

Resecting an Unresectable Tumor?

Shunzo Hatooka, MD

Introduction

Esophageal cancer is a highly malignant disease. The direct tumor invasion of adjacent organs is a highly advanced disease in patients with thoracic esophageal cancer. This invasive tumor is categorized as T4 in the TNM staging system. Data from Japanese tumor registries indicate that the incidence of clinical stage T4 is 15.2%, second only to clinical stage T3 at 37.6%.¹⁾ The results of esophagectomies in patients with pathological T4 tumors remain poor, with a five-year survival rate of 9.3%.²⁾ No standard treatment for these T4 tumors is well established, despite the large population of patients with thoracic esophageal cancer.

A computed tomographic scan of the chest and abdomen with intravenous contrast medium is used to detect metastatic disease and to establish the depth of tumor invasion. The detection accuracy of aortic involvement or tracheal invasion exceeds 90%, but is not yet 100%.³⁾ Therefore clinical T4 disease includes tumors that are assessed as absolutely unresectable or as presumably resectable if neoadjuvant therapy is given. At our institution, these presumably resectable tumors are treated as T3.5.

Three treatment options are available for patients with locally advanced cancers: definitive chemoradiation therapy (CRT), neoadjuvant CRT followed by surgery, and surgery followed by CRT. Fujita et al.⁴⁾ reported a prospective nonrandomized trial in which esophagectomy followed by CRT was compared with CRT followed by esophagectomy. The CRT-first group showed a significantly better five-year survival rate than the esophagectomy-first group (26% vs. 0%, respectively). Definitive CRT and neoadjuvant CRT

followed by surgery have been generally used in patients with clinical stage T4 disease.

Definitive CRT

Definitive CRT has curative potential in patients with locally advanced esophageal cancer. Ohtsu et al.⁵⁾ described 44 patients with clinical stage T4 and/or M1 lymph-node squamous cell carcinoma who received definitive CRT. The patients received two cycles of 5-fluorouracil (5-FU; 400 mg/m² per 24 hours on days 1–5 and 8–12) and cisplatin (40 mg/m² on days 1 and 8). Radiation therapy (60 Gy at 2 Gy/day) was given concurrently for six weeks, followed by two cycles of 5-FU (800 mg/m² per 24 hours for five days) and cisplatin (80 mg/m² on day 1). Nine (25%) of the 36 patients with T4 disease achieved a complete response, and the three-year survival rate of the 36 was 14%.

Definitive CRT was used by the Japan Clinical Oncology Group (JCOG 9516) to treat treated patients with clinical stage T4 and/or M1 lymph-node squamous cell carcinoma.⁶⁾ The patients received two cycles of 5-FU (700 mg/m² per 24 hours for four days) and cisplatin (70 mg/m² on day 1). Radiation therapy (60 Gy at 2 Gy/day) was given concurrently for six weeks. The complete response rate was 15%, and the two-year survival rate was 31.5%. In Japan, the nonsurgical treatment for locally advanced esophageal carcinoma is CRT (chemotherapy: cisplatin and 5-FU; radiation therapy: 60 Gy).

Conversely, the Radiation Therapy Oncology Group (RTOG) 85-01 trial⁷⁾ randomly assigned patients with squamous cell carcinoma or adenocarcinoma of the esophagus to radiation alone or CRT. Patients in the CRT group received four cycles of 5-FU (1000 mg/m² per 24 hours for four days) and cisplatin (75 mg/m² on day 1). Radiation therapy (50 Gy at 2 Gy/day) was given concurrently for five weeks. Patients in the radiation-only group received 64 Gy. The patients who received CRT had a significantly longer median survival relative to that of the radiation-only group (14 months vs. 9 months, respectively) and a higher five-year survival rate (26% vs. 0%, respectively). To improve these positive results, the INT 0123

From Department of Thoracic Surgery, Aichi Cancer Center Hospital, Nagoya, Japan

Received March 16, 2010; accepted for publication March 29, 2010
Address reprint requests to Shunzo Hatooka, MD: Department of Thoracic Surgery, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan.

©2010 The Editorial Committee of *Annals of Thoracic and Cardiovascular Surgery*. All rights reserved.

(RTOG 94-05) trial⁸) compared CRT using high-dose (64.8 Gy) vs. standard-dose (50.4 Gy). No significant difference was noted in median survival (13.0 vs. 18.1 months, respectively) or two-year survival (31% vs. 40%, respectively). The higher radiation dose did not increase survival. Based on these results, a combination of radiation therapy (50.4 Gy at 1.8 Gy/day) and concurrent chemotherapy (as in RTOG 85-01) is the standard protocol (known as the RTOG protocol) for nonsurgical treatment in Western countries.

Neoadjuvant CRT followed by surgery

Yano et al.⁹) described 45 patients with T4 tumors who received neoadjuvant CRT (40 Gy) followed by surgery. After CRT, 28 (62%) of the 45 patients underwent surgery. Eight (29%) of the 28 achieved a complete pathological response, and the 20 (71%) others had an R0 resection. The median survival time with surgery was 32 months, and a favorable outcome was achieved with CRT and surgery.

