

The efficiency of chemo-radiotherapy for localized recurrence of esophageal cancer after radical esophagectomy

Yoshihide Asaumi¹, Tamon Miyanaga¹, Yoji Nishida¹, Yasuo Hashizume¹, Hiroyasu Tamamura²

¹ Fukui Prefectural Hospital, Department of Surgery, Japan; ² Fukui Prefectural Hospital, Department of Radiology, Japan

Summary. *Background:* Radiation therapy for postoperative loco regional recurrence of esophageal cancer has been reported to be effective. The purpose of the present study was to evaluate the usefulness of radiotherapy combined with standard dose 5-fluorouracil (5FU) and cisplatin for the treatment of postoperative loco regional recurrent esophageal cancer. *Method:* Between 2004 and 2010, 10 patients with postoperative recurrence of esophageal cancer received concurrent chemoradiotherapy (CRT) using 5-FU and cisplatin. We evaluated the response rate, overall survival, and any adverse events. *Results:* Nine out of 10 patients had mediastinal lymph node recurrence, and 1 patient had a cervical lymph node recurrence. Nine patients were irradiated with 58-64Gy, and 1 patient could not complete CRT due to mediastinitis at 34Gy. Complete response (CR) was recognized in 4 patients (40%), and partial response (PR) in 4 patients (40%). The overall median survival time was 13 months. The histological type was a well-differentiated squamous cell carcinoma in 3 of the 4 patients where CR was obtained. CRT was discontinued with 1 patient who experienced a tracheomediastinal fistula. Because of hemorrhage due to radiation gastritis, transfusion of red cell concentrates was required. Steroids were required to treat intermittent pneumonitis. *Conclusion:* Chemoradiotherapy using 5-FU and cisplatin for loco regional postoperative recurrence of esophageal cancer was an effective therapy for well-differentiated squamous cell esophageal cancer, but one must beware of severe adverse events.

Key words: esophageal cancer, chemoradiation, localized recurrence

«L'EFFICACIA DELLA CHEMIORADIOTERAPIA PER LA RICOMPARSA LOCALIZZATA DEL CANCRO ESOFAGEO DOPO ESOFAGECTOMIA RADICALE»

Riassunto. *Background:* La radioterapia per la ricomparsa locoregionale post-operatoria del cancro esofageo viene ritenuta efficace. Lo scopo del presente studio è quello di valutare l'utilità della radioterapia combinata con dose standard di 5-fluorouracile (5FU) e cisplatino per il trattamento loco regionale postoperatorio di cancro esofageo ricorrente. *Metodi:* Tra il 2004 e il 2010, 10 pazienti con ricomparsa postoperatoria di cancro esofageo, sono stati trattati con chemioradioterapia (CRT) utilizzando 5-FU e cisplatino. E' stato valutato il tasso di risposta, la sopravvivenza generale ed ogni evento avverso. *Risultati:* Nove pazienti su dieci hanno sviluppato ricorrenze ai linfonodi mediastinici ed 1 paziente ai linfonodi cervicali. Nove pazienti sono stati irradiati con 58-64Gy e 1 paziente non ha potuto completare la CRT a causa di un mediastinite a 34 Gy. Una risposta completa (CR) è stata riscontrata in 4 pazienti (40%) ed una risposta parziale (PR) in altrettanti 4 pazienti (40%). Il tempo di sopravvivenza media generale è stato di 13 mesi. Il tipo istologico era il carcinoma squamocellulare ben differenziato riscontrato in 3 dei 4 pazienti dai quali era stata ottenuta una risposta completa. La CRT è stata discontinua con un paziente che ha sviluppato una fistola tracheomediastinica. A causa di emorragia dovuta ad una gastrite da radiazioni, è stata necessaria una trasfusione di concentrati eritrocitari. *Conclusioni:* La

chemioradioterapia con 5-FU e cisplatino per la ricorrenza locoregionale post-operatoria del cancro esofageo è da considerarsi una terapia efficace per il cancro esofageo squamocellulare, anche se non bisogna sottovalutare gli aspetti avversi.

