Nuclear Medicine & Radiation Therapy

Anbai et al., J Nucl Med Radiat Ther 2013, 4:2
http://dx.doi.org/10.4172/2155-9619.1000150

Research Article Open Access

Treatment Outcomes of Chemoradiotherapy for Patients with Advanced Esophageal Cancer

Akira Anbai*, Makoto Koga and Manabu Hashimoto

Department of Radiology and Radiation Oncology, Akita University Graduate School of Medicine, 1-1-1 Hondo Akita 010-8543, Japan

Abstract

Purpose: To evaluate the treatment outcomes of chemoradiotherapy for patients with advanced esophageal cancer and estimate the prognostic factors.

Materials and methods: Patients with advanced esophageal cancer, who were treated with chemoradiotherapy (CRT) between April 2003 and December 2010, were evaluated. Patients received concurrent chemoradiotherapy (cisplatin plus 5-fluorouracil and 61.2 Gy radiotherapy). Therapeutic response, overall survival time, and toxicity were examined and statistical evaluation was performed.

Results: One hundred and fourteen patients were treated with CRT. Among them, 84 patients (77.2%) received the complete course of CRT. Eighteen patients (15.8%) had a complete response, 90 patients (78.9%) had a partial response and 6 patients (5.3%) exhibited progressive disease. The mean follow-up period was 14.6 months (range, 2-90 months). The median overall survival time was 13.0 months. The 2-year and 3-year overall survival rates were 38.1% and 19.2%, respectively. Severe hematological toxicities included Grade 3 leukopenia in 40 patients (35.1%). Treatment-related death was estimated to have occurred in 7 patients. Performance status and body weight loss were identified as significant prognostic factors.

Conclusion: In our study, PS and body weight loss showed prognostic factors in CRT for advanced esophageal cancer.

Keywords: Esophageal cancer; Chemoradiotherapy; Toxicity; Prognostic factor

Introduction

Concurrent chemoradiotherapy (CRT) has been reported to significantly increase the survival rate of patients with esophageal cancer as compared with radiation therapy alone [1,2]. CRT is proposed to be the standard treatment for advanced esophageal cancer [3]. In our institute, CRT for advanced esophageal cancer has been started in April 2003. The purpose of this study was to examine the treatment outcomes of CRT for advanced esophageal cancer in our institution and analyze their prognostic factors.

Materials and Methods

Patient population

From April 2003 through December 2010, 439 patients were treated with radiotherapy in our institute. Among them, we retrospectively reviewed the records of patients treated with definitive CRT because of advanced stage disease.

Staging was based on complete medical history, physical examination, blood studies, plain chest radiographs, esophageal barium contrast examination, esophagogastroduodenoscopy (EGD), computed tomography scan, bone scintigraphy, magnetic resonance imaging and FDG-PET. Histological diagnoses of all patients were verified by EGD biopsy examinations.

Chemotherapy

Cisplatin (CDDP) and 5-fluorouracil (5-FU) were used for chemotherapy. CDDP (40 mg/m^2) was administered on days 1 and 8 by intravenous infusion over a period of ≥ 2 h, and 5-FU (400 mg/m^2) was administered on days 1-5 and again on days 8-12 by continuous infusion. This schedule was started concomitantly with radiotherapy and repeated every fifth week for 2 cycles. When Grade 3 hematologic toxicity developed, the second course of chemotherapy was delayed until recovery. Adjuvant chemotherapy after completion of radiotherapy was performed for patients who were deemed able to receive anticancer drugs.

Radiotherapy

High-energy X-rays (6 MV or 10 MV) were used for radiotherapy. All patients underwent three-dimensional radiotherapy planning. The Gross tumor volume (GTV) of the primary tumor was determined, and lymph nodes were judged to be positive for metastasis. The clinical targeted volume (CTV) was set at a 1 cm margin of the GTV and included prophylactic regional lymph nodes. The planning target volume (PTV) was defined as the CTV plus a 0.5- to 1-cm margin. The dose reference point was located at the iso-center. Anterior-posterior opposing portal irradiation was initiated at approximately 40 Gy, and oblique portal irradiation was then performed to spare the spinal cord from the radiation field. Patients received conventional fractionated radiation of 1.8 Gy per fraction, to a total dose of 59.4 - 61.2 Gy, 5 times a week over 7 to 9 weeks. Between 2003 and 2005, i. e. , in the early cases, the radiation dose was approximately 30 Gy and the split period

