Tumor Size Is a Critical Factor in Adjuvant Chemotherapy for T3-4aN0M0 Gastric Cancer Patients after D2 Gastrectomy

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Aim. To investigate whether tumor size is a reasonable indication for adjuvant chemotherapy for T3-4aN0M0 gastric cancer patients after D2 gastrectomy.

Method. We performed a retrospective study of 269 patients with a histological diagnosis of T3-4aN0M0 stage gastric cancer who underwent D2 radical surgery at the Sun Yat-sen University Cancer Center or the Sixth Affiliated Hospital of Sun Yat-sen University between January 2006 and December 2010. The follow-up lasted until June of 2015. Chi-square tests and Kaplan-Meier methods were employed to compare the clinicopathological variables and prognoses.

Result. For this group of patients, univariate analyses revealed that tumor size ($p < 0.001$), pathological T stage ($p < 0.001$), and tumor location ($p = 0.025$) were significant prognostic factors. Adjuvant chemotherapy did not exhibit prognostic benefits. For patients with tumors larger than 5 cm, univariate analysis revealed that tumor location ($p = 0.007$), Borrmann type ($p = 0.039$), postoperative chemotherapy ($p = 0.003$), and pathological T stage ($p < 0.001$) were significant prognostic factors. Multivariate analysis revealed that postoperative chemotherapy and pathological T stage were independent prognostic factors.

Conclusion. Our results imply that tumor size should be a critical factor in the decision to utilize adjuvant chemotherapy for T3-4aN0M0 gastric cancer patients after D2 gastrectomy. Additional randomized controlled trials are required before this conclusion can be considered definitive.

1. Background

Gastric cancers are the fourth most common malignancies worldwide, and they are the second most lethal [1–3]. Gastrectomy with D2 lymphadenectomy is recommended as a standard surgery for gastric cancer patients and results in improved overall survival [4–6]. Moreover, adjuvant chemotherapy has been proven to improve the overall survival of advanced gastric cancer patients after D2 gastrectomy [7, 8]. However, for N0 patients, particularly T3 and T4a patients, the use of adjuvant chemotherapy remains controversial. Although N0-group patients were not found to benefit from adjuvant chemotherapy in an ACTS trial, stage II gastric cancer patients without lymph node metastases were not separately analyzed, and there were only 112 patients in the N0 group [7]. Moreover, in the CLASSIC trial, the N0 group also exhibited no survival benefit following adjuvant chemotherapy [8]. Thus, the question of how to select N0 patients for adjuvant chemotherapy, particularly stage II patients, remains unresolved. The role of postoperative chemotherapy in T3-T4a gastric cancer patients is still controversial. In addition to TNM stage, other risk factors should be identified for this patient group to select for whom postoperative chemotherapy would be beneficial. Tumor size is also an important characteristic of gastric cancer, and we found that it was an informative factor for chemotherapy selection.

Tumor size is another factor that can be evaluated in gastric cancer patients, although it is not listed in the staging systems of the UICC or JGCA for gastric cancer [9, 10]. Obviously, larger tumors are more advanced. In the present study, we performed a retrospective analysis that focused on these N0-group gastric cancer patients, compared the prognoses...
Figure 1: The AUC was 0.751, and the largest Youden index was 0.398, corresponding to a tumor size of 4.75 cm. However, we believed that, in the clinic, 5 cm is a more appropriate cut-off value for doctors seeking to decide whether the patient should receive postoperative chemotherapy.

Table 1: Clinical pathological data of the gastric cancer patients.