Parole chiave: cancro dell'esofago, chemioradioterapia, ricomparsa localizzata

Introduction

Esophageal cancer has a poor prognosis, and recurrence after radical surgery is evident in approximately 40% of patients (1-3). Among the various forms of recurrence, loco regional recurrence occurs in 22-47% and distant metastasis in 39-51% of such patients (3, 4). Several treatments can be used for recurrence after radical esophagectomy, for example, chemotherapy, radiotherapy (RT), chemoradiotherapy (CRT), and surgery.

The outcomes of CRT are comparable to those of surgical treatment, and CRT is effective for local control of the tumor (5). The effects of CRT and RT on loco regional recurrence of esophageal cancer have been reported (6-8). Concurrent CRT yields better treatment results than RT alone in patients with localized esophageal cancer (9-11).

In the present study, we assessed the efficacy of CRT using 5-fluorouracil (5-FU) and cisplatin (CDDP) for loco regional recurrence of cervical and thoracic esophageal cancer after radical surgery.

Patients and methods

One hundred and fifty-nine patients with esophageal squamous cell carcinoma (SCC) were treated between January 2004 and December 2010 in our hospital, and radical esophagectomy was performed in 51 patients. Recurrence was observed in 20 of these patients, and 10 were treated with CRT using 5-FU and CDDP for loco regional recurrence. Four out of 10 patients received adjuvant chemotherapy prior to their surgery, which was carried out in August 2009.

Computed tomography (CT), and in some cases, positron emission tomography (PET) with [18F] fluorodeoxyglucose-CT were used to diagnose recurrence. The daily fractional dose of RT was 2 Gy,

administered 5 days a week. The total RT dose was 60 Gy. Seven patients received a continuous infusion of 5-FU 700 mg/m² on days 1-4 and days 29-32, and a 2-hour infusion of CDDP 70 mg/m² on day 1 and day 29 (Japan Clinical Oncology Group: JCOG9708 regimen) (12). Three patients received a continuous infusion of 5-FU 400 mg/m² on days 1-5, days 8-12, days 36-41, and days 43-48, and a 2-hour infusion of CDDP 40 mg/m² on day 1, day 8, day 36, and day 43 (similar to the JCOG9906 regimen) (13).

Local tumor response was evaluated using neck, chest, and abdominal CT with contrast enhancement according to the Response Evaluation Criteria in Solid Tumors (RECIST) (14). Adverse effects induced by CRT were assessed according to the National Cancer Institute Common Toxicity Criteria version 2.0.

Results

The characteristics of the patients who received CRT for recurrent lesions are summarized in Table 1. One patient was at pathological stage 0, 2 patients were at stage I, 2 were at stage II, and 5 were at stage III. CRT was discontinued in 1 patient because of a tracheo-mediastinal fistula on day 17. The other patients were treated according to the initial schedule.

A complete response (CR) was obtained in 4 patients (40%), and a partial response (PR), in 4 patients (40%). Thus, the overall CRT response rate (CR+PR) for loco regional recurrence of esophageal SCC was 80%. The histological type was a well-differentiated squamous cell carcinoma in 3 of the 4 people where CR was obtained (Table 2).

Table 3 shows the incidence of acute toxicity. Adverse short-term events were noted in 9 patients: 6 patients developed grades 2 and 3 leukopenia, 3 patients had grades 2 and 3 anemia, and 4 patients had nausea and appetite loss of grades 2 and 3.

Table 1. Characteristics of patients.

Gender	male 9	female 1
Age (years)	median 59.5 (range 52-73)	
Pathological stage	0	1
	I	2
	II	2
	III	5
Time to recurrence (day)	median 279,5 (range 112-749)	
Survival after CRT (day)	median 576 (range 111-1589)	
Adjuvant therapy (5-FU/CDDP)		
No	5	
Pre operative	4	
Post operative	1	

In addition, one case of grade 3 tracheomediastinal fistula dropped out of treatment. Mediastinitis was improved by antibiotic infusion. Late-stage grade 3 pneumonitis occurred in 1 case, and medication and oxygen administration were required. Furthermore, 1 patient experienced grade 3 bleeding from a reconstructed gastric tube and needed a transfusion and hyperbaric oxygen therapy.