***Corresponding author:** Akira Anbai, Department of Radiology and Radiation Oncology, Akita University Graduate School of Medicine, Hondo 1-1-1 Akita City Akita Prefecture 010-8543, Japan, Tel: 81-18-884-6179; Fax: 81-18-836-2623, E-mail: anbai@doc.med.akita-u.ac.jp

Received March 25, 2013; **Accepted** May 18, 2013; **Published** May 18, 2013

Citation: Anbai A, Koga M, Hashimoto M (2013) Treatment Outcomes of Chemoradiotherapy for Patients with Advanced Esophageal Cancer. J Nucl Med Radiat Ther 4: 150. doi:10.4172/2155-9619.1000150

was 10 to 14 days. After 2004, the irradiation period was not limited and irradiation was continued, unless cytopenia of Grade 3 or higher.

Response evaluation

Therapeutic effects were evaluated by computed tomography scan, esophageal barium contrast examination, and EGD. The response evaluation criteria were based on those of RECIST [4]. The National Cancer Institute Common Terminology Criteria for Adverse Events v. 3.0 were used to evaluate the observed toxicity.

Statistical analysis

The overall survival time was calculated from the date of treatment initiation to the date of death from any causes or to the last date of confirmation of survival. We estimated survival curves using the Kaplan-Meier method. Prognostic factors were examined by univariate analyses and multivariate analyses (Cox proportional hazards model). A P value of <0.05 was considered significant. All analyses were performed with PASW Statistics ver. 18.0 (SPSS, Chicago, IL, USA).

Results

Patient characteristics

One hundred fourteen patients were treated with CRT between April 2003 and December 2010. The patient characteristics are shown in table 1. The patients consisted of 109 men and 5 women whose ages ranged from 45 to 89 years with a median age of 67.5 years. Histopathological examination revealed adenocarcinoma in 1 patient and squamous cell carcinoma in the other 113 patients.

Characteristic	Number of patients	(%)
Age (years)		
Median	67.5	
Range	45–89	
Sex		
Men	109	95.6
Women	5	4.4
Performance status[a]		
0	24	21.1
1	63	55.3
2	27	23.6
Dysphagia		
Absent	9	7.9
Can eat solid	18	15.8
Can swallow semiliquid	42	36.8
Can swallow liquid	30	26.3
Aphagia	15	13.2
Location of primary tumor		
Upper thoracic	26	22.8
Middle thoracic	69	60.5
Lower thoracic	19	16.7
Primary tumor length		
<5 cm	27	23.7
≥ 5 cm	87	76.3
Clinical Stage[b]		
Stage III (T4N1M0)	28	24.6
Stage IVA	86	75.4
(T2-3N1M1a)	(35)	(30.7)
(T4N1M1a)	(51)	(44.7)

[a]According to ECOG performance status score.
[b]According to UICC 6th ed.

Table 1: Patient characteristics.

CR	PR	SD	PD	Response rate
18 (15.8%)	90 (78.9%)	0 (0%)	6 (5.3%)	97.4%

Abbreviations: CR=Complete Response; PR=Partial Response; SD=Stable Disease; PD=Progressive Disease.

Table 2: Response results.