| Clinical pathological data                  | Small gastric cancer patient group (n = 148 cases) | Large gastric cancer patient group (n = 121 cases) | p value |
|--------------------------------------------|---------------------------------------------------|---------------------------------------------------|---------|
| Age (years)                                | Median 23–79                                       | Cases 62 %                                       |         |
|                                            | Range 41–83                                        | Cases 58 %                                       |         |
| Sex                                        | Male 108 73.0                                      | Male 78 64.5                                      | 0.146   |
|                                            | Female 40 27.0                                     | Female 43 35.5                                    |         |
|                                            | Gastric cardia 55 37.2                              | Gastric cardia 75 62.0                            |         |
| Tumor location                             | Middle 21 14.2                                     | Middle 14 11.6                                   |         |
|                                            | Antrum 66 44.6                                     | Antrum 21 17.4                                   | <0.001  |
|                                            | Total stomach 6 4.1                                 | Total stomach 11 9.1                             |         |
| CEA level                                  | <5 μg/ml 135 93.1                                   | <5 μg/ml 93 76.9                                 | <0.001  |
|                                            | ≥5 μg/ml 10 6.9                                     | ≥5 μg/ml 28 23.1                                 |         |
|                                            | I 2 1.4                                           | I 2 1.7                                          |         |
|                                            | II 69 46.6                                        | II 50 43.1                                       | 0.145   |
|                                            | III 77 52.0                                       | III 65 43.8                                      |         |
|                                            | IV 0 0                                            | IV 4 6.2                                         |         |
|                                            | High differentiation 1                             | High differentiation 0                           |         |
|                                            | Median differentiation 37                         | Median differentiation 46                        | 0.103   |
|                                            | Low differentiation 87                             | Low differentiation 57                           |         |
|                                            | Poor differentiation* 23                          | Poor differentiation* 18                         |         |
|                                            | T3 130 87.8                                       | T3 97 80.2                                       | 0.093   |
|                                            | T4a 18 12.2                                       | T4a 24 19.8                                      |         |
|                                            | 15–29 121 81.8                                    | 15–29 106 87.6                                   | 0.237   |
|                                            | ≥30 27 18.2                                       | ≥30 15 12.4                                      |         |
|                                            | Without 56 37.8                                    | Without 33 27.3                                  | 0.070   |
|                                            | With 92 62.2                                      | With 88 72.7                                     |         |
*Poorly differentiated cells: signet ring cell carcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, etc.  **The T and N staging for this group of patients is according to the AJCC 7th TNM staging system for gastric cancer.
and one received the DX regimen (docetaxel: 75 mg/m²)

received the SOX regimen (oxaliplatin: 85 mg/m² D1 + S-1 

monitored every month for the 

After treatment, the patients were moni-

Table 1. 

Table 2: Univariate analysis of the overall survival in this group of 

| Variables                        | n  | Mean survival (months) | p value |
|----------------------------------|----|------------------------|---------|
| Postoperative chemotherapy       |    |                        | 0.543   |
| With                             | 180| 58.01                  |         |
| Without                          | 89 | 56.08                  |         |
| Tumor size                       |    |                        | <0.001  |
| <5 cm                            | 148| 63.25                  |         |
| ≥5 cm                            | 121| 47.95                  |         |
| Tumor location                   |    |                        | 0.025   |
| Upper                            | 130| 60.01                  |         |
| Middle                           | 35 | 46.20                  |         |
| Lower                            | 87 | 58.40                  |         |
| Total                            | 17 | 48.17                  |         |
| Serum CEA level (ng/ml)          |    |                        | 0.529   |
| Normal                           | 228| 57.36                  |         |
| Elevated                         | 38 | 56.55                  |         |
| Borrmann type                    |    |                        | 0.119   |
| I                                | 4  | 68.00                  |         |
| II                               | 119| 59.58                  |         |
| III                              | 142| 54.85                  |         |
| IV                               | 4  | 26.75                  |         |
| Histological grade               |    |                        | 0.300   |
| High differentiation             | 1  | 72.00                  |         |
| Median differentiation           | 83 | 61.71                  |         |
| Low differentiation              | 144| 61.05                  |         |
| Poor differentiation             | 41 | 46.85                  |         |
| T staging                        |    |                        | <0.001  |
| T3                               | 227| 59.61                  |         |
| T4a                              | 42 | 45.89                  |         |
| LN harvested                     |    |                        | 0.160   |
| 15–29                            | 227| 58.31                  |         |
| ≥30                              | 42 | 51.26                  |         |

according to different tumor size groups, and attempted to determine the prognostic value of tumor size in relation to adjuvant chemotherapy.