The 1-, 3-, and 5-year survival rates after recurrence for all 10 patients were 60%, 50%, 25% respectively, and the median survival time was 19 months (Fig. 1).

Discussion

The prognosis for patients with recurrent esophageal cancer after radical esophagectomy is

Table 3. Acute toxicity with CRT.

Acute toxicities	Toxicity grades, n			
	Grade 1	Grade 2	Grade 3	Grade 4
Hoematological				
Neutropenia	2	1	4	1
Anemia	2	2	1	
Thrombocytopenia	2			
Non-hoematological				
Digestive tract side effects	2	2	2	

poor, and the median survival time for these patients is estimated to be approximately 5–10 months (4, 15–17). Some studies have shown that RT and CRT have an effect on loco regional recurrence of esophageal SCC (7-10, 18). Our retrospective study also shows the effectiveness of CRT using 5-FU and CDDP for loco regional recurrence after radical esophagectomy. CR occurred in 40% of patients, and the median survival time after recurrence in these patients was 41 months. The treatment also has survival benefit for loco regional postoperative recurrence of esophageal cancer.

Chemoradiation therapy regimens using 5-FU and CDDP have been documented (7-11, 18, 19). We used a standard regimen of 5-FU and CDDP as indicated in the JCOG study (12, 13). It was important to use this standard regimen because it had been shown to have an effect in previous studies.

Several studies have shown the effect of CRT on primary esophageal cancer (11-13), and CRT for

Table 2. Clinical data of each patient.

No.	Gender	Age	Stage	Chemo	Effect of CRT	Pathology	Survival after CRT	State of the patients
1	M	71	II	FP700/70	SD	mod SCC	111	dead
2	M	52	III	FP700/70	PR	mod SCC	225	dead
3	M	58	I	FP400/40	PR	mod SCC	230	dead
4	F	55	III	FP700/70	SD	mod SCC	336	dead
5	M	57	III	FP400/70	PR	mod SCC	403	dead
6	M	71	III	FP700/70	CR	well SCC	794	alive
7	M	61	II	FP700/70	PR	mod SCC	848	alive
8	M	58	III	FP700/70	CR	well SCC	1067	alive
9	M	61	0	FP700/70	CR	well SCC	1409	dead
10	M	73	I	FP400/40	CR	mod SCC	1589	alive

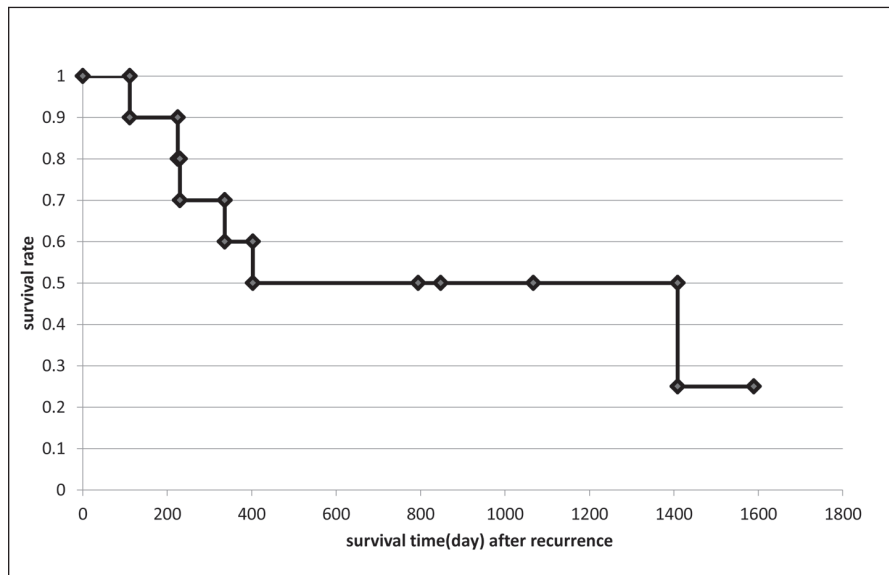


Figure 1. Overall survival rate of patients treated by CRT for loco regional recurrence after radical esophagectomy for squamous cell carcinoma of the esophagus.

