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***Retrospective Study***

**Aggressive surgical resection does not improve survival in operable oesophageal squamous cell carcinoma with N2-3 status**

ZhengYZ *et al.* Optimal treatment for oesophageal cancer

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**Abstract**

**AIM:** To investigate the influence of nodal status on response and attempted to clarify the optimal treatment for operable oesophageal squamous cell carcinoma squamous cell carcinoma (OSCC).

**METHODS:** We retrospectively analyzed 1490 OSCC patients who underwent transthoracic oesophagectomy and lymphadenectomy between December 1996 and December 2009 at the Sun Yat-sen University Cancer Center. The surgical approach and the number of resected lymph nodes (LNs) were considered in the assessment of surgery. Patients were classified according to their nodal statuses (N0 *vs* N1 *vs* N2-3). Overall survival was defined as the time from the date of death or final follow-up. Survival analysis was performed using the Kaplan-Meier method and differences between curves were assessed by the log-rank test. Univariate and multivariate Cox's regression were used to identify factors associated with prognosis. Statistical significance was assumed at a *P* < 0.05.

**RESULTS:** With a median time from surgery to the last censoring date for the entire cohort of 72.2 mo, a total of 631 patients were still alive at the last follow-up and the median survival time was 35.5 mo. The surgical approach (left transthoracic *vs* Ivor-Lewis/tri-incisional) was verified as independent prognostic significance in patients with N0 or N1 status but not in those with N2-3 status. Similar results were also observed with the number of resected LNs (≤ 14 *vs* ≥ 15).Compared with surgery alone, combined therapy was able to achieve better outcomes in patients with N1 and N2-3 status but not in those with N0 status. For those with N2-3 status, both the surgical approaches and resected LNs number did not reach significance by univariate analysis, with unadjusted HRs of 0.826 (95%CI: 0.644-1.058) and 0.849 (95%CI: 0.668-1.078), respectively and aggressiveness of surgery did not influence the outcome and the longest survival was observed in those patients who received the combined therapy.

**CONCLUSION**: Our results demonstrate the positive role of combined therapy in OSCC with LNM and further suggest that aggressive surgical resection does not improve survival in patients with N2-3 status.

**Key words:** Oesophageal neoplasm; Lymph nodes; Surgery; Prognosis

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**Core tip:** Oesophageal cancer is one of the most fatal malignant cancers worldwide, and survival is still unsatisfactory for locally advanced subjects. Until now, the optimal multimodality therapy has not yet been established. The assessment of nodal status might facilitate the selection of the most effective treatment for operable oesophageal squamous cell carcinoma (OSCC). We retrospectively analyzed 1490 OSCC patients classified according to their nodal statuses (N0 *vs* N1 *vs* N2-3). Our results demonstrate the positive role of combined therapy in OSCC with LNM and further suggest that aggressive surgical resection does not improve survival in patients with N2-3 status.

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**INTRODUCTION**

Oesophageal cancer is a frequent cause of death worldwide, and the traditional management has always been surgical resection[1-3]. In the past decades, great improvements in preoperative examination and surgical technology have led to significantly enhanced long-term survival[1-13]. However, survival is still unsatisfactory for locally advanced oesophageal cancer, which has prompted an evaluation of neoadjuvant (preoperative) and adjuvant (postoperative) combined-modality therapy[14-25]. Until now, the optimal multimodality therapy has not yet been established.

Lymph node metastasis (LNM) is one of the worst prognostic factors for localised oesophageal cancer. Furthermore, LNM decreases the curative effects of surgery[1, 3-5, 9-11] and enhances the necessity of multimodality treatment[14-20, 22]. Therefore, we speculated that the assessment of nodal status might facilitate the selection of the most effective treatment.

In this study, we recruited oesophageal squamous cell carcinoma (OSCC) patients who had undergone surgery at a Chinese institution over a 13-year period. The aim of this study was to investigate the influence of nodal status on therapeutic response and attempt to clarify the optimal treatment for operable OSCC.

