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Esophageal adenocarcinoma stage III: Survival based on pathological response to neoadjuvant treatment

Katrin Schwameis [a], Joerg Zehetner [a], Jeffrey A. Hagen [b], Daniel S. Oh [b], Stephanie G. Worrell [b], Kais Rona [a], Nathan Cheng [a], Jamil Samaan [a], Kyle M. Green [a], John C. Lipham [a, *]

[a] Division of General Surgery, Department of Surgery, Keck School of Medicine, University of Southern California, 1510 San Pablo Street, HCC I, 5th Floor, Los Angeles, CA 90033, United States
[b] Division of Thoracic Surgery, Department of Surgery, Keck School of Medicine, University of Southern California, 1510 San Pablo Street, HCC I, 5th Floor, Los Angeles, CA 90033, United States

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ABSTRACT

Background: Neoadjuvant chemoradiotherapy is the standard treatment for locally advanced esophageal adenocarcinomas (EAC). Pathological response is thought to be a major prognostic factor. Aims of this study were to determine the frequency of complete response and to compare the survival of complete and incomplete responders in stage III EAC.
Methods: A retrospective review was performed of all stage III patients that underwent neoadjuvant therapy followed by esophagectomy between 1999 and 2015. Patients were classified into complete (pCR) versus incomplete responders (pIR).
Results: 110 patients were included. Neoadjuvant chemotherapy was applied in 25 (23%) and chemoradiotherapy in 85 (77%) patients. Pathologic response was complete in 25% (n = 27) and was more common after chemoradiotherapy. Mean F/U interval was 36 months (0.3–173). There was a significant difference in the overall survival between complete and incomplete responders ($p = 0.036$). Median survival in the pIR group was 24.4 months and the median survival was not reached during the observation time in pCR. The 3-year-survival-rate was 70% in pCR and 40% in pIR ($p = 0.01$). Positive lymph nodes (ypN+) were present in 56 patients (51%). The 3-year-survival-rate was 59% in pIR with ypN0 and 29% in pIR with ypN+ ($p = 0.005$).
Conclusions: Complete response to neoadjuvant therapy has a significantly better overall and 3-year-survival after esophagectomy than incomplete response. In incomplete responders, residual lymph node disease was associated with a significantly worse survival. These findings suggest that the degree of pathologic response and lymph node status are major prognostic factors for survival in EAC patients with stage III disease.

1. Introduction

Over the last few decades, the rate of esophageal adenocarcinoma (EAC) has steadily increased in the western world. At the time of diagnosis at least 50% of patients present with locally advanced or metastasized disease [1]. In these patients, even if treated with a multimodal approach, outcome is poor with a 5-year-survival rate of approximately 17–19% [2,3]. The gold standard in the therapy of locally advanced EAC is neoadjuvant chemo(radio)therapy followed by esophagectomy.

The degree of pathologic response to neoadjuvant treatment is thought to be a major prognostic factor for survival [4]. Response to therapy may reflect tumor sensitivity and may allow conclusions about the tumor's biology [5]. The frequency of complete response has been reported to be about 10%–40% [1,6]. Complete (pCR) and partial responders (pPR) are thought to have a significant survival benefit over non-responders (pNR) [5,7–9]. Many of these findings, however, are based on studies that included a heterogenic patient population with mixed histology of EAC and squamous cell carcinoma (SCC), different stages of disease and various treatment

* Corresponding author.
E-mail address: John.Lipham@med.usc.edu (J.C. Lipham).

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approaches [10]. Furthermore, several subsequent trials have failed to reproduce the survival benefit of responders seen in these previous studies [5,10–12]

To our knowledge, this is the first study comparing the survival outcomes of complete versus incomplete responders following neoadjuvant treatment in stage III EAC. The aims of the study were to determine the frequency of complete response and to compare the survival of complete and incomplete responders to neoadjuvant chemo(radio)therapy in patients with stage III EAC.

2. Materials and methods

A retrospective chart review was performed of all patients that had undergone neoadjuvant chemo(radio)therapy followed by esophagectomy for stage III esophageal adenocarcinoma (EAC) between 01/1999 and 08/2015 at our institution. Patients with uncertain clinical stage or degree of pathological response and patients that were lost to follow up were excluded from the study.

Pathologic response was classified as either complete (no residual tumor; pCR) or incomplete (residual tumor; pIR) based on the pathology of the surgical specimen.

A detailed chart review was performed to obtain preoperative clinical and radiological data, histological results as well as outcome and survival parameters.

This study was approved by the Institutional Review Board of the University of Southern California.