### 2. Materials and Methods

#### 2.1. Ethics Statement. All of the patients provided written informed consent for their information to be stored in a hospital database. Study approval was obtained from independent ethics committees at the Sixth Affiliated Hospital of Sun Yat-sen University and the Cancer Center of Sun Yat-sen University. This study was undertaken in accordance with the ethical standards of the World Medical Association Declaration of Helsinki.

#### 2.2. Patient Inclusion and Exclusion Criteria. The inclusion criteria were as follows: (1) WHO performance status of 0 to 1; (2) histologically proven T3-4 adenocarcinoma of the stomach without evidence of lymph node metastasis; (3) no prior gastric surgery; (4) no previous radiotherapy or other treatments, including immunotherapy or traditional Chinese medicine; and (5) no synchronous or metachronous cancers.

#### 2.3. Chemotherapy. Various chemotherapeutic regimens were considered in our research: 36 patients received Xeloda (1000 mg/m², D1–14, Q3W, cycles: 5.67 ± 1.15); 67 patients received the XELOX regimen (oxaliplatin: 130 mg/m² D1 + Xeloda 1000 mg/m², D1–14, Q3W, cycles: 5.53 ± 1.55); and 44 patients received the FOLFOX regimen (oxaliplatin: 85 mg/m² D1 + CF 400 mg/m² D1 + S-Fu 2800 mg/m², D1-D2, Q2W, cycles: 8.52 ± 1.57). Of another 33 patients, 14 received the S-1 regimen (40–60 mg, bid, D1–14, Q3W, cycles: 5.71 ± 1.43); 13 received the CX regimen, (cisplatin: 60 mg/m² D1 + Xeloda 1000 mg/m², D1–14, Q3W, cycles: 4.92 ± 1.50); 5 received the SOX regimen (oxaliplatin: 85 mg/m² D1 + S-Fu 2800 mg/m², D1–14, Q3W, cycles: 4.92 ± 1.50); and one received the DX regimen (docetaxel: 75 mg/m² D1 + Xeloda 1000 mg/m², D1–14, Q3W, cycles: 5).

#### 2.4. Patient Characteristics. From January 2006 to December 2010, 269 consecutive patients with a histological diagnosis of T3-4N0 gastric cancer who underwent D2 radical surgery at the Sixth Affiliated Hospital of Sun Yat-sen University or the Sun Yat-sen University Cancer Center were included in this study. We divided the patients according to tumor size. The clinicopathological factors are presented in Table 1.

#### 2.5. Follow-Up. After treatment, the patients were monitored every month for the first year, every 3 months for the second year, and every 6 months thereafter, with regular follow-up assessments. Telephone calls and letters were used to follow up on the patients who were not able to attend regular follow-up assessments. Complete data were collected for all 269 patients through December 2014. The following-up period ranged from 6 months to 90 months (median: 46 months).

#### 2.6. Statistical Methods. A chi-square test was used to compare the categorical variables between the palliative operation group and the other groups. Student’s t-tests were used to compare the continuous variables. Univariate survival analyses were performed using Kaplan-Meier methods. The survival curves were compared with the log-rank test. The statistical analyses were performed with SPSS software version 20.0 (SPSS Inc., Chicago, IL) for Windows. Statistical significance was defined as p < 0.05.

### 3. Result

#### 3.1. Univariate Analyses of the Prognoses of Gastric Cancer Patients. According to the Kaplan-Meier analysis, tumor size
Figure 2: Univariate analysis of 267 T$_{3-4}$aN0M0 gastric cancer patients. (a) The mean survival times of patients with tumor sizes smaller than 5 cm and larger than 5 cm were 63.25 and 47.95 months, respectively ($p < 0.001$). (b) The mean survival times of the T3 and T4a patients in the study were 59.61 and 45.89 months, respectively ($p < 0.001$). (c) Tumor location was also a prognostic factor for this group of patients ($p = 0.025$). (d) Adjuvant chemotherapy did not have a prognostic benefit for this group of gastric cancer patients ($p = 0.543$).
Table 3: Multivariate analyses of overall survival in gastric cancer patients (Cox’s regression model).