**MATERIALS AND METHODS**

***Patient selection***

This study was approved by the Medical Ethics Committee of Sun Yat-sen University Cancer Center. Informed written consent was obtained from all participants. Patients diagnosed with OSCC who underwent transthoracic oesophagectomy and lymphadenectomy, at the thoracic surgery department of Sun Yat-sen University Cancer Center from December 1996 and December 2009 were screened for study recruitment. Our institutional electronic medical record system was initiated in December 1996; therefore, this was considered the date after which highly reliable data could be obtained.

All patients with pathologically confirmed OSCC who fit the following inclusion criteria were included for analysis: (1) pathologic T status as T1, T2, T3, or T4a; (2) pathologic stage of I, II, or III; (3) microscopically complete resection (R0); and (4) patients who underwent surgery or surgery followed by cytotoxic chemotherapy/radiotherapy. Patients with T1N0 were excluded because most of them were treated with endoscopic resection. We did not include patients who received neoadjuvant treatment due to the limited power in predicting the number of LNMs prior to surgery that was observed during the study period.

Preoperative examination included physical examination, blood test, chest X-ray, barium oesophagography, endoscopy, and computed tomography scans of the chest, abdomen and cervical region. If tracheal invasion was suspected, a bronchoscope test was recommended. Endoscopic ultrasonography was widely applied beginning in 2003. PET/CT was initiated in 2005 but was used for few cases due to its high cost. Pathologic staging was performed based on the 7th American Joint Committee on Cancer (AJCC) staging system[26].

***Surgical procedure***

Surgical approaches applied in this study included left transthoracic, Ivor-Lewis, and tri-incisional procedure, which were mainly selected based on tumour location and preoperative inspection results. For patients with middle/lower thoracic OSCC with no evidence of superior mediastinum metastasis, we generally performed left transthoracic oesophagectomy. For patients with middle/lower thoracic OSCC with evidence of superior mediastinum metastasis, we performed Ivor-Lewis/tri-incisional oesophagectomy. In patients with upper thoracic OSCC, we only carried out tri-incisional procedure.

Lymphadenectomy extent was influenced by the surgical approach. For left transthoracic oesophagectomy, we could not achieve upper mediastinal lymphadenectomy in most cases and instead performed standard two-field lymphadenectomy, including subcarinal, lower mediastinal and upper abdominal dissections. However, for Ivor-Lewis or tri-incisional oesophagectomy, an additional upper mediastinal dissection was completed in most cases by so-called extended two-field lymphadenectomy. Cervical lymphadenectomy was not routinely carried out.

***Adjuvant treatment***

Because there were no standard guidelines for the adjuvant treatment of OSCC, treatment options were selected based on tumour stage, the doctor's opinion, and the patient's desires. In our hospital, adjuvant treatment was started at 4-6 wk after operation, mostly in patients with LNM. Chemotherapy was typically applied as platinum-based two-drug regimen for 4-6 cycles. Radiotherapy was mainly delivered to the position of the anastomosis, mediastinum, pericardium, and left epiplioc lymphatic vessels, at a total dose of 50-60 Gy.

***Follow-up***

After completion of primary treatment, the patients were asked to participate in outpatient follow up every three months for the first two years, every six months for years 3-5, and every 12 mo thereafter. Regular assessment included physical examination, blood test, endoscopy, chest X-ray, and ultrasound test. Computed tomography scans of the chest, abdomen and cervical region were performed at least once a year. For those could not afford regular follow up visits, a telephone follow up was performed. Survival status was reclassified using the best available methods in March 2014. The median time from surgery to the last censoring date for the entire cohort was 72.2 mo.

***Statistical analysis***

Statistical analysis was performed using SPSS 19.0 software package (SPSS, Inc., Chicago, IL). We defined death as the event and overall survival (OS) as the time from the date of surgery to the date of death or final follow-up. Survival analysis was performed using the Kaplan-Meier method and differences between curves were assessed by the log-rank test. Univariate and multivariate Cox's regression were used to identify factors associated with prognosis. Statistical significance was assumed at a *P* < 0.05. The statistical methods of this study were reviewed by Yin Guo from Sun Yat-sen University Cancer Center.

