Remnant lymph node metastases after neoadjuvant therapy and surgery in patients with pathologic T0 esophageal carcinoma: impact on prognosis

A systematic review and meta-analysis

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Abstract

Background: The aim of this study was to evaluate the outcomes of patients with pathologic T0 esophageal carcinoma after neoadjuvant therapy and surgery.

Methods: We searched PubMed, Embase, Cochrane Library, and Medline databases from inception up to November 12, 2016. The meta-analysis was performed to compare odds ratios (OR) for overall survival (OS), disease-free survival (DFS), local control (LC), and distant control (DC).

Results: Eight published studies of 837 patients were included in the meta-analysis. Data showed that the ypT0N1 group was associated with worse outcomes compared with the ypT0N0 group. The pooled OR and 95% confidence interval (CI) for 3-year and 5-year OS were 3.08 [2.07, 4.57] and 4.27 [2.76, 6.59], respectively. Whereas, the pooled OR and 95% CI for 3-year and 5-year DFS were 3.90 [2.08, 7.34] and 5.17 [1.93, 13.87], respectively. The pooled OR and 95% CI for LR and DR were 4.52 [1.72, 11.91] and 2.65 [1.38, 5.09], respectively.

Conclusions: Remnant lymph node metastases after neoadjuvant therapy and surgery in patients with pathologic T0 esophageal carcinoma portend poor survival, and it is an important prognostic factor.

Abbreviations: AJCC = The American Joint Committee on Cancer, CRT = chemoradiotherapy, DC = distant control, DFS = disease-free survival, LC = local control, OR = odds ratios, OS = overall survival, pCR = pathologic complete response, TNM = tumor-node-metastasis, ypT0N0= complete response in the primary esophageal carcinoma and lymph nodes, ypT0N1= complete response in the primary esophageal carcinoma with residual tumor in lymph nodes.

Keywords: esophageal carcinoma, neoadjuvant therapy, pathologic complete response, remnant lymph node metastases, surgery

1. Introduction

Surgical resection is the standard treatment for resectable esophageal carcinoma, but the long-term outcome is not satisfactory. Previous studies have revealed that neoadjuvant therapy could improve treatment efficacy and survival for locoregionally advanced esophageal carcinoma patients.[1–4] Moreover, posttherapy pathologic stage was considered the best available predictors of outcome for patients after neoadjuvant chemoradiotherapy (CRT).[5] Patients obtained a pathologic complete response (pCR) had a significantly improved long-term survival compared with pathologic partial response patients.[6] Recently, Gabriel et al[7] reported that patients with clinically node-negative esophageal carcinoma benefited from neoadjuvant CRT, however, patients with clinically node-positive did not get overall survival (OS) benefit compared with surgery alone.

As far as we know, patients with a complete response in the primary esophageal carcinoma with residual tumor in lymph nodes (ypT0N1) have not been well characterized in the literatures, and this stage has not been included in the American Joint Committee on Cancer (AJCC) esophageal staging systems 7th edition of tumor-node-metastasis (TNM) criteria. Kim et al[8] reported that patients with ypT0N1 disease had lower 5-year survival than complete response in the primary esophageal carcinoma and lymph nodes (ypT0N0) patients, and similar to pathologic TNM stage II. However, Cho et al[9] showed that residual lymph node metastases did not influence prognosis in pathologic T0 patients after neoadjuvant CRT.

Therefore, we conducted a systematic review of the current literatures to assess the survival outcomes of patients with...
pathologic T0 esophageal carcinoma after neoadjuvant therapy and surgical treatment.

2. Materials and methods

All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

2.1. Literature search

We searched PubMed, Embase, the Cochrane Library, and Medline databases from inception up to November 12, 2016 by using the following primary keywords relating to esophageal carcinoma, surgery, and neoadjuvant chemoradiotherapy. The database search was restricted to human research articles written in English.

2.2. Selection criteria

The following eligibility criteria were applied: (1) all the patients included were esophageal carcinoma; (2) survival data were reported or could be extrapolated based on published data; (3) patients were treated with neoadjuvant chemotherapy, radiotherapy, or CRT. Exclusion criteria: (1) reviews, case reports, editorials, commentaries, and letters; (2) duplicate publications; (3) absence of critical information for the calculation date.

