Survival outcomes of locally advanced gastric cancer cases with pathological complete response received neoadjuvant chemotherapy

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Abstract

Objective: The aim of this study is to explore the survival situation of locally advanced gastric cancer (GC) patients with pathological complete response (pCR) following neoadjuvant chemotherapy (NAC).

Methods: The clinical data of 13 patients with locally advanced GC who achieved a treated pCR with NAC following by surgical resection between January 2015 and December 2019 at Affiliated Cancer Hospital of Nanjing Medical University were analyzed retrospectively.

Results: Only 9.4% (13/138) can be classified as achieving pCR and these 13 cases of locally advanced GC patients are entered into the present study. The median follow-up period of the survivors was 38 (range: 9-68) months. As a whole, the overall survival (OS) rates at 1 and 3 years were 92% (95% confidence interval [CI] 78-100) and 84% (95% CI 65-100), and the RFS rates at 1 and 3 years were 85% (95% CI 66-100) and 76% (95% CI 53-98).

Conclusions: Although a pCR was a relatively rare event, locally advanced GC patients who achieved pCR with NAC have a good prognosis.

KEYWORDS
gastric cancer, neoadjuvant chemotherapy, pathological complete response

1 | INTRODUCTION

Gastric cancer (GC) is one of the most common malignant tumors and the second leading cause of cancer death in worldwide.1 Although surgical resection with D2 lymphadenectomy remains a mainstay of treatment for GC, the survival outcome of this treatment modality remained poor with a 5-year relative survival rate of 17.9%-54.2%.2 In recent years, neoadjuvant chemotherapy (NAC) represents a promising strategy which is associated with a high R0 resection rate and downstaging, in hopes to improve the overall survival (OS) of GC. Recent studies have shown that the survival benefit of NAC is dependent on the pathological response to chemotherapy drugs, especially in those GC patients with pathological complete response (pCR) following NAC are more inclined to have ideal recurrence-free survival (RFS) and OS.3-5 However, a pCR was a relatively rare event and only a few sporadic case reports showed a certain survival benefit of a pCR. Therefore, we conducted a deep research to explore the survival situation of advanced GC patients with pCR following NAC.

2 | MATERIALS AND METHODS

2.1 | Specimens collection

A total of 138 patients were identified from the locally advanced GC patients who received preoperative NAC at Affiliated Cancer Hospital...
of Nanjing Medical University between January 2015 and December 2019. Inclusion criteria were as follows: (a) patients with histologically confirmed adenocarcinoma of the stomatogastric cancer in a clinical stage of T3N+ or T4N0/+ as evaluated by abdominal-pelvic computed tomography; (b) patients who underwent NAC followed by gastrectomy with standardized D2 lymphadenectomy; (c) patients achieved a treated pCR after NAC following by surgical resection; (d) all available clinical information such as gender, age, primary site, pathological type, tumor staging information according to the staging system of American Joint Committee on Cancer (AJCC) eighth edition, treatment strategies, follow-up, and so on were retrieved. Patients with insufficient information or non-pCR were excluded from the study. All patients received written informed consent. The study was authorized by the Ethics Committee of Jiangsu Cancer Hospital. At last, 13 cases of locally advanced GC patients who achieved a treated pCR following surgical resection were classified as follow-up studies.

2.2 | Chemotherapy

The chemotherapy regimen adopted for NAC mainly consisted of DOS (or its derived regimen DOF or DOX), FOLFOX (or its derived regimen such as SOX or XELOX) and EEOX. (a) DOS: docetaxel 75 mg/m² intravenous injection + oxaliplatin 130 mg/m² intravenous injection + tegafur gimeracil oteracil potassium capsule 40-60 mg bid D1-D14; every 3 weeks; (b) DOF: docetaxel 75 mg/m² + oxaliplatin 130 mg/m² + fluorouracil 2400 mg/m² intravenous injection over 48 hours; every 3 weeks; (c) DOX: docetaxel 75 mg/m² + oxaliplatin 130 mg/m² + capecitabine 1000 mg/m² bid D1-D14; every 3 weeks; (d) SOX: oxaliplatin 130 mg/m² intravenous injection + tegafur gimeracil oteracil potassium capsule 40-60 mg bid D1-D14; every 3 weeks; (e) XELOX: oxaliplatin 130 mg/m² + capecitabine 1000 mg/m² bid D1-D14; every 3 weeks; and (f) EEOX: epirubicin 20 mg/m² + etoposide 75 mg/m² + oxaliplatin 100 mg/m² transcatheter arterial chemotherapy.

2.3 | Surgery

After NAC and preoperative staging, a thorough examination of the abdominal cavity was routinely performed by CT, endoscope, GI, and other imaging examinations. All patients received curative tumor resection (total or distal gastrectomy) with D2 lymphadenectomy. PCR was defined as the absence of residual cancer cell in the primary tumor or no residual tumor cell is present in the resected specimen after resection specimens were examined by the pathologist. According to the eighth AJCC Tumor, Node, Metastasis staging system, pathological tumor staging was carried out, also.