**RESULTS**

***Patient characteristics***

A total of 1490 patients were enrolled as the target population. There were 1150 male and 340 female patients with a median age of 58 years (range, 30-88). In this study, 4.1% (61/1490) of the patients were pathologically diagnosed as stage I, 48.6% (724/1490) as stage II, and 47.3% (705/1490) as stage III. The most applied approach was left transthoracic oesophagectomy (917/1490, 61.5%) and the median number of resected lymph nodes (LNs) was 14 (range, 1-91). Combined therapy was used for 319 patients, including 194 who received adjuvant chemotherapy, 91 who received adjuvant chemoradiotherapy, and 34 who received adjuvant radiotherapy. The patient characteristics are listed in Table 1.

***Influence of nodal status on therapeutic response***

A total of 631 patients were still alive at the last follow up, and the median survival time was 35.5 mo. To investigate the influence of nodal status on therapeutic response, we divided the entire cohort based on their nodal status (N0 *vs* N1 *vs* N2-3).

The influence of nodal status on surgery is shown in Table 2. The patients with a status of N0 or N1 who underwent the Ivor-Lewis/tri-incisional procedure presented with significantly better survival compared with those who underwent left transthoracic oesophagectomy, with adjusted HRs of 0.632 (95%CI: 0.499-0.801) and 0.661 (95%CI: 0.516-0.847), respectively (Figure 1). Similar results were also observed for the resected LNs number (Figure 2). For the patients with N2-3 status, both the surgical approaches and resected LNs number did not reach significance by univariate analysis, with unadjusted HRs of 0.826 (95%CI: 0.644-1.058) and 0.849 (95%CI: 0.668-1.078), respectively. Our results suggested the poor cure effect of surgery in the patients with N2-3 status.

The influence of nodal status on combined therapy is shown in Table 3. Compared with surgery alone, the combined therapy did not generate better outcomes in the patients with N0 status (unadjusted HR = 0.878, 95%CI: 0.617-1.249). For those with N1 or N2-3 status, we observed survival benefits in those who received the combined therapy, with adjusted HRs of 0.712 (95%CI: 0.537-0.944) and 0.672 (95%CI: 0.521-0.867), respectively (Figure 3). Our data supported the use of combined therapy to treat OSCC with LNM.

***Searching for optimal treatment for patients with N0, N1, and N2-3 statuses***

To search for an optimal treatment, we defined extensive surgery as Ivor-Lewis/tri-incisional procedure with resection of ≥ 15 LNs, and limited surgery as the other procedures assessed. Therefore, patients were classified into four groups based on their therapeutic regimens, including Group A (limited surgery alone), Group B (extensive surgery alone), Group C (limited surgery followed by adjuvant treatment), and group D (extensive surgery followed by adjuvant treatment). Based on our results, the prognosis of patients with N0 status who underwent surgery alone was comparable to that of the combined therapy, and the longest survival times were observed in Group B and Group D (Figure 4A). The optimal treatment for the patients with N1 status was extensive surgery followed by adjuvant treatment (Group D) (Figure 4B). The outcomes of limited surgery for the patients with N2-3 status were similar to those of extensive surgery, and the best cure effects were observed in Group C and Group D (Figure 4C).

**DISCUSSION**

In this study, we investigated the influence of nodal status on therapeutic responses to different treatments for operable OSCC. Based on results, adopting combined therapy improved the outcomes of the nodal-positive patients except for those with N0 status. Furthermore, aggressive did not improve survival in patients with N2-3 status.

