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Original Article

The impact of pathological complete response after neoadjuvant chemoradiotherapy in locally advanced squamous cell carcinoma of esophagus

Jing-Wei Lin [a], Chung-Ping Hsu [b], Hui-Ling Yeh [a,*], Cheng-Yen Chuang [b], Chih-Hung Lin [b]

[a] *Department of Radiation Oncology, Taichung Veterans General Hospital, Taichung, Taiwan, ROC*
[b] *Division of Thoracic Surgery, Taichung Veterans General Hospital, Taichung, Taiwan, ROC*

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Abstract

Background: The impact of pathological complete response after neoadjuvant chemoradiotherapy on survival of patients with squamous cell carcinoma of esophagus is still controversial. We retrospectively investigated the survival outcome in this group of patients.
Methods: Ninety-eight patients with locally advanced squamous cell carcinoma of esophagus, who received neoadjuvant chemoradiotherapy were included in this retrospective analysis. Treatment protocols were radiotherapy with standard dose 50.4 Gy/28 fr, and chemotherapy with cisplatin 20 mg/m^2 and 5-FU 800 mg/m^2 for 4 days given on week 1 and 5. After neoadjuvant chemoradiotherapy is completed, patients who were eligible for surgery received surgery within 4−6 weeks. Patients who were not suitable for surgery were shifted to definite chemoradiotherapy. The primary end points were overall survival and progression-free survival.
Results: Sixty-eight patients out of the ninety-eight patients received surgery after neoadjuvant chemoradiotherapy. There were 32 patients who achieved pathological complete response with a pCR rate of 47%. Thirty patients were shifted to definite concurrent chemoradiotherapy. The 2-year overall survival rate was 81.3% in the patients whose tumors showed a pCR and 58.3% in the patients with tumors that had a pathological partial response ($p = 0.025$). The 2-year overall survival in patients who received neoadjuvant chemoradiotherapy followed by surgery and definite chemoradiotherapy were 69.1% and 40.0%, respectively. There are 13 patients experienced grade 3−4 adverse event.
Conclusion: Pathological complete response after neoadjuvant chemoradiotherapy is associated with a significant survival benefit in patients with locally advanced squamous cell carcinoma of esophagus. The toxicities related to neoadjuvant chemoradiotherapy were tolerable.

Keywords: Esophageal cancer; Neoadjuvant chemoradiotherapy; Pathological complete response; Squamous cell carcinoma

1. Introduction

Esophageal cancer is a highly lethal disease with a poor prognosis even under adequate treatments. In contrast to most Western countries, squamous cell carcinoma comprised most of the histology subtype of esophageal cancer in Asia. The incidence rate of squamous cell carcinoma (SCC) in esophageal cancer patients was 90.8% in Taiwan in 2010.[1] The 5-year overall survival rate of patients with esophageal cancer after surgery alone was less than 25%. Neoadjuvant chemoradiotherapy (CCRT) had been demonstrated to improve the survival and local control of locally advanced stage of esophageal cancer in several clinical trials and meta-analyses.[2] The rationale for introducing neoadjuvant CCRT for patients who have locally advanced esophageal cancer is to improve the survival of the patients by eradicating microscopic metastasis before radical surgery, and to improve the local

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

* Corresponding author. Dr. Hui-Ling Yeh, Department of Radiation Oncology, Taichung Veterans General Hospital, 1650, Section 4, Taiwan Boulevard, Taichung 407, Taiwan, ROC.
E-mail address: hlyeh@vghtc.gov.tw (H.-L. Yeh).

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control of the disease by increasing the complete resection rate after downsizing and downstaging of the tumor. There are at least two meta-analyses of randomized trials for neoadjuvant CCRT that showed a clear benefit in survival among patients with adenocarcinoma in the comparison of surgery alone.[3,4] Although the pathologic complete response (pCR) of the tumor was found to be as high as 47% with a median survival of 55 months in a phase II study in patients with adenocarcinoma and squamous cell carcinoma (SCC), the impact of pCR on survival in esophageal SCC after neoadjuvant CCRT is still controversial.[5]

This study retrospectively analyzed the results of patients who achieve pCR and who has less than pCR after neoadjuvant CCRT. The purpose of this study was to determine the impact of pCR rate on survival in locally advanced SCC of the esophagus.