| Variable                        | HR    | 95% CI          | p value |
|---------------------------------|-------|-----------------|---------|
| OS in gastric cancer patients   |       |                 |         |
| Tumor size                      | 2.780 | 1.894–4.081     | <0.001  |
| CEA level                       | 0.936 | 0.510–1.717     | 0.831   |
| Tumor location                  | 1.221 | 1.023–1.458     | 0.027   |
| Pathological T staging          | 2.101 | 1.342–3.289     | 0.001   |

OS, overall survival; HR, hazard ratio; CI, confidence interval.

Figure 3: In the group of patients with tumor sizes of less than 5 cm, the median survival times of the chemotherapy and without chemotherapy groups were 64.43 months and 62.38 months, respectively (p = 0.776).

3.2. Multivariate Analysis of the Prognoses of Gastric Cancer Patients. Furthermore, we used the Cox regression model to analyze these risk factors in order to identify the independent risk factors. The results revealed that tumor size, tumor location, and pathological T stage were the only independent prognostic risk factors. All of these results are presented in Table 3.

3.3. Postoperative Chemotherapy Brings No Benefits for Stage II Gastric Cancer Patients with Tumors Less Than 5 cm in Size. In the group of patients with tumor sizes of less than 5 cm, the postoperative chemotherapy did not show any benefit. As shown in Figure 3, the median survival times of the chemotherapy and without chemotherapy groups were 64.43 months and 62.38 months, respectively (p = 0.776).

3.4. Univariate Analyses of the Prognoses of Gastric Cancer Patients with Tumors Greater Than 5 cm in Size. We first compared the clinicopathological factors between the postoperative chemotherapy and no postoperative chemotherapy groups of gastric cancer patients with tumors greater than 5 cm (Table 4). Kaplan-Meier analysis revealed that tumor location (p = 0.007), Borrmann type (p = 0.039), postoperative chemotherapy (p = 0.003), and pathological T
stage ($p < 0.001$) were prognostic risk factors (Table 5). The survival curves are illustrated in Figure 4.

3.5. Multivariate Analysis of the Prognoses of Gastric Cancer Patients with Tumors Greater Than 5 cm in Size. Furthermore, we used the Cox regression model to analyze these risk factors in order to identify the independent risk factors for gastric cancer patients. Multivariate analysis revealed that Borrmann type, postoperative chemotherapy, and pathological T stage were independent prognostic factors for these patients (Table 6).

4. Discussion

Pathological stage can be used for gastric cancer patients to predict the risk of recurrence and prognosis. Stage I gastric cancer patients have a very low risk of recurrence [11] and are thus not indicated for postoperative chemotherapy. In contrast, stage IV gastric cancer patients can only accept palliative therapy, surgery, chemotherapy, and other treatments [12]. Until now, there has been great variability among the outcomes of patients with stage II/III GC; some patients are prone to suffer from locoregional or distant recurrence even after complete curative resection, whereas others achieve long-term survival [13]. Particularly for stage II gastric cancer patients, the controversy regarding the use of adjuvant chemotherapy following D2 gastrectomy persisted until the completion of the ACTS-GC and CLASSIC trials. The five-year outcomes of the ACTS-GC trial (S-1 versus surgery only) and the CLASSIC trial both indicated that stage II gastric cancer patients can benefit from postoperative chemotherapy [14, 15]. However, in these two clinical trials, the stage II gastric cancer patients included the T2N1M0 and T1N2M0 groups. Moreover, in the CLASSIC trial, the hazard ratio for adjuvant chemotherapy for N0 patients was 0.79 (CI: 0.39–1.60); thus, adjuvant chemotherapy was not advantageous in terms of prognostic improvement. Therefore, whether adjuvant chemotherapy is beneficial for lymph node-negative stage II gastric cancer patients remains unknown.

Because of the controversy regarding the role of postoperative chemotherapy in stage II gastric cancer patients, at our institution, we allowed patients and their relatives to decide whether the patients would receive postoperative chemotherapy.