2.4 | Statistical analysis

The RFS was defined as the period from the initiation of NAC to the recurrence or death, and the OS as the period from the initiation of NAC to any cause of death. The Kaplan-Meier method was conducted to estimate the RFS and OS. The software program used for this analysis was SPSS 16.0 software (SPSS Inc., Chicago, Illinois).

3 | RESULTS

A total of 138 patients were identified from the locally advanced GC patients who received preoperative NAC at Affiliated Cancer Hospital of Nanjing Medical University between January 2015 and December 2019. Only 9.4% (13/138) can be classified as achieving pCR and these 13 cases of locally advanced GC patients are entered into the present study. The baseline characteristics of these 13 AGC patients were shown in Table 1. A male-to-female ratio was 7:6 means there was a pretty balance of patients on the trial. The median age of the study cohort was 66 years old (range: 29-74). The proportion of tumor site was 46%, 15%, and 39% in the cancer of gastric upper.

| No. | Gender | Age (years) | Tumor site | Histology WHO | Tumor differentiation | Clinical staging |
|-----|--------|-------------|------------|---------------|----------------------|-----------------|
| 1   | Male   | 66          | Upper      | Adenocarcinoma | Poorly              | T4N+M0          |
| 2   | Male   | 58          | Upper      | Adenocarcinoma | Poorly              | T4N+M0          |
| 3   | Male   | 67          | Upper      | Adenocarcinoma | Moderately-poorly   | T4N+M0          |
| 4   | Male   | 67          | Upper      | Adenocarcinoma | Moderately          | T4N+M0          |
| 5   | Female | 29          | Upper      | Adenocarcinoma | Poorly              | T4N+M0          |
| 6   | Female | 74          | Middle     | Adenocarcinoma | Moderately-poorly   | T4N+M0          |
| 7   | Male   | 68          | Lower      | Adenocarcinoma | Poorly              | T4N+M0          |
| 8   | Female | 71          | Lower      | Adenocarcinoma | Moderately-poorly   | T4N+M0          |
| 9   | Female | 68          | Lower      | Adenocarcinoma | Poorly              | T4N+M0          |
| 10  | Female | 54          | Lower      | Adenocarcinoma | Poorly              | T4N+M0          |
| 11  | Female | 62          | Lower      | Adenocarcinoma | Poorly              | T4N+M0          |
| 12  | Male   | 64          | Upper      | Adenocarcinoma | Poorly              | T4N+M0          |
| 13  | Male   | 48          | Middle     | Adenocarcinoma | Moderately-poorly   | T4N+M0          |
middle, and lower, respectively. Overall, the majority of the AGC were poorly differentiated adenocarcinoma and clinical T4N+ disease.

These 13 AGC patients received treatments as described in Table 2. Patients received a median of two cycles of NAC before surgery. Oxaliplatin-based (13/13, 100%) and fluoropyrimidine-based (11/13, 85%) of NAC regimens were adopted. After NAC, these 13 AGC patients received subsequent radical resection surgery. The majority of the surgical procedures were total and distal gastrectomy with standardized D2 lymphadenectomy. In all 13 AGC patients, no surgical complications were reported. The median dissected lymph node number of the study cohort was 17 (range: 9-26). No lymph node metastasis was found in these 13 AGC patients which could be classified as achieving pN0. After surgery, most patients (12/13, 92%) received adjuvant chemotherapy following the previous regimens.

The median follow-up period of the survivors was 38 (range: 9-68) months. Only three patients developed recurrence: to the lung.

### TABLE 2  Treatment and follow-up of the 13 cases of advanced gastric cancer

| No. | Regimen of NAC | Course of NAC | Surgical procedure | Complication | Lymph node | Course of adjuvant chemotherapy | Follow-up (months) |
|-----|---------------|--------------|-------------------|--------------|------------|-------------------------------|-------------------|
| 1   | EEOX          | 3            | Total gastrectomy | None         | (0/12)     | 1                             | 47                |
| 2   | SOX           | 2            | Total gastrectomy | None         | (0/14)     | 2                             | 11                |
| 3   | DOX           | 4            | Total gastrectomy | None         | (0/24)     | 2                             | 48                |
| 4   | SOX           | 2            | Total gastrectomy | None         | (0/22)     | 0                             | 38                |
| 5   | DOF           | 2            | Total gastrectomy | None         | (0/16)     | 4                             | 68                |
| 6   | XELOX         | 2            | Distal gastrectomy| None         | (0/11)     | 3                             | 66                |
| 7   | DOS           | 5            | Distal gastrectomy| None         | (0/26)     | 1                             | 36                |
| 8   | XELOX         | 4            | Total gastrectomy | None         | (0/23)     | 4                             | 58                |
| 9   | EEOX          | 3            | Distal gastrectomy| None         | (0/9)      | 1                             | 59                |
| 10  | DOS           | 4            | Distal gastrectomy| None         | (0/12)     | 2                             | 18                |
| 11  | SOX           | 2            | Distal gastrectomy| None         | (0/18)     | 3                             | 13                |
| 12  | SOX           | 2            | Total gastrectomy | None         | (0/19)     | 3                             | 26                |
| 13  | DOS           | 2            | Distal gastrectomy| None         | (0/17)     | 4                             | 29                |