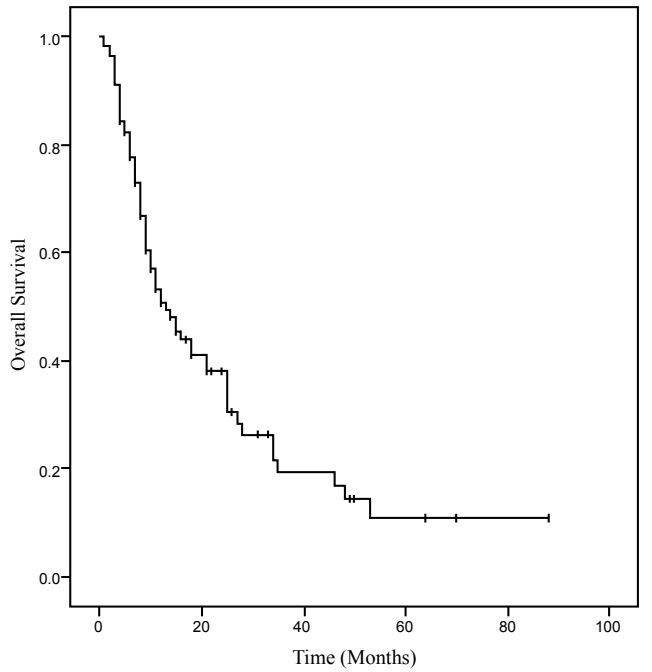

Figure 1: Overall survival time curve for all patient. The 2-year and 3-year overall survival rates were 38.1% and 19.2%.

Clinical outcomes

One hundred and six patients (93.0%) were irradiated with 59.4 Gy or over, and 3 patients (2.6%) were irradiated with 50 to 59 Gy. Irradiation did not reach 50 Gy in 5 patients. Fifty-six patients received adjuvant chemotherapy with CDDP/5-FU, nedaplatin/5-FU, or S-1 in our institute or at another hospital. Table 2 shows the therapeutic response in 114 patients treated with CRT. Eighteen patients (15.8%) achieved CR, and 90 patients (78.9%) achieved PR. The response rate was 94.7%. The mean follow-up period was 14.6 months (median, 9 months; range, 2-90 months). The median overall survival time was 13.0 months (95% confidence interval [CI], 8.3-17.7 months). The 2-year survival rate was 38.1% (95% CI, 27.7%-48.5%). The 3-year survival rate was 19.2% (95% CI, 8.8%-29.6%) (Figure 1). Recurrence was observed in 9 of the 18 patients who achieved CR during the follow-up period. Six patients experienced local recurrence. One patient had both local recurrence and distant metastasis concurrently. One patient showed cervical lymph node recurrence within the irradiated field. One patient developed a distant metastasis.

Toxicity profile

Table 3 shows the incidences of acute toxicities associated with CRT. Grade 3 leukopenia was observed in 40 patients (35.1%). Grade 3 neutropenia occurred in 14 patients (12.3%). Grade 3 anemia occurred in 15 patients (13.2%). Eight patients (7.0%) developed Grade 3-4 thrombocytopenia. Grade 3 or higher severe esophageal ulcer and fistula formation were observed in 8 patients (7.0%), and 3 patients died because of respiratory failure due to pneumonia followed by fistula

Toxicity	Grade			
	3	4	5	≥ Grade 3 (%)
White blood cell count decreased	40	0	0	35.1
Neutrophil count decreased	14	0	0	12.3
Anemia	15	0	0	13.2
Platelet count decreased	7	1	0	7.0
Esophagitis	26	0	0	22.8
Esophageal ulcer, Esophageal fistula	1	4	3	7.0
Dyspnea, Pneumonitis	3	3	1	6.1
Pleural effusion	8	4	1	11.4
Pericardial effusion	9	2	1	10.5
CNS cerebrovascular ischemia	0	0	1	0.8

Table 3: Summary of toxicity.

Prognostic factor	Univariate *P*	Multivariate *P*	Hazard ratio	95% CI[a]
Age, <75 vs. ≥ 75 years	0.61	_b	_b	_b
Sex	0.57	_b	_b	_b
Performance status, 0 or 1 vs. 2	0.04	0.01	1.64	1.12-2.39
Dysphagia	0.10	0.71	1.08	0.73-1.59
Body weight loss ≥ 10%, yes vs. no	0.02	0.03	1.79	1.06-3.01
Anemia, yes vs. no	0.92	_b	_b	_b
T-stage, T2or 3 vs. T4	0.92	_b	_b	_b
Lymphnode N1 vs. M1(LYM)	0.47	0.13	1.19	0.95-1.51
Primary tumor length, <5 vs. ≥ 5 cm	0.19	0.27	1.50	0.73-3.09

[a]Confidence interval.
[b]Excluded from multivariate analyses because of P ≥ 0.5 in univariate analyses.
Values of P<0.05 were considered significant.