Fujita et al.¹⁰) also reported a prospective nonrandomized trial in patients with T4 esophageal carcinoma, comparing CRT (36 Gy) with and without surgery. Among the responders, the five-year survival rate of 23% was the same in both groups. Among the nonresponders, patients who underwent surgery showed a tendency to survive longer than those who did not. Definitive CRTs were preferred for responders and esophagectomies for nonresponders.

In contrast, Ikeda et al.¹¹) described 37 patients with clinical stage T4 tumors who received definitive CRTs. Later, 12 of the 13 patients who had undergone salvage surgery had an R0 resection. The five-year survival rate was 57% among these 13 patients. Thus a good clinical outcome was observed in patients treated with definitive CRTs followed by salvage surgery.

Difference between definitive CRT and neoadjuvant CRT

The main difference between definitive and neoadjuvant CRT is the radiation dose. It ranges from 20 Gy to 45 Gy in neoadjuvant trials, whereas more than 50 Gy is generally considered to be definitive. Most combination chemotherapy drug regimens used cisplatin and 5-FU. A difference of only 10 Gy in the radiation dose is estimated to be small if the definitive dose is 50.4 Gy, as in Western countries. Therefore the major difference between these two therapies may be whether or not an operation is scheduled.

Benefits from surgery after CRT

The benefits of surgery after CRT are unknown. Two important randomized trials have been conducted for the treatment of locally advanced esophageal carcinoma (French and German studies). These trials concluded that the addition of surgery after CRT confers no survival benefits.

The French study¹²) randomized 259 patients with a tumor response to CRT into two groups, one treated with either surgery, the other with continued CRT. There was no significant difference in the two-year survival rates of the two (34% vs. 40%, respectively) or in the two-year local control rate (66% vs. 57%, respectively).

The German study¹³) randomized 172 patients with T3 or T4 tumors for treatment with induction chemotherapy followed by CRT (40 Gy); this was then followed by surgery or with the same chemotherapy followed by CRT (65 Gy). The survival data were identical for the two groups in terms of the two-year survival rate (40% vs. 35%, respectively). Local control was better in the group treated with surgery. The clinical tumor response to induction chemotherapy was the only independent prognostic factor. Among responders to chemotherapy, the survival data did not differ, being consistent with the study by Fujita et al. and with the French study.^{10,12}) Among the nonresponders to chemotherapy, the survival data were poor in the definitive CRT group, whereas surgery improved survival, especially if complete resection was achieved. These findings are compatible with the results of the study by Fujita et al.¹⁰)

Conclusion

Patients with clinical stage T4 esophageal tumors should receive definitive CRT (the RTOG protocol), and if their response to it is poor, salvage esophagectomy should be performed only in those patients for whom complete surgical resection is confidently expected.

References

1. Ide H, Ozawa S, Matsubara H, Saito T, Shinoda M, et al. Comprehensive Registry of Esophageal Cancer in Japan, 2000. *Esophagus* 2009; **6**: 27–47.
2. Ozawa S, Tachimori Y, Baba H, Matsubara H, Muro K, et al. Comprehensive Registry of Esophageal Cancer in Japan, 2001. *Esophagus* 2009; **6**: 95–110.
3. Devita VT, Hellmann S and Rosenberg SA. *Cancer Principles and Practice of oncology*. Philadelphia: Lippincott Williams & Wilkins, 2008; pp 989–1043.

4. Fujita H, Sueyoshi S, Tanaka T, Tanaka Y, Sasahara H, et al. Prospective non-randomized trial comparing esophagectomy-followed-by-chemoradiotherapy versus chemoradiotherapy-followed-by-esophagectomy for T4 esophageal cancers. *J Surg Oncol* 2005; **90**: 209–19.
5. Ohtsu A, Boku N, Muro K, Chin K, Muto M, et al. Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. *J Clin Oncol* 1999; **17**: 2915–21.
6. Ishida K, Ando N, Yamamoto S, Ide H, Shinoda M. Phase II study of cisplatin and 5-fluorouracil with concurrent radiotherapy in advanced squamous cell carcinoma of the esophagus: a Japan Esophageal Oncology Group (JEOG)/Japan Clinical Oncology Group trial (JCOG9516). *Jpn J Clin Oncol* 2004; **34**: 615–9.
7. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA* 1999; **281**: 1623–7.
8. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol* 2002; **20**: 1167–74.
9. Yano M, Tsujinaka T, Shiozaki H, Inoue M, Doki Y, et al. Concurrent chemotherapy (5-fluorouracil and cisplatin) and radiation therapy followed by surgery for T4 squamous cell carcinoma of the esophagus. *J Surg Oncol* 1999; **70**: 25–32.
10. Fujita H, Sueyoshi S, Tanaka T, Tanaka Y, Matono S, et al. Esophagectomy: is it necessary after chemoradiotherapy for a locally advanced T4 esophageal cancer? Prospective nonrandomized trial comparing chemoradiotherapy with surgery versus without surgery. *World J Surg* 2005; **29**: 25–30.
11. Ikeda K, Ishida K, Sato N, Koeda K, Aoki K, et al. Chemoradiotherapy followed by surgery for thoracic esophageal cancer potentially or actually involving adjacent organs. *Dis Esophagus* 2001; **14**: 197–201.
12. Bedenne L, Michel P, Bouche O, Milan C, Mariette C, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. *J Clin Oncol* 2007; **25**: 1160–8.
13. Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol* 2005; **23**: 2310–7.