loco regional recurrence of esophageal cancer could potentially be a curative treatment. In fact, the standard treatment strategy in Japan for resectable advanced esophageal cancer is neoadjuvant chemotherapy using 5-FU combined with CDDP and radical esophagectomy (20). In our study, 4 patients received adjuvant chemotherapy using 5-FU and CDDP prior to surgery: 2 of these achieved CR following CRT for recurrence and 2 showed PR after adjuvant therapy.

The clinico-pathological feature of the CR cases was well-differentiated SCC in 3 of the 4 patients. There was no correlation between the effect of salvage CRT on recurrent tumor size and the number of lymph nodes. The law regarding the effect of radiation therapy is better evidenced in undifferentiated tumors, and the tumor size is also critical for the effect. These theories were not confirmed in our experience; however, some gene-repairing biomarkers have been shown to relate to radiation therapy effectiveness in the case of cervical cancer (21, 22). Thus differences in radiation therapy outcome may become apparent from examination of some tumor differentiation biomarkers in esophageal cancer.

Acute toxicity of grades 2 and 3 caused by CRT occurred at a high rate. However, supportive therapy for chemotherapy has improved, and CRT is now more acceptable for recurrence patients. In our study, a fatal adverse event occurred in 1 case because of a

tracheo-mediastinal fistula. Additionally, bleeding from a reconstructed gastric tube occurred at a late phase in 1 case. Since it is hard to predict fatal adverse events, careful observation is necessary during and after CRT.

In conclusion, CRT using standard dose 5-FU and CDDP for loco regional postoperative recurrence of esophageal SCC was an effective therapy, but attention to severe adverse events also proved necessary.

References

1. Port JL, Nasar A, Lee PC, *et al.* Definitive Therapy for Isolated Esophageal Metastases Prolongs Survival. *Ann Thorac Surg* 2012; 94: 413-20.
2. Miyata H, Yamasaki M, Kurokawa Y, *et al.* Survival Factors in Patients with Recurrence After Curative Resection of Esophageal Squamous Cell Carcinomas. *Ann Surg Oncol* 2011; 18: 3353-61.
3. Kato H, Fukuchi M, Miyazaki T, *et al.* Classification of recurrent esophageal cancer after radical esophagectomy with two- or three-field lymphadenectomy. *Anticancer Res* 2005; 25: 3461-8.
4. Nakagawa S, Kanda T, Kosugi S, *et al.* Recurrence pattern of squamous cell carcinoma of the thoracic esophagus after extended radical esophagectomy with three-field lymphadenectomy. *J Am Coll Surg* 2004; 198: 205-11.
5. Hironaka S, Ohtsu A, Boku N, *et al.* Nonrandomized comparison between definitive chemoradiotherapy and radical surgery in patients with T(2-3)N(any)M(0) squamous

