Radiotherapy and Oncology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Clinical efficacy and failure pattern in patients with cervical esophageal cancer treated with definitive chemoradiotherapy

Peng Zhang [1], Mian Xi [1], Lei Zhao, Bo Qiu, Hui Liu, Yong-Hong Hu, Meng-Zhong Liu *

Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangdong Esophageal Cancer Institute, Department of Radiation Oncology, Cancer Center, Sun Yat-sen University, Guangzhou, PR China

ARTICLE INFO

Article history:
Received 21 November 2014
Received in revised form 23 June 2015
Accepted 16 July 2015
Available online xxxx

Keywords:
Failure pattern
Prognosis
Cervical esophageal cancer
Chemoradiotherapy
Prognostic factor

ABSTRACT

Background: Data on cervical esophageal cancer (CEC) based on modern radiotherapy technique are rare. We aimed to analyze the clinical efficacy and failure pattern of patients with CEC who underwent definitive chemoradiotherapy.

Methods: Between February 2002 and October 2013, 102 patients with CEC treated with definitive chemoradiotherapy were retrospectively analyzed. All patients received concurrent platinum-based chemotherapy with conformal radiotherapy (50–70 Gy in 25–35 fractions, 5 fractions per week over 5–7 weeks). Overall survival (OS), progression-free survival (PFS) and loco-regional failure-free survival (LRFFS) were calculated.

Results: The 3-year OS, PFS and LRFFS rates for the entire sample were 39.3%, 33.6% and 35.3%, respectively. During follow-up, 32, 26, and 41 patients had developed local, regional, and distant failure, respectively. Sex and hoarseness were independent prognostic indicators for OS ($P = 0.011$, $P < 0.001$; respectively) and PFS ($P = 0.008$, $P = 0.001$; respectively). Hoarseness was the only independent prognostic factor for LRFFS ($P = 0.002$).

Conclusions: Distant metastasis was the most common failure pattern in CEC patients undergoing definitive chemoradiotherapy. Hoarseness was an independent prognostic factor for OS, PFS, and LRFFS.

 Radiotherapy and Oncology xxx (2015) xxx–xxx

Cervical esophageal cancer (CEC) is relatively uncommon, with an incidence rate of <1 per 100,000 [1]. The prognosis of CEC is poor, which could be related to the delayed diagnosis and abundant lymphatic drainage of the cervical esophagus. Due to the unique anatomical position between the lower border of the cricoid cartilage and the thoracic esophagus inlet, CEC easily and frequently invades upwards to the hypopharynx and downwards to the thoracic esophagus [2].

The RTOG 85-01 trial indicated that concurrent chemoradiotherapy is currently considered the standard treatment for inoperable esophageal cancer [3]. However, loco-regional tumor control and the prognosis for patients with esophageal cancer after concurrent chemoradiotherapy remain poor: approximately 50–60% patients fail loco-regionally due to persistent disease or local recurrence [4]. Recent conformal radiotherapy technology, including three-dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT), delivers high doses accurately to the target volume in esophageal cancer, and spares normal tissues [5,6]. Bedford et al. reported that conformal radiotherapy techniques could be expected to increase local tumor control by 15–25% [6]. Accordingly, patients with CEC could potentially benefit from advanced conformal radiotherapy, which might reduce toxicity and improve clinical outcomes.

Data on patients with CEC treated with 3DCRT/IMRT and concurrent chemotherapy are rare. The purpose of this study was to analyze the clinical efficacy and failure pattern following definitive chemoradiotherapy and to explore the possible prognostic factors related to survival in patients with CEC.

Materials and methods

Between February 2002 and October 2013, we respectively reviewed 102 patients diagnosed with CEC and who received definitive chemoradiotherapy at the Sun Yat-sen University Cancer Center. The primary tumor center was between the cricopharyngeus muscle and the thoracic esophagus inlet [7]. All patients had pathologically proven squamous cell carcinoma with or without superior hypopharyngeal extension or inferior thoracic esophageal extension. Patients recruited to our study had no distant organ metastasis or abdominal lymphadenopathy; no history of radiotherapy or chemotherapy; and Eastern Cooperative

* Corresponding author at: Department of Radiation, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou, Guangdong 510060, PR China.
E-mail address: liumengzhong@126.com (M.-Z. Liu).
[1] Peng Zhang and Mian Xi contributed equally to this work.

http://dx.doi.org/10.1016/j.radonc.2015.07.011
0167-8140/

Oncology Group (ECOG) performance status ⩽3. All patients were staged according to the sixth edition of the American Joint Committee on Cancer (AJCC) staging system.

Patient immobilization, simulation, and treatment planning were performed according to standard protocols for patients with esophageal carcinoma receiving conformal radiotherapy in our department [8]. All patients received 3DCRT or IMRT with 6–8 MV photon beams. A total prescription dose of 50–70 Gy was delivered to gross tumor volume (GTV) in 25–35 fractions, with five fractions per week over 5–7 weeks. Prophylactic treatment (50–54 Gy) was delivered to the clinical target volume (CTV). GTV was defined as the primary tumor (GTV-T) and involved lymph nodes (GTV-LN) on the planning CT scan performed by the attending radiation oncologist using all available resources, including barium esophagography, laryngoscopy image, and diagnostic CT image data. The CTV included the CTV-T and CTV-LN. CTV-T was defined as the GTV-T plus the volume of a 3-cm margin in the cranial–caudal direction and a 1-cm radial margin. The CTV-LN encompassed the elective nodal regions, including bilateral levels II–IV of the cervical lymph node area, supraclavicular fossa, and upper mediastinal area. The cranial and caudal limits of the CTV-LN were the caudal edge of the lateral process of the atlas and trachea bifurcation, respectively [9,10]. The planning target volume was determined by adding 0.8-cm radial margin to the CTV [8].