2. Methods

2.1. Patient population

From October 2007 to December 2013, 98 patients with histologically proven SCC of the esophagus, AJCC clinical stage T2-4N0-3M0, who received neoadjuvant CCRT at Taichung Veterans General Hospital, were enrolled in this study. All patients were diagnosed by esophagoscopic biopsy. Complete cancer staging surveys were performed in all patients, including history taking, physical examination, laboratory tests, transesophageal endoscopic ultrasound (EUS), chest and abdominal CT scan, barium esophagogram, bronchoscopy, ultrasound of abdomen, and FDG-PET/CT scan. The staging system in this study utilized the seventh edition of the American Joint Committee on Cancer Tumor-Node-Metastasis (TNM) classification.[6] Patients with distant metastatic disease at diagnosis, incomplete treatment, adenocarcinoma histology, chemotherapy regimen other than cisplatin and 5-FU, radiation dose less than 50 Gy or more than 50.4 Gy were excluded from this study. After neoadjuvant CCRT was complete, tumor re-staging surveys included EUS, chest and abdominal CT scan, and FDG-PET/CT scan were performed again to evaluate the treatment response and multidisciplinary team meeting was conducted. Patients with disease progression, poor performance status or refusal to undergo surgery were shifted to definite concurrent CCRT (Fig. 1). All patients were provided written informed consent. This study was a retrospective analysis of information from patients' medical records, pathology databases, and electronic imaging systems.

2.2. Chemotherapy

Chemotherapy was given concomitantly with cisplatin 20 mg/m^2 iv for 1 h and fluorouracil 800 mg/m^2 iv for 24 h daily on Day 1 to Day 4 (cycle 1), and Day 29 to Day 32 (cycle 2) of radiotherapy. Patients who were not suitable for operation were shifted to definite CCRT and two additional cycles of chemotherapy were given using the same regimen as above. Pre-chemotherapy evaluations were performed every time before chemotherapy, including physical examination, vital sign, white blood count, hemoglobin, platelet, liver function, renal functions, chest X-ray, and urine analysis. Chemotherapy was administered only when the patient was without infection sign, and ANC >1500/μL, Hb >10 g/dL, platelet >100,000/μL, as well as normal liver functions and renal functions.

2.3. Radiotherapy

All patients underwent CT simulation in a supine position with their arms above their heads. A customized vacuum bag was used for immobilization. The CT images were taken at a 5-mm thickness throughout the neck and the thorax for upper and middle thoracic tumor or thorax and abdomen for lower thoracic tumor. The gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV) and organs at risk (OARs) were outlined on the CT image. GTV was defined as gross tumor of the esophagus and enlarged lymph node according to the PET-CT scan. CTV was delineated from the GTV plus margin of 1 cm radially, 5 cm margin cephalic and caudal, and including the lymph nodes over the mediastinum and supraclavicular regions for upper or middle thoracic tumors, or the lymph nodes over the celiac trunk area for lower thoracic tumors. PTV was defined as CTV plus 5 mm margin to overcome the daily setup error and internal organ motion.

The intensity-modulated radiation therapy (IMRT) plan using the multiple field technique was delivered to each patient by a linear accelerator (Varian 2100EX with a 120-leaf Millennium multileaf collimator, Varian Oncology Systems, Palo Alto, CA, USA) using 6 MV photons. Dose calculations were performed using the Varian Eclipse planning system (versions 6.5 to 7.2.24) (Varian Medical Systems Inc., Worldwide Headquarters 3100 Hansen Way, Palo Alto, CA 94304, USA) based on the pencil beam model. A total dose of 50−50.4 Gy was prescribed to the PTV such that 95% of the PTV received 100% of the prescribed dose. The dosage constraints for organs at risk (OARs) were <18 Gy for mean lung dose, <20% for lung volume that received >20 Gy (V20), and <15% for heart volume that received >30 Gy (V30), and <50 Gy for the total spinal cord. Radiotherapy was performed 5 days per week, with a daily dose of 180 cGy for a total course of 5−6 weeks (Fig. 2).

2.4. Surgery

Surgery was performed 4−6 weeks after complete neoadjuvant CCRT. The surgical procedure included thoracoscopic esophagectomy, at least 2-field lymph node dissection and esophagus reconstruction with gastric tube. Extended lymph node dissection including mediastinal lymph nodes (Group 2, Group 4, Group 7, Group 8, and other enlarged lymph nodes suspected to be malignant) and bilateral recurrent laryngeal lymph nodes were removed by the chest surgeon. Further, radical neck lymph nodes dissection was performed

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