2.3. Data extraction

Data from eligible studies were extract independently by 2 reviewers. The following data were collected: title and year of the publication, name of the first author, country, study period, study design, mean age, number of pCR and ypT0N1 patients, induction therapy, and survival outcome. The primary endpoint of this meta-analysis was the 3, 5-year OS and the secondary endpoint was the 3, 5-year disease-free survival (DFS), local recurrence (LR), and distant recurrence (DR). We extracted survival outcome data directly or calculated from the Kaplan-Meier survival curves.

2.4. Statistical analysis

The meta-analysis was carried out using Revman 5.3 software (The Nordic Cochrane Centre, Copenhagen, Denmark). We analyzed survival outcomes using odds ratio (OR) with 95% CI. We extracted data from the primary studies firstly. For studies reporting only available in the figures, we calculated ORs and its 95% CI using Engauge Digitizer Version 4.1, OR > 1 indicated a better survival for groups of ypT0N0 and the 95% CI did not overlap 1 with \( P < .05 \) was considered statistically significant difference. We assessed heterogeneity using the X² test with significance defined as \( P < .10 \), and using I² with a maximum value of 50% for low heterogeneity. The fixed-effects model was used for \( P > .10 \) or \( I^2 \leq 50\% \). If not, a random effect model was used. Funnel plot would be made to examine for publication bias if sufficient studies were identified.

2.5. Quality assessment

Study quality assessment was guided by the Newcastle-Ottawa Scale according to the following 3 items: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively.

3. Results

3.1. Study characteristics

The literature search of databases identified 768 records. After scanning titles and abstracts, 212 records that report on duplicates and unrelated studies were excluded. As is shown in Fig. 1, additional 30 studies were further excluded for reviews (n=14), and insufficient data (n=16). In the present meta-analysis that included 8 studies, a total of 837 patients that performed neoadjuvant therapy and surgery in patients with ypT0 esophageal carcinoma.

The details characteristics of the included studies are showed in Table 1. All the patients in the 8 studies were treated with nCRT except for 1 study patients were treated with nRT. The mean age of patients was 60 years and older.

Assessing the quality of nonrandomized studies with the Newcastle-Ottawa Scale is given in Table 2. The final scores varied from 5 to 7.

3.2. Overall survival

OS was the primary endpoints. One hundred thirty one patients with ypT0N1 and 706 patients with ypT0N0 included in the 8 studies provided data for OS analysis. The pooled OR and 95% CI by comparing the ypT0N1 and ypT0N0 on 3-year and 5-year OS were 3.08 (95% CI =2.07–4.57, \( P < .001 \)) and 4.27 (95% CI =2.76–6.59, \( P < .001 \)) (Fig. 2), indicating that patients with ypT0N0 have better overall survival than patients with ypT0N1.

3.3. Disease-free survival

Three studies including 183 patients reported 3-year DFS, and 4 studies including 280 patients reported 5-year DFS. The pooled analysis showed that compared with ypT0N0, ypT0N1 significantly declined 3-year DFS (OR =3.90; 95% CI =2.08–7.34, \( P < .001 \)) and 5-year DFS (OR =5.17; 95% CI =1.93–13.87; \( P < .001 \)) (Fig. 3).

3.4. Local recurrence and distant recurrence

Four studies including 576 patients reported LR, and 3 studies including 476 patients reported DR. The pooled analysis showed that compared with ypT0N0, ypT0N1 significantly risen LR (OR =4.52; 95% CI =1.72–11.91; \( P = .002 \)) and DR (OR =2.65; 95% CI =1.38–5.09; \( P = .003 \)) (Fig. 4).

3.5. Heterogeneity and publication bias

The heterogeneity of 5-year DFS (heterogeneity \( X^2 =6.96, \ P = .07; \ I^2 =57\% \)) and LR (heterogeneity \( X^2 =7.03, \ P = .07; \ I^2 =57\% \)) was found. No heterogeneity was found in other survival outcomes. There was no show any publication bias with the funnel plot in 3-year OS and 5-year OS (Supplemental Content, http://links.lww.com/MD/B776).