Induction chemotherapy (ICT) was administered using platinum-based regimens in 18 patients (17.6%). Concurrent chemotherapy was administered using regimens that included cisplatin plus 5-fluorouracil and cisplatin plus docetaxel. Thirty-nine patients were concurrently treated with docetaxel and cisplatin regimens: 13 were treated with docetaxel (60 mg/m^2) on Day 1 and 29, and cisplatin (80 mg/m^2) on Day 1 and 29 [8]; 26 were treated with cisplatin (30 mg/m^2) and docetaxel (30 mg/m^2) weekly for at least 4 weeks [11]. Another 63 patients were concurrently treated with cisplatin (60 mg/m^2) on Day 1 and 29 and with 5-fluorouracil (300 mg/m^2/24 h) on Day 1–3 and Day 29–31 [12].

After the end of treatment, patients were evaluated with physical examination, barium swallow, endoscopy, and CT scan at three-month intervals for two years, and 6 months thereafter. The National Cancer Institute Common Toxicity Criteria (version 3.0) was used to score acute and late treatment toxicity. Treatment failure was considered to have occurred if pathologically proven or documented radiographically by serial progression [13]. Local failure was defined as the persistence or recurrence of the primary tumor, and regional failure was referred to the persistence or recurrence of the regional lymph nodes [14]. Distant failure was defined as the metastasis to any site beyond the primary tumor and regional lymph nodes. All failure patterns were analyzed regardless of the record of previous failure [13]. Progression-free survival (PFS), loco-regional failure-free survival (LRFFS) and overall survival (OS) were defined as the time from the diagnosis of CEC to the first detection of tumor progression, local–regional tumor persistence or recurrence, and death from any cause or last follow-up, respectively.

The last follow-up was on August 31, 2014. Survival analyses were carried out using the Kaplan–Meier method, and differences between curves were analyzed using the log-rank test. The Cox proportional hazards model was used to test independent factors of OS, PFS and LRFFS. The criterion for statistical significance was set at $\alpha = 0.05$; P-values were determined from two-sided tests. All statistical analyses were performed using SPSS v16.0 (SPSS, Chicago, IL, USA).

Results

The patient characteristics are detailed in Table 1. According to the AJCC staging system (6th edition), 32 patients had stage II disease; 70 patients had stage III disease. Fifty-six patients were treated with 3DCRT; 46 received IMRT. The median radiation dose was 60 Gy (range, 50–70 Gy) and only 12 patients received a total dose of <60 Gy. A total of 86 patients received radiation doses of 60–66 Gy and 4 patients received >66 Gy (including three who received 70 Gy).

Table 1
Demographic and pathological characteristics of the study population.

Characteristic	No. of patients (%)
Age (years), median (range)	61 (36–75)
Sex	
Male	54 (52.9%)
Female	48 (47.1%)
ECOG performance status	
0–1	92 (90.2%)
2–3	10 (9.8%)
Hypopharyngeal extension	
Yes	23 (22.5%)
No	79 (77.5%)
Pathological grade	
G1–2	67 (65.7%)
G3–4, *x*	35 (34.3%)
Weight loss	
⩾10%	15 (14.7%)
<10%	87 (82.3%)
Hoarseness	
Yes	12 (11.8%)
No	90 (88.2%)
T stage	
T1–3	58 (56.9%)
T4	44 (43.1%)
N stage	
N0	18 (17.6%)
N1	84 (82.4%)
TNM stage	
II	32 (31.4%)
III	70 (68.6%)
Radiation dose (Gy)	
<60	12 (11.8%)
⩾60	90 (88.2%)
Induction chemotherapy	
Yes	18 (17.6%)
No	84 (82.4%)
Concurrent chemotherapy	
Cisplatin + 5-fluorouracil	63 (61.8%)
Cisplatin + docetaxel	39 (38.2%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group.

At a median follow-up interval of 47 months, the 3-year OS, PFS, and LRFFS rates for the entire sample were 39.3%, 33.6% and 35.3%, respectively (Fig. 1). The median OS, PFS, and LRFFS were 27 months, 17 months, and 17 months, respectively. As shown in Table 2, univariate analysis suggested that hoarseness and ICT were significantly associated with OS, PFS, and LRFFS. In addition, hypopharyngeal extension ($P = 0.021$) was also significantly associated with PFS. The 3-year OS, PFS, and LRFFS rates of patients with hoarseness were significantly worse than patients without hoarseness (0% vs. 44.7%, $P < 0.001$; 0% vs. 41.1%, $P < 0.001$; 0% vs. 43.5%, $P < 0.001$; respectively). The 3-year OS, PFS and LRFFS rates of patients who received ICT were significantly worse than patients who did not receive ICT (11.1% vs. 45.5%, $P = 0.016$; 11.1% vs. 40.5%, $P = 0.019$; 11.1% vs. 43.2%, $P = 0.041$; respectively). Clinical variables that were statistically significant ($P < 0.1$) in univariate analysis were analyzed further in multivariate analysis with stepwise selection of variables. Multivariate analysis revealed that sex and hoarseness were independent prognostic factors related to OS

Please cite this article in press as: Zhang P et al. Clinical efficacy and failure pattern in patients with cervical esophageal cancer treated with definitive chemoradiotherapy. Radiother Oncol (2015), http://dx.doi.org/10.1016/j.radonc.2015.07.011