Table 4: Uni- and multivariate analyses of prognostic factors.

formation. In addition, Grade 3 or higher severe lung disorders were found in 7 patients (6.1%), pleural effusion in 13 (11.4%), pericardial effusion in 12 (10.5%), and 3 patients died because of cardiopulmonary disorders. One patient developed Grade 5 cerebrovascular ischemia. Toxicities such as esophageal fistula, radiation pneumonitis, pleural effusion, pericardial effusion, and cerebral infarction may have contributed to the deaths of 7 patients (6.1%).

Analyses of prognostic factors

Table 4 shows the univariate and multivariate analyses of prognostic factors. Some of the prognostic factors for overall survival were evaluated. In this study, PS and body weight loss ≥ 10% were identified as factors significantly associated with survival.

Discussion

Esophageal cancer is a disease with a poor prognosis, and surgical resection has long been the first choice for curative treatment. Radiation therapy is often performed in patients with unresectable cancer or patients in whom surgery is considered difficult because of older age or comorbidities. However, since 1992, the efficacy of CRT has been well documented, and CRT has been clearly shown to improve cure rates compared with radiotherapy alone [1,2,5-9]. Currently, the guidelines of the National Comprehensive Cancer Network recommend CRT for esophageal cancer such as medically unfit for surgery or surgery not elected case [3].

We examined the CRT outcomes in patients with advanced esophageal cancer, and obtained CR rate of 15.8% and 3-year survival rate of 19.2%. Regarding the general therapeutic results for patients with advanced stage, the 3-year survival rates reportedly ranged from 10% to 36% [5-7].

In our institute, the primary aim of CRT is to achieve a radical cure of cancer in patients without distant metastasis. For this purpose, we thought that the radiation doses delivered to the GTV should be as high as possible. It appears that the CRT methods for esophageal cancer are slightly different between Western countries and Japan. In western countries, CRT generally consists of radiation with a total dose of 50.4 Gy plus 4 courses of CDDP/5-FU chemotherapy. These methods were based on the INT 0123 (Radiation Therapy Oncology Group [RTOG] 94-05) Phase III trial [10]. In contrast, Many institutions perform chemoradiotherapy with doses of 60 Gy and 2 or more courses of CDDP/5-FU infusion [11,12].

It is well known that esophageal cancer is associated with widespread lymph node metastases [13]. In some cases, lymph node metastases of esophageal cancer also spread over 3 regions (cervix, thorax, and abdomen) regardless of the size of primary tumor [14]. In such cases, it is essential to carefully determine the radiation field and dose.

The incidence of symptoms of acute hematological toxicities or esophagitis tends to correlate with the irradiated volume and total dose. In this study, the incidence of acute toxicities was almost the same as previously reported except for a rather high incidence of esophagitis [15]. However, all symptoms could be controlled by conservative treatment. Seven patients were provided with treatment related to death according to the criteria of CTCAE v. 3.0. However, all patients in which fistula occurred had a severe ulcer in the primary site before CRT.

The patients with locally advanced esophageal cancer had various conditions that primary tumor, lymph node metastasis and physical status. We evaluated prognostic factors and in our study performance status and body weight loss ≥ 10% were identified as factors significantly associated with survival.

It is well known that many cases of advanced esophageal cancer develop recurrence after chemoradiotherapy, even if CR is achieved [16]. Half of the cases in our study developed recurrences. If tumor cells remain localized at the site of origin, a salvage operation can be performed. However, some patients had lymph node metastases or distant metastases, resulting in a poor outcome.

In our series, 114 patients with advanced esophageal cancer were treated with CRT. Eighteen patients achieved CR. The median overall survival was 13.0 months, and the 3-year survival rate was 19.2%. Our treatment outcomes were at the same level as those reported in previous studies [5-7], and the appearances of toxicities was also similar. Thus, CRT appears to be a useful method for treating advanced esophageal cancer.

References

1. Al-Sarraf M, Reddy MS (2002) Nasopharyngeal carcinoma. Curr Treat Options Oncol 3: 21-32.
2. Chan AT, Teo PM, Johnson PJ (2002) Nasopharyngeal carcinoma. Ann Oncol 13: 1007-1015.
3. Thompson GM, Migdal CS, Whittle RJ (1983) Radiation retinopathy following treatment of posterior nasal space carcinoma. Br J Ophthalmol 67: 609-614.

