Radiotherapy and Oncology 113 (2014) 182–187

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Phase II trial

Involved-field irradiation concurrently combined with nedaplatin/5-fluorouracil for inoperable esophageal cancer on basis of ^{18}FDG-PET scans: A phase II study

Hideomi Yamashita *, Mami Omori, Ryousuke Takenaka, Kae Okuma, Reiko Kobayashi, Kuni Ohtomo, Keiichi Nakagawa

Department of Radiology, University of Tokyo Hospital, Japan

ARTICLE INFO

Article history:
Received 5 September 2014
Received in revised form 23 October 2014
Accepted 3 November 2014
Available online 23 November 2014

Keywords:
Esophageal cancer
Combined modality therapy
Involved-field radiotherapy
Nedaplatin
5-Fluorouracil

ABSTRACT

Purpose: A prospective study was performed on chemoradiotherapy (CRT) for esophageal cancer using involved-field radiation therapy (IFRT) based on 18-fluorodeoxyglucose positron-emission tomography. The goal of this phase II study was to evaluate the efficacy of the IFRT procedure in newly diagnosed esophageal cancer.

Patients and methods: Eligible patients were adults with newly diagnosed untreated, inoperable esophageal cancer in stages I–IV with lymph node metastases. Patients received nedaplatin 80 mg/m^2 per day on day 1, 5-fluorouracil 800 mg/m^2 on days 1–4 intravenously repeated every 28 days for 2–4 cycles, and combined IFRT. Elective nodal irradiation was not performed. Irradiation was applied only to the primary tumor and positive lymph nodes.

Results: From September 2009 to July 2012, of the 63 patients enrolled, 58 were evaluable for response. The primary end point of isolated out-of-field loco-regional nodal recurrence was seen in only two patients. The expectant rate was assumed to be less than 5%. The threshold value was set as 10% to calculate the number of registrations. Progression-free and overall survival rates at 36 months were 47.7% and 51.1%, respectively. The median progression-free survival was 34.6 months, and overall survival was 38.4 months. Salvage surgery was tried for 11 patients (17.5%) due to residual or recurrent disease.

Conclusion: The primary end point of the trial was demonstrated, indicating the efficacy of IFRT in the treatment of inoperable esophageal cancer mostly of squamous cell carcinoma.

Concurrent chemoradiotherapy (CRT) is well established as a standard approach to treat esophageal cancer. Many published reports indicate that prophylactic lymph node (LN) irradiation for esophageal cancer can lead to improved survival [1–3]. Therefore peri-esophageal nodes are recommended for inclusion in the treatment field. This is elective nodal irradiation (ENI) for CRT of loco-regional advanced esophageal cancer with the obvious treatment-related toxicities. The radiation fields were decreased to a greater degree in the RTOG94–05 trial than in the RTOG85–01 trial [4].

The standard Japanese treatment for operable esophageal cancer consists of neoadjuvant chemotherapy followed by esophagectomy with three-field lymph node dissection. This has resulted in a 5-year survival rate of 37–61% [5–7]. There is a lack of consensus on the design of an optimal radiation field with several different investigators recently reporting conflicting results on the role of extensive or ENI in definitive CRT for esophageal cancer [8–11]. The present prospective study reports the first recurrent patterns as the primary endpoint for patients with locally advanced esophageal cancer treated with nedaplatin (NDP), 5-FU and radiotherapy (RT) at our institution.

Patients and methods

A prospective study (P2010052-11Z, UMIN000007209) of CRT for inoperable esophageal cancer is in progress based on defining the RT field by 18-fluorodeoxyglucose (^{18}FDG) positron-emission tomography (PET). This study was approved by the Institutional Review Board of what institution? The primary endpoint was in determining isolated LN recurrence rate and the secondary endpoints were focused on complete response rate, progression-free survival time, and the frequency and grade of toxicities. The threshold for the isolated LN recurrence rate was set at 10%.

* Corresponding author at: Department of Radiology, University of Tokyo Hospital, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.
E-mail address: yamachan07291973@yahoo.co.jp (H. Yamashita).

http://dx.doi.org/10.1016/j.radonc.2014.11.004
0167-8140/

Radiotherapy planning and target volume definition

All patients received selective LN irradiation and were treated with 50.4 Gy delivered over 5.6 weeks at 1.8 Gy per fraction or 50 Gy in 25 fractions over 5 weeks. Tumor volume was visualized on computed tomography (CT) and/or PET and endoscopic extension and used to define gross tumor volume (GTV) for each patient. All LNs with a diameter at least one cm in short axis in CT or positive by ^{18}FDG-PET (excluding physiological accumulation) were included in the GTV. The GTV was contoured on the planning CT by referring to the PET/CT images on the monitor adjacent to the Pinnacle^3 planning machine. The clinical target volume (CTV) was generated by using no radial margin and 2 cm longitudinal margins to the GTV-primary, and by using no margins for the GTV-LNs. The planning target volume (PTV) was then generated by applying a 5 mm radial margin and a 10 mm longitudinal margin to the CTV. No elective irradiation was performed on the mediastinal LNs. PTV-min was more than 90% of the prescribed dose and PTV $\geqslant$107% was less than 5%. Depending on the lesion in some cases, PTV was sometimes split and the irradiated fields were divided into separate parts.

