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Original Article

Definite intensity-modulated radiotherapy with concurrent chemotherapy more than 4 cycles improved survival for patients with locally-advanced or inoperable esophageal squamous cell carcinoma

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Abstract We investigated which prognostic factor could improve survival for esophageal cancer patients who received definite concurrent chemoradiation (CCRT). Eighty patients with age ≥18, Karnofsky Performance Scale (KPS) ≥ 60, and clinical stage T1-4N0-3M0 esophageal squamous cell carcinoma were enrolled from July 2004 to December 2015. They underwent definite intensity-modulated radiotherapy (IMRT) with or without simultaneous integrated boost to the primary tumor, and reception of concurrent chemotherapy ≥ 1 cycle. The primary endpoints were overall survival (OS), locoregional progression-free survival (LRPFS) and distant metastasis-free survival (DMFS). The median follow-up duration for alive patients was 21.5 months. The rates of 2-, 3- and 5-year OS/LRPFS/DMFS were 23.8%/53.5%/49.3%, 19.1%/44.6%/49.3%, and 13.0%/44.6%/43.9%, respectively. Only the non-clinical complete response (non-cCR) after CCRT was an independent poor prognostic factor in OS (HR 3.101, 95% CI 1.535–6.265, $p = 0.0016$). Radiation dose >50.4 Gy and chemotherapy ≥4 cycles significantly predicted better LRPFS ($p = 0.0361$ and 0.0163, respectively). Poorly differentiated tumor and stage III disease have poor DMFS ($p = 0.0336$ and 0.0411, respectively), and chemotherapy ≥ 4 cycles was a better predictor ($p = 0.0004$). In subgroup analysis, patients who received radiation dose ≤50.4 Gy with concurrent chemotherapy ≥4 cycles had the

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best survival outcome with 1-, 2-, 3- and 5-year survival rates of 73.7%, 39.4%, 31.5% and 17.5%, respectively. In conclusion, definite radiotherapy with concurrent chemotherapy ≥4 cycles improved the survival for patients with inoperable or locally-advanced esophageal squamous cell carcinoma.

Introduction

Cancer of the esophagus is a fatal disease and ranked the 6th most common cause of cancer-related death worldwide [1]. The squamous cell carcinoma accounts for the majority of the esophageal cancer (>90%) in Taiwan [2]. According to the increasing evidence of previous published literature, the trimodality therapy including neoadjuvant CCRT followed by surgery has become the standard of treatment for locally-advanced esophageal cancer [3—10].

Although trimodality therapy can achieve a better survival benefit, many factors, such as tumor size, location, extent of tumor involvement, patients' performance status, and comorbidities dramatically influence the probability of surgery. Only 30—40% of patients can receive operation as initial therapy or as one component of the multimodality treatment [11]. The standard non-surgical treatment option is mainly based on the results of the Radiation Therapy Oncology Group (RTOG) 85-01, which showed the definite CCRT had better 5-year survival rate than radiation alone and a projected 10-year survival rate of 20% [12,13].

However, there are still several questions needed to be overcome. Firstly, the high local recurrence rate of 46% after definite CCRT in the RTOG 85-01 study is of concern, and a subsequent study (INT 0123) failed to show better local control by escalating the radiation dose up to 64.8 Gy [14]. This dose-escalation study failed to demonstrate improved local control might be attributed to its conventional radiation technique (Both of the RTOG 85-01 and INT 0123 were conducted before the era of 3D-conformal radiotherapy [3D-CRT]), which had higher treatment-related toxicities. The ≥ grade 3 treatment-related toxicities in the RTOG 85-01 study and the INT 0123 study were 48% and 71%, respectively. The modern technology of IMRT is an advanced form of 3D-CRT, which uses non-uniform radiation beams to maximize the radiation dose of the target volume and simultaneously minimize the radiation dose of the surrounding normal tissues. The IMRT is better than conventional 3D-CRT in treating esophageal cancer not only in dose homogeneity of target volume, but also in decreasing the radiation dose to the organs at risk [15—19]. Most importantly, by using IMRT with simultaneous integrated boost to the primary tumor, it is possible to do dose escalation of the target volume with safety dose constrains of the surrounding normal tissues. It is speculated that using modern technique of IMRT with dose escalation of the target volume can achieve better local control without increasing treatment-related toxicities.

Secondary, the chemotherapy was prescribed for total of 4 cycles in the protocol of the RTOG 85-01 study, but about one-fifth of patients had distant metastasis. It is reasonable to interpret that adding more cycles of chemotherapy can decrease the rate of distant metastasis, and further improve the survival outcome.

In current study, we will illustrate the treatment outcomes for patients with locally-advanced or inoperable esophageal squamous cell carcinoma who underwent definite CCRT by using IMRT with or without simultaneous integrated boost and a total chemotherapy ≥ or <4 cycles.

Methods

Patients

From July 2004 to December 2015, 92 patients with locally advanced esophageal cancer were retrospectively reviewed. The eligibility criteria included (1) age ≥ 18 years old, (2) biopsy-proved squamous cell carcinoma of esophagus, (3) KPS ≥ 60, (4) clinical stage T1-4N0-3M0 according to the American Joint Committee on Cancer (AJCC) TNM staging 7th edition, (5) patients who received definite IMRT with or without simultaneous integrated boost to the primary tumor, and (6) patients who received concurrent chemotherapy ≥ 1 cycle. Exclusion criteria included (1) initial distant metastatic disease, (2) adenocarcinoma of esophagus, (3) incomplete treatment course of definite CCRT, and (4) disease progression during the definite CCRT. Four patients were initially diagnosed with metastatic disease, three had adenocarcinoma, four had incomplete definite CCRT, and one had disease progression (brain metastasis) during the period of definite CCRT. Therefore, 80 patients were enrolled into the analysis.

All patients received a complete pretreatment staging workup, including medical history, physical examination, gastroscopy, bronchoscopy, biopsy of esophagus, complete blood cell count, serologic biochemistry data of liver and kidney, chest X-ray, diagnostic chest computed tomography scan, abdominal sonography, and whole body bone scan. The positron emission tomography scan was performed if clinical indicated. Tumor staging was defined based on the AJCC clinical stages, 7th edition.

Definite CCRT

The radiotherapy treatment plan was performed according to the protocol described in our previous studies [15,16]. All patients underwent IMRT with or without simultaneous integrated boost to the gross esophageal tumor plus concurrent chemotherapy. The treatment planning of IMRT was the Eclipse treatment planning

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