Abbreviations: DOF, docetaxel + oxaliplatin + fluorouracil; DOS, docetaxel + oxaliplatin + tegafur, gimeracil and oteracil potassium capsule; DOX, docetaxel + oxaliplatin + capecitabine; EEOX, epirubicin + etoposide + oxaliplatin; NAC, neoadjuvant chemotherapy; SOX, oxaliplatin + tegafur, gimeracil and oteracil potassium capsule; XELOX, capecitabine + oxaliplatin.
in one patient, adrenal gland in one, and multiple abdominal metastases in one and two died of GC. As a whole, the OS rates at 1 and 3 years were 92% (95% confidence interval [CI] 78-100) and 84% (95% CI 65-100; Figure 1), and the RFS rates at 1 and 3 years were 85% (95% CI 66-100) and 76% (95% CI 53-98; Figure 2).

4 | DISCUSSION

Advanced GC without distant metastasis remains a potentially curable disease, but the survival remains unsatisfactory in this condition due to the high unresectability rate and the high recurrence rate at presentation.6 NAC has several potential benefits for advanced GC and is emerging as a common perioperative treatment. This treatment can elicit tumor downstaging and improve R0 resection rate.7 Compared with adjuvant chemotherapy, NAC has higher patient tolerability and a higher rate of chemotherapy completion.7 Compared with adjuvant chemotherapy, NAC has higher patient tolerability and a higher rate of chemotherapy completion. Although high-intensity chemotherapy induces a high overall response rate, a few advanced gastric patients can achieve a pathologically complete response.8

PCR means no residual tumor cell is present in the resected specimen, which is used as the universal and objective marker for high sensitivity to NAC. GC patients who achieved pCR with NAC have favorable tumor downstaging and a good prognosis. However, a pCR is a relatively rare event in GC. Our research shows that 9.4% of GC patients achieved pCR after NAC, which is similar to previous reports (8.4%-17.4%).9 Although there is only a minority of patients who can achieve pCR, the present study shows that the GC patients who benefited from NAC have an excellent RFS and OS, which was similar to that of the stage I/II patients.

The pathological response to chemotherapy drugs is the key factor for GC patients treated with NAC. To achieve a pCR, several investigators have tried to screen out some influence factors of response to NAC.10 The selection of NAC regimen for GC should take into account the patient’s physical condition, complications and chemotherapy drug toxicity, and other factors. At present, the chemotherapy regimen adopted for NAC mainly consisted of DOS and FOLFOX (or its derived regimen such as SOX or XELOX).11 In our study, the different chemotherapy regimens have the same result, especially platinum-based and fluoropyrimidine-based chemotherapy are more likely to achieve a pCR. So, which chemotherapy regimen is the best choice is still inconclusive and needs to be verified in large-scale clinical studies. Similarly, the pathological response was almost equivalent between the two- and four-course arms, as well as between the 5-FU plus cisplatin and paclitaxel plus cisplatin regimens. Unlike previous studies,12 our research showed that most cases with two-course of NAC had achieved a pCR, a large number of clinical studies are still needed to confirm the conclusion. Lymph node metastasis is one of the important prognostic factors. It was reported that downstaging to T0N0 showed a favorable survival outcome with a 5-year relative survival rate of 89%.13 In our study, the rate of patients with pN0 GC is 100%, which indicates these patients will have the lowest risk for recurrence and metastasis and better outcomes.

We should consider the potential limitations of this study. First, in this research, the number of samples enrolled underwent surgery in the recent 2-3 years; there were insufficient survival events to analyze the impact of pCR on OS rate. Second, the number of GC patients who achieved pCR was too small to endow a strong statistical significance. Therefore, a larger sample size should be considered in further studies. Last, the chemotherapy regimen in our study was not unified, which may be associated with different responses and resulted in a possibility of selection bias.
CONCLUSIONS

In conclusion, although a pCR was a relatively rare event, locally advanced GC patients who achieved pCR with NAC have a good prognosis. A larger sample size should be considered in further studies.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Qing Hu: Conception, design and manuscript writing. Jian Wang: Collection and assembly of data. Weiguo Xu: Data analysis. Peng Shao: Investigation. Gang Li: Design, review and editing. All authors: final approval of manuscript.

ETHICS STATEMENT

The study was approved by the Jiangsu Cancer Hospital Ethics Committee and all patients gave written informed consent.

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