4. Discussion

Previous studies have proved that neoadjuvant therapy is superior to surgery alone for locoregionally advanced esophageal carcinoma patients.\(^\text{[2,4]}\) Moreover, complete response is essential to improve survival of patients with esophageal carcinoma.\(^\text{[17–19]}\)

Neoadjuvant therapy and surgery have become a common treatment for locally advanced esophageal carcinoma. However,
the current AJCC staging system does not apply to guide prognosis after nCRT. Patients who appear to residual nodal metastases after neoadjuvant therapy and surgery in patients with pathologic complete response of the primary tumor esophageal carcinoma. This small group of patients with ypT0N1 has not been well characterized. Some studies reported residual nodal metastases was an important prognostic indicator for survival, but others reported it did not impact on prognosis. Therefore, the influence of residual nodal disease on survival needs to be further studied. This is the first meta-analysis of outcomes of survival of patients with pathologic T0 esophageal carcinoma after neoadjuvant therapy and surgery.

| Author     | Year | Country | Study design | Treatment | Pathologic stage | No. of patients | Mean age (y) | Median survival (mo) |
|------------|------|---------|--------------|-----------|------------------|----------------|-------------|---------------------|
| Wang Q[10] | 2015 | China   | Cohort study | nRT       | ypT0N0           | 78             | 55          | NA                  |
|            |      |         |              |           | ypT0N1           | 22             | NA          |                     |
| Cho HJ[9]  | 2015 | Korea   | Cohort study | nCRT      | ypT0N0           | 103            | 62.7        | NA                  |
|            |      |         |              |           | ypT0N1           | 20             | 61.3        | NA                  |
| Blackham AU[11] | 2015 | USA     | Cohort study | nCRT      | ypT0N0           | 196            | 62.9        | 92.2                |
|            |      |         |              |           | ypT0N1           | 14             | 63.3        | 14.8                |
| Kim MP[8]  | 2010 | USA     | Cohort study | nCRT      | ypT0N0           | 123            | 60          | NA                  |
|            |      |         |              |           | ypT0N1           | 20             | 60          | 44                  |
| Tong DK[12] | 2010 | China   | Cohort study | nCRT      | ypT0N0           | 55             | 65          | 124.8               |
|            |      |         |              |           | ypT0N1           | 20             | 65          | 21.1                |
| Reynolds JV[13] | 2007 | Ireland | Cohort study | nCRT      | ypT0N0           | 61             | 62          | 55                  |
|            |      |         |              |           | ypT0N1           | 14             | 55          | 14                  |
| Swisher SG[14] | 2005 | USA     | Cohort study | nCRT      | ypT0N0           | 66             | 61          | 133.2               |
|            |      |         |              |           | ypT0N1           | 12             | 61          | 59.7                |
| Law S[15]  | 2003 | China   | Cohort study | nCRT      | ypT0N0           | 24             | 64.5        | NA                  |
|            |      |         |              |           | ypT0N1           | 9              | 21          | 21.1                |

NA = not applicable, nCRT = neoadjuvant chemoradiotherapy, nRT = neoadjuvant radiotherapy.
Bedenne et al.\(^{21}\) reported that the addition of surgery after chemoradiation in patients with clinical complete response was no benefit compared with the continuation of additional chemoradiation. Complete clinical response to chemoradiotherapy may not translate into pathologic complete response. This treatment strategy may lead to inadequately treating patients with persistent regional disease. It is difficult to predict residual nodal metastasis by PET or CT scan\(^{16}\) and most ypT0N1 patients were thought to ypT0N0.\(^{8}\) Previous reports showed that the incidence of ypT0N1 patients after induction chemoradiation therapy was 5% to 10%.\(^{8,20,15}\) Kim et al.\(^{8}\) reported 5-year survival of patients with ypT0N1 was similar to pathologic partial response stage II patients and he recommended complete resection regional disease in patients who can tolerate esophagectomy. Tong et al.\(^{12}\) showed that the pretherapeutic clinical TNM stage had no prognostic value in nCRT patients and lymph nodal status was an important prognostic factor. While Cho et al.\(^{9}\) reported residual node metastases did not significantly impact on survival. In the study, he found the left gastric arterial lymph node was more common for residual lymph nodal metastasis. Our data in the present study suggested that the group of ypT0N1 was associated with worse survival outcomes (OS and DFS) compared with ypT0N0 group.