Table 4: Clinical pathological data of the gastric cancer patients whose tumor size is larger than 5 cm.

| Clinical pathological data | Without postoperative chemotherapy group ($n = 33$ cases) | With postoperative chemotherapy group ($n = 88$ cases) | $p$ value |
|---------------------------|--------------------------------------------------------|------------------------------------------------------|----------|
| Age (years)               | Median 58 23–79                                       | 62 41–83                                             | 0.368    |
|                           | Range 23–79                                           | 41–83                                                |          |
| Sex                       | Male 20 60.6                                          | 58 65.9                                              | 0.639    |
|                           | Female 13 39.4                                        | 30 34.1                                              |          |
| Tumor location            | Gastric cardia 20 60.6                                 | 55 62.5                                              |          |
|                           | Middle 5 15.2                                         | 9 10.2                                               | 0.296    |
|                           | Antrum 4 12.1                                         | 17 19.3                                              |          |
|                           | Total stomach 4 12.1                                  | 7 8.0                                                |          |
| CEA level                 | $<5\,\mu$g/ml 27 81.8                                 | 66 75.0                                              |          |
|                           | $\geq5\,\mu$g/ml 6 18.2                               | 22 25.0                                              |          |
|                           | I 1 3.0                                               | 1 1.1                                                |          |
|                           | II 12 36.4                                            | 38 43.2                                              | 0.819    |
|                           | III 19 57.6                                           | 46 52.3                                              |          |
|                           | IV 1 3.0                                              | 3 3.4                                                |          |
| Histological grade        | High differentiation 0 0.0                             | 0 0                                                  |          |
|                           | Median differentiation 8 24.2                          | 38 43.2                                              | 0.077    |
|                           | Low differentiation 21 63.6                            | 36 40.9                                              |          |
|                           | Poor differentiation*                                 | 4 12.1                                               | 14 15.9  |
| T staging**               | T3 25 75.8                                            | 72 81.8                                              | 0.307    |
|                           | T4a 8 24.2                                            | 16 18.2                                              |          |
|                           | 15−29 32 97.0                                         | 74 84.1                                              | 0.045    |
| LN harvested              | $\geq30$ 1 3.0                                        | 14 15.9                                              |          |

*Poorly differentiated cells: signet ring cell carcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, etc. **The T and N staging for this group of patients is according to the AJCC 7th TNM staging system for gastric cancer.
because of the fear of chemotherapy-related adverse events, and others refused for economic reasons.

In the present study, we demonstrated that adjuvant chemotherapy does not benefit the survival of stage II gastric cancer patients without lymph node metastasis. The median survivals of the patients who did and did not receive adjuvant chemotherapy were 58.0 months and 56.1 months, respectively.

Precision therapy is thought to be the direction of future treatment strategies. Before molecular pathological techniques can be widely used to treat gastric cancer, it is important to determine how stage II gastric cancer patients can be properly selected to receive adjuvant chemotherapy to improve survival.

Although tumor size is not included in the current TNM staging system of the 7th AJCC, this factor still plays an important role in the prediction of the prognoses of gastric cancers due to the ease of its measurement. In Adachi’s report, tumor size was strongly correlated with tumor progression parameters, such as the depth of invasion, the degree of lymph node metastasis, and the stage of the disease [16]. Wang et al. suggested that tumor size can efficiently and reliably reflect lymph node status [17]. In the present trial, we found that tumor size was an independent prognostic factor for our group of T3-4aN0M0 gastric cancer patients. Moreover, among these T3-4aN0M0 gastric cancer patients with tumors greater than 5 cm, adjuvant chemotherapy was an independent prognostic factor. This finding indicates that adjuvant chemotherapy can benefit gastric cancer patients with tumors greater than 5 cm. In our study, we found that, among gastric cancer patients with tumor sizes larger than 5 cm, postoperative chemotherapy improved the prognosis. We therefore propose that postoperative chemotherapy should be performed in this group of patients.