Surgical resection has long been applied as a mainstay treatment for oesophageal cancer[2, 6, 27]. Previous studies have proven that performing aggressive surgical resection is very important to achieving long-term survival[1, 4, 5, 10, 11]. However, recent studies have indicated that the curative effects of surgical resection might be invalid for patients with multiple LNMs. For instance, Tabire *et al*[6] have concluded that the 5-year survival rate for patients with ≥ 5 LNMs is merely 9.1% even after McKeown oesophagectomy and three-field lymphadenectomy, which is in accordance with Mariette *et al*[13] Likewise, Nishimaki *et al*[9] have investigated the outcomes of extended radical oesophagectomy in 190 patients and have observed that no patients with ≥ 5 LNMs survive beyond five years.Thus, in this study, we first grouped the nodal status according to LNM number (0 *vs* 1-2 *vs* 3-4 *vs* 5-6 *vs* ≥ 7). We found that the positive effect of aggressive surgery on survival is insignificant in patients with 3-4, 5-6, and ≥ 7 LNMs (data not shown), which led us to adopt our current grouping program (N0 *vs* N1 *vs* N2-3). Our finding indicated that prognosis could not be improved in patients with N2-3 status solely by performing more aggressive surgery.

In recent years, there has been increasing research studies performed in search of an effective multidisciplinary treatment for oesophageal cancer[14, 15, 17-22, 24, 25, 28-30]. In this study, we observed that combined therapy generated better outcomes only in nodal-positive patients compared with surgery alone, which is quite similar with previous studies[14-17]. For example, Ando *et al*[14] have enrolled 242 localised OSCC and have that found adjuvant chemotherapy prevents recurrence in patients with LNM, which was further supported by additional studies[15, 17]. Further, Lyu *et al*[16] have supported the positive role of adjuvant chemotherapy in enhancing long-term survival in OSCC with LNM.

Recent studies have also reported that neoadjuvant chemoradiotherapy associated with better outcomes than surgery alone for oesophageal cancer, especially in patients with LNM[18-20, 22, 25, 28, 30]. Additionally, in the final analysis of the randomised controlled phase III trial FFCD 9901, Mariette et al. have negated the value of neoadjuvant chemoradiotherapy for stage I or II oesophageal cancer[21]. Notably, most of these patients were clinically staged as N0 status (74.2%). Recently, Okumura et al. have proved that neoadjuvant chemoradiotherapy improves the outcomes of patients with ≥ 4 LNMs similar to those with 1-3 LNMs treated with surgery alone[23]. Thus, we also support the positive role of neoadjuvant treatment for oesophageal cancer with LNM. However, because we did not include patients who underwent neoadjuvant treatment, our results are unpersuasive in this regard.

Based on our results, we appeal to carry out intraoperative frozen sectioning of suspicious LNs and oppose the performing of excessively aggressive surgery for patients with ≥ 3 LNM (at least N2 status), because conservative surgical procedure would decrease peroperative morbidity[12]. In addition, the pathological stage of OSCC with ≥ 3 LNM is at least IIIA according to the 7th AJCC staging system[26], supporting the use of multimodality treatment suggested by our study and previous investigations[14-17]. Although a more aggressive lymphadenectomy might facilitate the acquisition of more accurate staging information in theory[31-34], it would not alter the treatment choice. Furthermore, long-term survival did not differ between the limited dissection and aggressive lymphadenectomy groups in this study.

These finding should be considered in the context of certain weaknesses in our study design. First, the study is retrospective in nature. Second, heterogeneities, including those associated with the basic characteristics of patients or the determination of treatment, were unavoidable due to the long study period, although we conducted subgroup analysis and multivariate analysis to minimise these confounders. However, we believe it is this unselective and non-matching population that resulted in the more generalised significance of this study. Third, because patients who received neoadjuvant treatment were not investigated, further studies are critical to validate our results.

Our results indicate the positive role of combined therapy in OSCC with LNM and further suggest that aggressive surgical resection does not improve survival in patients with N2-3 status.

**COMMENTS**

***Background***

Oesophageal cancer is a frequent cause of death worldwide, and the traditional management has always been surgical resection. In the past decades, great improvements inpreoperative examination and surgical technology have led to significantly enhanced long-term survival. However, survival is still unsatisfactory for locally advanced oesophageal cancer, which has prompted an evaluation of neoadjuvant (preoperative) and adjuvant (postoperative) combined-modality therapy. Until now, the optimal combined-modality therapy. Until now, the optimal multimodality therapy has not yet been established.