At least four fields were used: two anterior–posterior opposed fields and two anterior–posterior oblique opposed fields to remove the spinal cord from the radiation fields. If necessary, one/two beams were added with the field-in-field technique. Mean lung dose had to be kept at or below 20 Gy and V20 (=the lung volume rate receiving over 20 Gy) <20%. Spinal cord dose had to be kept at or below 45 Gy. The constraint for the heart was D75% <45 Gy and mean heart dose <30 Gy. Treatment was delivered by linear accelerators with 6–10 MV photons. A standardized uptake value by ^{18}FDG-PET on the highest image pixel in the tumor regions (SUVmax) of 2.5 or more was considered positive. A PET-CT match was not performed for delineation of GTV. Image guided RT was performed daily using cone beam CT.

Chemotherapy regimen

All patients received chemotherapy concurrently with irradiation. Chemotherapy consisted of two cycles of 5-FU (800 mg/m^2/day, days 1–4 and days 29–32, continuous) combined with NDP (80 mg/m^2, day 1 and day 29, bolus); standard techniques were used for hydration and alkalization. For a patient 75 years or older, reductions were made to an 80% dose. Chemotherapy was started on the first day of irradiation. After concurrent CRT, in the adjuvant setting one or two cycles of the same dose of chemotherapy were added for patients who still had sufficient bone-marrow function and performance status and who did not refuse additional chemotherapy.

Patients

The stage of esophageal cancer was classified according to the UICC version 7.0 [12].

The inclusion criteria were: (a) lower and upper age limits were 20 and 85 years; (b) histopathologically proven squamous cell carcinoma or adenocarcinoma of esophagus; (c) clinical stage I without indication for endoscopic sub-mucosal dissection or endoscopic mucosal resection (EMR), clinical stages II–III, clinical stage IV consisting of metastases in the cervical/celiac lymph nodes; (d) Karnofsky-performance status (K-PS) $\geqslant$70%; (e) white blood cell counts of 4000–12000/mm^3, neutrophil >2000/mm^3, platelets >100,000/mm^3, hemoglobin >9.0 g/dL, total-bilirubin <1.5 mg/dL, glutamate oxaloacetate transaminase/glutamate pyruvate transaminase <76/72 U/L, creatinine <1.2 mg/dL, and partial pressure of arterial oxygen >70 mmHg.

The exclusion criteria were: (a) presence of serious complications including fresh gastrointestinal bleeding, active infection, heart failure, renal insufficiency, liver failure, or diabetes that was difficult to control; (b) presence of active overlapping cancer; (c) having metastasis to other organs from esophageal cancer; (d) with a history of RT for the same lesion; (e) with a history of chemotherapy; (f) having contra-indication to receiving NDP/5-FU; (g) having drug hypersensitivity to NDP/5-FU.

This study was planned for more than 60 patients. The primary objective of this study was to determine the rate of isolated LN recurrence. The aim of this prospective study was to evaluate the frequency of the first recurrence from the LN region that was omitted from irradiation, and to confirm that it does not significantly increase in comparison with ENI in published reports.

The check for recurrence was performed using serum tumor markers (carcino-embryonic antigen, squamous cell carcinoma-related antigen [SCC], cytokeratin 19 fragment [CYFRA], p53 antibody) every month after completion of treatment [29–31] and upper gastrointestinal endoscopy (±biopsy) plus enhanced CT scan from the upper neck LN to the bottom of the pelvis scheduled every three months. When a recurrence was questionable by any of the above examinations, FDG-PET was also performed.

From January 2010 to July 2012, 63 cases were registered. In all cases, more than 24 months had passed after starting RT. Blood counts and laboratory tests were performed once a week.

Toxicity assessment

Toxicities were classified in accordance with the National Cancer Institute Common Toxicity Criteria version 4.0. In this study, early toxicities were defined as what occurred within 3 months after completion of RT.

Statistical analysis

The Kaplan–Meier method was used for estimation of overall survival and progression-free survival. The times for survival were calculated from the start of RT. A p value of less than 0.05 was considered statistically significant.

Results

The characteristics of the 63 patients (55 males and 8 females) are listed in Table 1. The median age was 67.5 years, ranging from 47 to 84 years. The tumor histology was squamous cell carcinoma in 59 patients. The sub-sites of the primary tumors included cervical/upper/middle/lower thoracic portions, with the following distribution: 5%/19%/49%/27%. Clinical stage I had 14%, II–III had 59%, and IV had 27%. In the total of all patients, 25% were 75 years or older. K-PS before treatment was 70–80% in 8 cases. The mean ± SD for weight loss was 3.4 ± 4.5 kg (median; 2.0 kg, range; 0–28.0 kg) before treatment. Body weight loss of more than 5 kg before CRT was seen in 18 cases. For dysphagia score before CRT, 9 cases were unable to swallow anything/total dysphagia, 15 cases were able to swallow liquids only, 9 cases were able to swallow only semi solid foods, and 28 cases were able to eat normal diet/no dysphagia. Tumor length in the cranio-caudal direction before CRT was over 5.0 cm in 33 cases. The median of 63 SUVmax values in primary tumor and LN metastases was 12.2 (range; 0–36) and 3.2 (range; 0–36.2), respectively. Supraclavicular LN metastasis was seen in 13 cases (21%) and abdominal para-aortic LN metastasis in 7 cases (11%), although these metastases involved distant and not regional LNs. The irradiation fields were removed from the right recurrent nerve LN in 24 cases, subcarinal LN in 13 cases, and cardiac LN in 33 cases. These exclusions were examples of elective nodal areas.

Finally, 60 patients completed RT as planned and 59 patients completed at least two cycles of chemotherapy as planned. Three