4. Aristizabal S, Caldwell WL, Avila J (1977) The relationship of time-dose fractionation factors to complications in the treatment of pituitary tumors by irradiation. Int J Radiat Oncol Biol Phys 2: 667-673.

5. Goldsmith BJ, Rosenthal SA, Wara WM, Larson DA (1992) Optic neuropathy after irradiation of meningioma. Radiology 185: 71-76.

6. Guy J, Mancuso A, Beck R, Moster ML, Sedwick LA, et al. (1991) Radiation-induced optic neuropathy: a magnetic resonance imaging study. J Neurosurg 74: 426-432.

7. Jiang GL, Tucker SL, Guttenberger R, Peters LJ, Morrison WH, et al. (1994) Radiation-induced injury to the visual pathway. Radiother Oncol 30: 17-25.

8. Nakissa N, Rubin P, Strohl R, Keys H (1983) Ocular and orbital complications following radiation therapy of paranasal sinus malignancies and review of literature. Cancer 51: 980-986.

9. Parsons JT, Bova FJ, Fitzgerald CR, Mendenhall WM, Million RR (1994) Radiation optic neuropathy after megavoltage external-beam irradiation: analysis of time-dose factors. Int J Radiat Oncol Biol Phys 30: 755-763.

10. Parsons JT, Fitzgerald CR, Hood CI, Ellingwood KE, Bova FJ, et al. (1983) The effects of irradiation on the eye and optic nerve. Int J Radiat Oncol Biol Phys 9: 609-622.

11. Takeda A, Shigematsu N, Suzuki S, Fujii M, Kawata T, et al. (1999) Late retinal complications of radiation therapy for nasal and paranasal malignancies: relationship between irradiated-dose area and severity. Int J Radiat Oncol Biol Phys 44: 599-605.

12. Cackett P, Stebbing J, Dhillon B (2003) Complications of therapy and a diagnostic dilemma case. Case 1. Radiation maculopathy following treatment of nasopharyngeal carcinoma. J Clin Oncol 21: 4650-4651.

13. Wijers OB, Levendag PC, Luyten GP, Bakker BA, Freling NJ, et al. (1999) Radiation-induced bilateral optic neuropathy in cancer of the nasopharynx. Case failure analysis and a review of the literature. Strahlenther Onkol 175: 21-27.

14. Monroe AT, Bhandare N, Morris CG, Mendenhall WM (2005) Preventing radiation retinopathy with hyperfractionation. Int J Radiat Oncol Biol Phys 61: 856-864.

15. Archer DB, Amoaku WM, Gardiner TA (1991) Radiation retinopathy--clinical, histopathological, ultrastructural and experimental correlations. Eye (Lond) 5 : 239-251.

16. Malik A, Golnik K (2012) Hyperbaric oxygen therapy in the treatment of radiation optic neuropathy. J Neuroophthalmol 32: 128-131.

17. Zamber RW, Kinyoun JL (1992) Radiation retinopathy. West J Med 157: 530-533.

18. Kline LB, Kim JY, Ceballos R (1985) Radiation optic neuropathy. Ophthalmology 92: 1118-1126.

19. Carvounis PE, Katz B (2003) Gamma knife radiosurgery in neuro-ophthalmology. Curr Opin Ophthalmol 14: 317-324.

20. Hayreh SS (1970) Post-radiation retinopathy. A fluorescence fundus angiographic study. Br J Ophthalmol 54: 705-714.

21. Finger PT, Kurli M (2005) Laser photocoagulation for radiation retinopathy after ophthalmic plaque radiation therapy. Br J Ophthalmol 89: 730-738.

22. Lee MS, Borruat FX (2011) Should patients with radiation-induced optic neuropathy receive any treatment? J Neuroophthalmol 31: 83-88.

Citation: Anbai A, Koga M, Hashimoto M (2013) Treatment Outcomes of Chemoradiotherapy for Patients with Advanced Esophageal Cancer. J Nucl Med Radiat Ther 4: 150. doi:10.4172/2155-9619.1000150