***Research frontiers***

Lymph node metastasis (LNM) is one of the worst prognostic factors for localized oesophageal cancer. Furthermore, LNM decreases the curative effects of surgery and enhances the necessity of multimodality treatment. Therefore, we speculated that the assessment of nodal status might facilitate the selection of the most effective treatment.

***Innovations and breakthroughs***

With a median follow-up time of 72.2 mo, a total of 1490 patients were analyzed for survival and the median survival time was 35.5 mo. The surgical approach (left transthoracic *vs* Ivor-Lewis/tri-incisional) was verified as independent prognostic significance in patients with N0 or N1 status but not in those with N2-3 status. Similar results were also observed with the number of resected LNs (≤ 14 *vs* ≥ 15). Compared with surgery alone, combined therapy was able to achieve better outcomes in patients with N1 and N2-3 status but not in those with N0 status. For those with N2-3 status, both the surgical approaches and resected LNs number did not reach significance by univariate analysis, with unadjusted HRs of 0.826 (95%CI: 0.644-1.058) and 0.849 (95%CI: 0.668-1.078), respectively and aggressiveness of surgery did not influence the outcome and the longest survival was observed in those patients who received the combined therapy.

***Applications***

Our results demonstrate the positive role of combined therapy in OSCC with LNM and aggressive surgical resection does not improve survival in patients with N2-3 status.

***Terminology***

Group A, patients who received left transthoracic surgery alone; Group B, patients who received Ivor-Lewis or tri-incisional surgery alone; Group C, patients who received left transthoracic surgery followed by adjuvant treatment; Group D, patients who received Ivor-Lewis or tri-incisional surgery followed by adjuvant treatment.

***Peer-review***

This retrospective study with a great cohort of patients with esophageal squamous cell carcinoma (*n* = 1490) contributes to the existing literature about surgical therapy of esophageal cancer. It adds relevant data and concludes that aggressive surgery is not justified at an advanced tumor stage. The limitations of this study are clear and declared by the authors. The aspect of a neoadjuvant therapy is not included but discussed and answered in other studies. Minor language and grammar revision is necessary. More figures could help to summarize the most important aspects.

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**Figure 1 Overall survival curves stratified by surgical approaches for oesophageal squamous cell carcinoma patients with N0 status (A), N1 status (B), and N2-3 status (C) (Log-rank test).**

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**Figure 2 Overall survival curves stratified by resected lymph nodes for oesophageal squamous cell carcinoma patients with N0 status (A), N1 status (B), and N2-3 status (C) (Log-rank test).**

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**Figure 3 Overall survival curves stratified by treatment for oesophageal squamous cell carcinoma patients with N0 status (A), N1 status (B), and N2-3 status (C) (Log-rank test).**

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**Figure 4 Overall survival curves stratified by therapeutic regimens for oesophageal squamous cell carcinoma patients with N0 status (A), N1 status (B), and N2-3 status (C) (Log-rank test).** Abbreviation: Group A, limited surgery alone; Group B, extensive surgery alone; Group C, limited surgery followed by adjuvant treatment; Group D, extensive surgery followed by adjuvant treatment.

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**Table 1 Patients characteristics*****n* (%)**

|  |  |
| --- | --- |
| Variable | Case |
| Total | 1490 |
| Sex |  |
| Male | 1150 (77.2) |
| Female | 340 (22.8) |
| Age (yr) |  |
| ≤ 58 | 796 (53.4) |
| > 58 | 694 (46.6) |
| Tumor location |  |
| Upper thoracic | 181 (12.1) |
| Middle thoracic | 831 (55.8) |
| Lower thoracic | 478 (32.1) |
| Pathological T status |  |
| T1 | 6 (0.4) |
| T2 | 373 (25.0) |
| T3 | 1039 (69.7) |
| T4a | 72 (4.8) |
| Pathological N |  |
| N0 | 727 (48.8) |
| N1 | 419 (28.1) |
| N2 | 267 (17.9) |
| N3 | 77 (5.2) |
| Tumor cell differentiation |  |
| Well | 349 (23.4) |
| Moderate | 727 (48.8) |
| Poor | 414 (27.8) |
| Surgical approach |  |
| Left thoracotomy | 917 (61.5) |
| Ivor-Lewis/Tri-incisional | 573 (38.5) |
| Resected lymph nodes number |  |
| ≤ 14 | 764 (51.3) |
| ≥ 15 | 726 (48.7) |
| Received treatment |  |
| Surgery alone | 1171 (78.6) |
| Combined treatment | 319 (21.4) |