It is reported locoregional recurrence was more common in ypT0N1 patients.\(^{11}\) Furthermore, the ypT0N1 group was demonstrated to have higher rate of local recurrence, regional recurrence, and distant recurrence compared with ypT0N0 and similar recurrence patterns with partial responders.\(^{8}\) In this study, the group of ypT0N1 had the higher local recurrence and distant recurrence. This indicated that complete surgical resection

| Table 2 |
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| The Newcastle-Ottawa Scale for assessing the quality of studies. |
| Studies | Selection | Comparability | Assessment of outcome | Total quality score |
| --- | --- | --- | --- | --- |
| Wang Q\(^{10}\) | 3 | 2 | 3 | 8 |
| Cho HJ\(^{9}\) | 3 | 2 | 4 | 9 |
| Blackham AU\(^{11}\) | 3 | 1 | 3 | 7 |
| Kim MP\(^{9}\) | 3 | 2 | 4 | 9 |
| Tong DK\(^{12}\) | 3 | 2 | 3 | 8 |
| Reynolds JV\(^{13}\) | 3 | 1 | 2 | 6 |
| Swisher SG\(^{14}\) | 3 | 1 | 3 | 7 |
| Law S\(^{15}\) | 3 | 2 | 3 | 6 |

| Figure 2. Forest plot of the comparison between ypT0N1 and ypT0N0 treatment for 3-year and 5-year OS. ypT0N1 = complete response in the primary esophageal carcinoma with residual tumor in lymph nodes, ypT0N0 = complete response in the primary esophageal carcinoma and lymph nodes, OS = overall survival. |
of the primary tumor site and lymph nodes are important after neoadjuvant therapy. Thus, residual nodal metastases impact on the prognosis of patients with pCR of the primary tumor after neoadjuvant CRT and surgery. These findings may aid the design of future clinical trials.

There are several limitations in our study. Most importantly, all are retrospective studies with a small cohort of patients. Second, the response to neoadjuvant CRT can differ according to different histology of the tumor, however, most of the studies included in adenocarcinoma and squamous cell carcinoma patients. The squamous cell carcinoma patients showed a better survival outcome than those with adenocarcinoma. In addition, the radiation dose and fractionation and chemotherapy agents were different.

5. Conclusions
In summary, remnant lymph node metastases after neoadjuvant therapy and surgery in patients with pathologic T0 esophageal carcinoma portend poor survival, and it is an important

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A. 3-year DFS

| Study or Subgroup | ypT0N1 | ypT0N0 | Odds Ratio | M-H. Fixed, 95% CI |
|-------------------|--------|--------|------------|--------------------|
| Blackburn AU 2015 | 12     | 14     | 77         | 196                |
| Cho HJ 2015       | 10     | 20     | 33         | 103                |
| Wang Q 2015       | 17     | 22     | 34         | 78                 |
| Total (95% CI)    | 56     | 377    | 100.0%     | 3.90 (2.08, 7.34) |
| Total events      | 29     | 144    |            |                    |
| Heterogeneity: Ch² = 2.90, df = 2 (P = 0.25); I² = 29% |
| Test for overall effect: Z = 4.22 (P < 0.0001) |

B. 5-year DFS

| Study or Subgroup | ypT0N1 | ypT0N0 | Odds Ratio | M-H. Random, 95% CI |
|-------------------|--------|--------|------------|---------------------|
| Blackburn AU 2015 | 13     | 20     | 94         | 196                |
| Cho HJ 2015       | 12     | 20     | 49         | 103                |
| Kim MP 2010       | 16     | 20     | 38         | 123                |
| Wang Q 2015       | 19     | 22     | 39         | 78                 |
| Total (95% CI)    | 76     | 220    | 100.0%     | 5.17 (1.93, 13.87) |
| Total events      | 60     | 220    |            |                     |
| Heterogeneity: Tau² = 0.56; Ch² = 6.96, df = 3 (P = 0.07); I² = 57% |
| Test for overall effect: Z = 3.26 (P = 0.001) |

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Figure 3. Forest plot of the comparison between ypT0N1 and ypT0N0 treatment for 3-year and 5-year DFS. ypT0N1 = complete response in the primary esophageal carcinoma with residual tumor in lymph nodes, ypT0N0 = complete response in the primary esophageal carcinoma and lymph nodes, DFS = disease-free survival.

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Figure 4. Forest plot of the comparison between ypT0N1 and ypT0N0 treatment for LR and DR. ypT0N1 = complete response in the primary esophageal carcinoma with residual tumor in lymph nodes, ypT0N0 = complete response in the primary esophageal carcinoma and lymph nodes, DFS = disease-free survival.
prognostic factor. Future modifications should consider patients after neoadjuvant therapy and ypT0N1 should be included in the modified staging system of esophageal cancer.

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