2.1. Preoperative evaluation and neoadjuvant therapy

Preoperative diagnostics included upper GI endoscopy with biopsies, endoscopic ultrasound (EUS), computed tomography and Fluorodeoxyglucose (FDG) positron emission tomography (PET) scans of the chest and abdomen. Clinical tumor staging was based on the latest edition of the TNM staging system of the American Joint Committee on Cancer (AJCC) and then Union of International Cancer Control (UICC) for esophageal adenocarcinoma. All preoperative imaging studies were re-reviewed for the present trial and restaged if appropriate using the 7th edition of the TNM system of AJCC [13]

Neoadjuvant treatment consisted of either chemo- or chemoradiotherapy and was conducted following guidelines of the National Comprehensive Cancer Network (NCCN). Type and dosage of chemotherapy and radiation were at the discretion of the oncologists. The most commonly used chemotherapy regimens were combinations of platinum/taxanes or 5-FU/platinum. 45 Gy of radiation was administered in patients receiving chemoradiotherapy.

2.2. Surgery

After completion of neoadjuvant therapy patients underwent esophagectomy. All operations were performed with curative intent. The surgical approach was either minimally invasive, hybrid or open. In the majority of cases a transthoracic En-bloc esophagectomy (EBE) with systematic two-field lymphadenectomy and reconstruction by gastric pull-up was performed. If the stomach was unsuitable a colon interposition was performed. Detailed descriptions of the surgical technique have been published previously [14,15]. A smaller percentage of patients underwent resection with intrathoracic anastomosis (Ivor Lewis procedure) or transhiatal esophagectomy with anastomosis in the neck.

2.3. Pathological examination and classification of pathological response

All esophagectomy specimens were examined by specialized GI pathologists at the Department of Pathology at the University of Southern California (USC).

Tumor type and differentiation, invasion depth, vascular and lymph vessel invasion, lymph node status and margins were assessed.

A pathologic complete response (pCR) was defined as a specimen free of vital tumor cells. All other cases were considered incomplete response (pIR). Patients with complete response of the primary tumor but viable tumor cells in lymph nodes were considered incomplete responders.

2.4. Statistical analysis

Statistical analysis was performed using SPSS® statistics 20.0 (IBM, Armonk, NY). Data were described using median (interquartile range) or mean (range). Statistical analysis appropriate for non-parametric data was used. Categorical variables were assessed using the Fisher exact test and continuous data using the Wilcoxon Rank test as appropriate. Survival was calculated using the Kaplan-Meier method and compared using the log-rank test. Statistical significance was defined as a p-value < 0.05. P-values were derived from two-tailed tests.

3. Results

There were 110 patients with stage III esophageal adenocarcinoma that met inclusion criteria. Ninety-nine patients were males and 11 patients were females. The mean age was 64 years (range, 27–85) at time of surgery. Neoadjuvant therapy consisted of chemotherapy only in 25 patients (23%) and chemoradiotherapy in 85 patients (77%).

The surgical approach was open, minimally invasive and hybrid in 85 (77%), 9 (8%) and 16 (15%) cases, respectively. A transthoracic En-bloc esophagectomy was performed in 84% (n = 92) while 3% (n = 3) underwent an Ivor-Lewis and 14% (n = 15) a transhiatal esophagectomy. R0 resection was achieved in 97% (n = 107) of cases. The majority of patients were reconstructed by gastric pull up. In 4 patients (4%) a colon interposition was performed.

The tumor was located at the esophagogastric junction in 23 cases (21%) and in the distal esophagus in 87 cases (79%). Well, moderate and poor differentiation was seen in 0%, 40% and 60%, respectively.

Positive lymph nodes (ypN+) were present in 56 patients (51%). The median number of lymph nodes examined was 34 (IQR, 24–44) in ypN + patients and 27 (IQR, 23–35) in the ypN- patients.

The median number of positive lymph nodes in ypN + patients was 4 (IQR, 2–9). 70 patients had lymphovascular invasion (LVI) with 22 (33%) of these patients also having positive lymph node involvement.

Complete pathologic response was seen in 25% of patients (n = 27) with 27% achieving pCR after chemoradiotherapy compared to 16% after chemotherapy alone ($p = 0.303$). The rate of complete pathologic response was 25% in tumors of the distal esophagus and 22% in EGJ tumors ($p = 1.00$). In two pIR patients, the residual disease was present only in the lymph nodes. Table 1 shows demographic and clinical data.

Comparing pIR patients with and without lymph node metastases, no significant differences were detected for age ($p = 0.387$), gender ($p = 1$), type of surgery ($p = 0.532$), type of neoadjuvant treatment ($p = 1$), tumor location ($p = 1$) and histological grading ($p = 0.319$). A significant higher percentage of pIR yN + patients showed lymph vessel invasion (LVI) compared to pIR ypN0 patients ($p < 0.001$).

Adjuvant chemotherapy was given in 17 pIR patients. Mean F/U interval was 36 months (0.3–173). There was a significant