**Table 2 Influence of surgical parameters on survival for patients with N0, N1, and N2-3 status**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Surgical approach** | |  | **Resected lymph nodes** | |  |
| **Factors** | **Left transthoracic** | **Ivor-Lewis/Tri-incisional** |  | **≤ 14** | **≥ 15** |  |
| In patients with N0 status (*n* = 727) | | | | | | |
| No. at risk | 445 | 282 |  | 391 | 336 |  |
| No. of events | 204 | 106 |  | 215 | 95 |  |
| aHR (95%CI) | 1 | 0.632 (0.499-0.801) |  | 1 | 0.478 (0.375-0.609) |  |
| *P*1 |  | < 0.001 |  |  | < 0.001 |  |
| In patients with N1 status (*n* = 419) | | | | | | |
| No. at risk | 254 | 165 |  | 219 | 200 |  |
| No. of events | 183 | 97 |  | 174 | 106 |  |
| aHR (95%CI) | 1 | 0.661 (0.516-0.847) |  | 1 | 0.464 (0.364-0.592) |  |
| *P*1 |  | 0.001 |  |  | < 0.001 |  |
| In patients with N2-3 status (*n* = 344) | | | | | | |
| No. at risk | 218 | 126 |  | 154 | 190 |  |
| No. of events | 170 | 99 |  | 127 | 142 |  |
| uHR (95%CI) | 1 | 0.826 (0.644-1.058) |  | 1 | 0.849 (0.668-1.078) |  |
| *P*2 |  | 0.130 |  |  | 0.179 |  |

2Multivariate analysis adjusted for sex (male/female), age (≤ 58/> 58), tumor location (upper/mid/lower), pathological T status (T1/T2/T3/T4a), and tumor cell differentiation (well/moderate/poor); 2Univariate analysis. aHR:Adjusted hazard ratio;uHR: Unadjusted hazard ratio.

**Table 3 Influence of combined therapy on survival for patients with N0, N1, and N2-3 status**

|  |  |  |  |
| --- | --- | --- | --- |
| **Factors** | **Surgery alone** | **Combined therapy** |  |
| In patients with N0 status (*n* = 727) | | | |
| No. at risk | 644 | 83 |  |
| No. of events | 275 | 35 |  |
| μHR (95%CI) | 1 | 0.878 (0.617-1.249) |  |
| *P*1 |  | 0.469 |  |
| In patients with N1 status (*n* = 419) | | | |
| No. at risk | 313 | 106 |  |
| No. of events | 217 | 63 |  |
| aHR (95%CI) | 1 | 0.712 (0.537-0.944) |  |
| *P*2 |  | 0.018 |  |
| In patients with N2-3 status (*n* = 344) | | | |
| No. at risk | 214 | 130 |  |
| No. of events | 169 | 100 |  |
| aHR (95%CI) | 1 | 0.672 (0.521-0.867) |  |
| *P*3 |  | 0.002 |  |

1Univariate analysis; 2Multivariate analysis adjusted for sex (male/female), age (≤ 58/> 58), tumor location (upper/mid/lower), pathological T status (T1/T2/T3/T4a), and tumor cell differentiation (well/moderate/poor); 3Multivariate analysis adjusted for sex (male/female), age (≤ 58/> 58), tumor location (upper/mid/lower), pathological T status (T1/T2/T3/T4a), nodal status (N2/N3), and tumor cell differentiation (well/moderate/poor). aHR,Adjusted hazard ratio;uHR: Unadjusted hazard ratio.