 cases with cardiac carcinoma and found that the incidences of LN metastasis were 68% for Siewert’s type II tumors, and 94% for Siewert’s type III tumors. In the present study, 82.2% of patients had LN metastasis. For these patients, it is better to determine the extent of lymphadenectomy according to the extent of LN metastases preoperatively or intraoperatively. However, it is difficult to achieve as there is lack of reliable measures for clinical diagnosis preoperatively and for comprehensive LN biopsy intraoperatively [20-21]. If the LNs were not completely removed, the probability of residual tumor cells would increase, leading to poor prognosis. Therefore, some investigators advocated removing adequate LNs intraoperatively to avoid this situation [22-24]. However, it is not certain how many LNs need to be dissected in a D2 lymphadenectomy. Liu et al. [25] showed, in 147 patients with adenocarcinoma of the stomach who had undergone gastrectomy with curative intent, that for stage III disease, removal of >15 LNs

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**Table 3 Five-year overall survival by stage subgroups and total number of LNs dissected**

| Total LN count | Stage II | Stage III | Stage IV | Total |
|----------------|---------|-----------|---------|-------|
| < 15 LN         | 7.14%   | 20.04%    | 4.36%   | 24.34%|
| 15-24 LN       | 0.017   | 0.251     | 0.022   | 0.290 |
| ≥ 25 LN        | 0.27%   | 0.0302    | 0.0109  | 0.0381 |

**Table 4 Overall survival by total LN count, each stage subgroup cut point analysis**

| Total LN count | Stage II | Stage III | Stage IV | Total |
|----------------|---------|-----------|---------|-------|
| N0 < 15        | 0.017   | 0.251     | 0.022   | 0.290 |
| N1 15-24       | 0.27%   | 0.0302    | 0.0109  | 0.0381 |
| N2 ≥ 25        | 1.20%   | 0.2726    | 0.0302  | 0.0153 |

**Table 5 Overall five-year survival by stage subgroup and number of negative LNs**

| N0 OS (%) | N1 OS (%) | N2 OS (%) | N3 OS (%) | Total |
|-----------|-----------|-----------|-----------|-------|
| T2        | 40.0%     | 40.0%     | 40.0%     | 40.0% |
| T3        | 40.0%     | 40.0%     | 40.0%     | 40.0% |
| T4        | 40.0%     | 40.0%     | 40.0%     | 40.0% |

| P value |
|---------|
| 0.4907  |
| 0.0001  |
| 0.0328  |
| 0.0055  |
| 0.0114  |

NA: Not applicable; OS: Overall survival rate.
appeared to provide a considerable survival advantage, compared with removal of < 15 LNs. Another study favoring this opinion was from Barboux et al [26]. They suggested that patients with Siewert type II and III adenocarcinoma of the gastroesophageal junction (GEJ) should undergo adequate lymphadenectomy to permit examination of \( \geq 15 \) LNs, allowing accurate identification of prognostic variables. Removal of \( \geq 15 \) LNs is associated with more accurate survival estimates for patients with advanced disease. For adenocarcinoma of the GEJ, a minimum removal of 25 LNs was recommended by Gee et al [27]. Our present observations showed that better long-term survival outcomes were obtained with higher numbers of LNs resected during D2 lymphadenectomy. This is consistent with the research results of Schwarz et al [28]. We suggest that for adequate LN resection, including total LNs and the number of negative LNs, the removal of 20 LNs for stage I, 25 LNs for stage II, 30 LNs for stage IV and 15 LNs for the entire cohort be recommended during D2 radical dissection.

Total LNs and number of negative LNs can reflect the extent of LN dissection and influence survival [29,30]. In the present study, total LN count or negative LN counts turned out to be independent protective factors, according to the symbols of regression coefficient. These two factors behaved interchangeably, and maintained a similar significance level when substituted for each other. Furthermore, an impact of total LNs or negative LNs on survival was observed. In the univariate survival analysis, higher total LN counts may translate into better outcomes. The effect was much more significant with T4 and N2, N3 disease. We thus postulate that even in locally advanced disease with adjacent organ invasion or advanced nodal involvement that is still resectable, adequate LN dissection influences survival.

The contribution of negative LN counts to the prognosis of patients is partly due to LN micrometastases. In patients without lymph metastases identified by HE staining, about 20% had LN micrometastases [31]. del Casar et al [32] reviewed 144 patients with primary gastric adenocarcinoma who underwent surgery and found that lymphatic and/or blood vessel tumor invasion (LBVI) was present in 46 patients (31.9%), which was significantly associated with a poorer overall patients’ survival. Therefore, curability was reported as one of the most reliable predictors of long-term survival for LN-negative gastric carcinoma patients [33]. A similar study [34] examined the impact of the number of negative LNs on survival. The study was conducted in patients with stage III colon cancer, and demonstrated that a higher number of negative nodes was associated with better survival. In our study, the impact of negative LN on survival in these stage patients also showed an obvious trend toward better survival for higher negative LN counts. For every ten extra LNs added to the negative LN count, the calculated overall survival increased by 6.09% for stage III, and 7.65% for stage IV patients, based on the linear regression. Generally, better long term survival was observed with higher total LNs or negative LNs, showing the contribution of sufficient lymphadenectomy toward reducing residual tumor cells. For the curative-intent gastrectomy of locally advanced disease, retrieval and examination of adequate numbers of LNs is suggested for gastric cancer located in the cardia and fundus.

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