- cell carcinoma of the esophagus. *Int J Radiat Oncol Biol Phys* 2003; 57: 425-33.
6. Ariga H, Nemoto K, Miyazaki S, *et al.* Prospective comparison of surgery alone and chemoradiotherapy with selective surgery in resectable squamous cell carcinoma of the esophagus. *Int J Radiat Oncol Bio Pys* 2009; 75: 348-56.
 7. Jingu K, Nemoto K, Matsushita H, *et al.* Results of radiation therapy combined with nedaplatin (cis-diammine-glycopolatinum) and 5-Fluorouracil for postoperative loco-regional recurrent esophageal cancer. *BMC Cancer* 2006; 6: 50-9.
 8. Baxi SH, Burmeister B, Harvey JA, *et al.* Salvage definitive chemo-radiotherapy for locally recurrent oesophageal carcinoma after primary surgery: Retrospective review. *J Med Imaging and Radiation Oncology* 2008; 52: 583-7.
 9. Yamashita H, Nakagawa M, Tago N, *et al.* Salvage radiotherapy for postoperative loco-regional recurrence of esophageal cancer. *Dis Esophagus* 2005; 18: 215-20.
 10. Al-sarraf M, Martz K, Herskovic A, *et al.* Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. *J Clin Oncol* 1992; 15: 277-84.
 11. Cooper JS, Herskovic A, Macdonald JS, *et al.* Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 58-01). Radiation Therapy Oncology Group. *JAMA* 1999; 281: 1623-7.
 12. Kato H, Sato A, Fukuda H, *et al.* A phase II trial of chemoradiotherapy for stage I esophageal squamous cell carcinoma: Japan Clinical Oncology Group Study (JCOG9708). *Jpn J Clin Oncol* 2009; 39: 638-43.
 13. Kato K, Muro K, Minashi K, *et al.* Phase II study of chemoradiotherapy with 5-fluorouracil and cisplatin for Stage II-III esophageal squamous cell carcinoma: JCOG trial (JCOG 9906); Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group (JCOG). *Int J Radiat Oncol Biol Phys* 2011; 81: 684-90.
 14. Therasse P, Van Glabbeke M, Van Oosterom AT, *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United State, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; 92: 205-16.
 15. Mariett C, Balon JM, Piessen G, *et al.* Pattern of recurrence following complete resection of esophageal carcinoma and factors predictive of recurrent disease. *Cancer* 2003; 97: 1616-23.
 16. Matsubara T, Ueda M, Takahashi T, *et al.* Localization of recurrent disease after extended lymph node dissection for carcinoma of the thoracic esophagus. *J Am Coll Surg* 1996; 182: 340-6.
 17. Hulscher JB, Van Sandick JW, Tijssen JG, *et al.* The recurrence pattern of esophageal carcinoma after transhiatal resection. *J Am Coll Surg* 2000; 191: 143-8.
 18. Nishimura Y, Koike R, Nakamatsu K, *et al.* Concurrent chemoradiotherapy with protracted infusion of 5-FU and Cisplatin for postoperative recurrent or residual esophageal cancer. *J Clin Oncol* 2003; 33: 341-5.
 19. Tsuchida E, Sakai K, Matsumoto Y, *et al.* Concurrent chemoradiotherapy using low dose continuous infusion of 5-fluorouracil for postoperative regional lymph node recurrence of esophageal squamous cell carcinoma. *Esophagus* 2005; 2: 25-31.
 20. Ando N, Kato H, Igaki H, *et al.* A randomized trial Comparing Postoperative Adjuvant Chemotherapy with Cisplatin and 5-Fluorouracil Versus Preoperative Chemotherapy for Localized Advanced Squamous Cell Carcinoma of Thoracic Esophagus (JCOG9907) *Ann Surg Oncol* 2012; 19: 68-74.
 21. Kitahara O, Toyomasa Katagiri T, Tsunoda T, *et al.* Classification of sensitivity or resistance of cervical cancers to ionizing radiation according to expression profiles of 62 genes selected by cDNA microarray analysis. *Neoplasia* 2002; 4: 295-303.
 22. Wilson CR, Davidson SE, Margison GP, *et al.* Expression of Ku70 correlates with survival in carcinoma of the cervix. *Br J Cancer* 2000; 83: 1702-6.
- Received: 9.1.2014
Accepted: 28.4.2014
Address: Yoshihide Asaumi
Fukui Prefectural Hospital, Department of Surgery
910-8526 Fukui
Yotsui 2-8-1 Fukui City Fukui Prefecture, Japan
Tel. +81-776-54-5151
E-mail: yasaumi@hb.tp1.jp