The accurate cancer staging of each patient in clinical practice is crucial for helping clinicians select treatment plans. Although our sample was small, our results imply that tumor size may be useful for guiding adjuvant treatments for T3-4aN0M0 gastric cancer patients. However, this study was a retrospective study and thus has limitations, such as confounding factors. Additional experiments and clinical trials are necessary to validate tumor size as a critical factor in determining whether adjuvant chemotherapy should be utilized for T3-4aN0M0 patients following D2 gastrectomy.

| Variables                      | n   | Mean survival (months) | p value |
|-------------------------------|-----|------------------------|---------|
| **Postoperative chemotherapy**|     |                        | 0.003   |
| With                          | 88  | 51.23                  |         |
| Without                       | 33  | 38.93                  |         |
| **Tumor location**            |     |                        | 0.007   |
| Upper                         | 75  | 51.68                  |         |
| Middle                        | 14  | 34.24                  |         |
| Lower                         | 21  | 47.61                  |         |
| Total                         | 11  | 36.12                  |         |
| **Serum CEA level (ng/ml)**   |     |                        | 0.105   |
| Normal                        | 93  | 46.19                  |         |
| Elevated                      | 28  | 45.55                  |         |
| **Borrmann type**             |     |                        | 0.039   |
| I                             | 2   | 66.48                  |         |
| II                            | 50  | 53.52                  |         |
| III                           | 65  | 43.49                  |         |
| IV                            | 4   | 26.75                  |         |
| **Histological grade**        |     |                        | 0.217   |
| High differentiation          | 0   | —                      |         |
| Median differentiation         | 46  | 53.26                  |         |
| Low differentiation            | 57  | 43.27                  |         |
| Poor differentiation           | 18  | 44.77                  |         |
| **T staging**                 |     |                        | <0.001  |
| T3                            | 97  | 53.39                  |         |
| T4a                           | 24  | 26.74                  |         |
| **LN harvested**              |     |                        | 0.479   |
| 15–29                         | 106 | 47.49                  |         |
| ≥30                           | 15  | 49.29                  |         |

| Variables                      | n   | Mean survival (months) | p value |
|-------------------------------|-----|------------------------|---------|
| **Histological grade**        |     |                        | 0.217   |
| High differentiation          | 0   | —                      |         |
| Median differentiation         | 46  | 53.26                  |         |
| Low differentiation            | 57  | 43.27                  |         |
| Poor differentiation           | 18  | 44.77                  |         |
| **T staging**                 |     |                        | <0.001  |
| T3                            | 97  | 53.39                  |         |
| T4a                           | 24  | 26.74                  |         |
| **LN harvested**              |     |                        | 0.479   |
| 15–29                         | 106 | 47.49                  |         |
| ≥30                           | 15  | 49.29                  |         |

Table 5: Univariate analysis of the overall survival in this group of gastric cancer patients.
Figure 4: Univariate analysis of the prognosis of gastric cancer patients with tumor sizes larger than 5 cm. (a) The tumor location ($p = 0.007$), (b) Borrmann type ($p = 0.039$), (c) postoperative chemotherapy ($p = 0.003$), and (d) pathological T staging ($p < 0.001$) were the prognostic factors for these gastric cancer patients.
Table 6: Multivariate analyses of overall survival in gastric cancer patients whose tumor size was larger than 5 cm (Cox’s regression model).

| Variable                                           | HR    | 95% CI      | p value |
|----------------------------------------------------|-------|-------------|---------|
| OS in gastric cancer patients whose tumor size was larger than 5 cm |       |             |         |
| Borrmann type                                      | 1.644 | 1.039–2.600 | 0.034   |
| Tumor location                                     | 1.116 | 0.858–1.451 | 0.414   |
| Pathological T staging                              | 4.761 | 2.836–9.487 | <0.001  |
| Postoperative chemotherapy                         | 0.489 | 0.281–0.851 | 0.011   |

OS, overall survival; HR, hazard ratio; CI, confidence interval.

Competing Interests

The authors declare that they have no competing interest.

Authors’ Contributions

Shi Chen, Li-Ying Ou-Yang, and Run-Cong Nie contributed equally to this work.

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