# Proton Beam Therapy with High-Dose Irradiation for Superficial and Advanced Esophageal Carcinomas[1]

**Shohei Koyama[2] and Hirohiko Tsujii[3]**

Department of Internal Medicine [S. K.], and Proton Medical Research Center [H. T.], Institute of Clinical Medicine, University of Tsukuba, Tsukuba-City, Ibaraki 305-8575, Japan

## ABSTRACT

***Purpose:*** **With the aim of improving the results of treatment for esophageal carcinoma, we have investigated the efficacy and toxicity associated with the use of a 250-MeV proton beam for radical radiation therapy in esophageal carcinoma.**

***Experimental Design:*** **Thirty patients with esophageal carcinoma (superficial, $n = 13$; advanced, $n = 17$) had been treated with proton beam therapy alone or with photon therapy followed by proton beam therapy. In combination therapy with photon and proton beams, one fraction dose was 1.8–2.0 Gy for photon and 2.5–3.7 Gy (mean, 3.1 Gy) for proton beam. In proton beam therapy alone, one fraction dose was 3.1–3.6 Gy (mean, 3.2 Gy). Overall mean total doses of the irradiation were 77.7 Gy in superficial carcinoma and 80.7 Gy in advanced carcinoma, respectively.**

***Results:*** **Mean overall actuarial survival in patients with superficial and advanced carcinomas was 60.1 and 38.6 months, respectively. The local recurrence and disease-specific survival rates for patients with superficial carcinoma were 0 and 100% at 5 years, and 0 and 87.5% at 10 years, respectively; the same rates for the patients with advanced carcinoma were 56.6 and 49.0% at 5 years, 78.3 and 38.1% at 10 years, respectively. Radiation-induced esophageal ulcer without injury of adjacent organs occurred in 20 (66.7%) of 30 treated patients.**

***Conclusions:*** **Better local control and 5- and 10-year disease-specific survival rates were achieved by a higher dose of irradiation with well-defined proton fields in superficial and advanced esophageal carcinomas.**

## INTRODUCTION

In the treatment of advanced esophageal carcinoma, conventional X-ray (photon) radiotherapy alone has been reported to have a 5-year survival rate with disappointing results of only 6–10% (1–7). Such unfavorable results of the treatment may be caused by the inclusion of patients who have large tumor with stricture, regional lymph node metastasis, or poor medical condition in the case of indication for radiotherapy. Another critical reason may be the delivery of inadequate doses to the primary tumor and/or poor targeting technique. Thus, radiotherapy alone has resulted in frequent local failure, local recurrence, and distant metastasis. Recently, however, the radiation has been combined with chemotherapy as primary treatment to achieve successful results (4–7). These studies produced a significant survival advantage for patients with localized esophageal cancer who received chemoradiotherapy, although the 3- and 5-year survival rates were still low.

On the other hand, esophageal cancer characteristically presents late in the course of disease because of the relatively asymptomatic interval from the onset of disease to diagnosis. However, the detection rate of superficial esophageal cancer has gradually increased in Japan, mainly because of the availability of Lugol dye endoscopy (8). Accordingly, the effectiveness of definitive radiation therapy in superficial esophageal carcinoma has extensively been studied by Japanese study groups (9, 10). Excellent local control and survival rates have been reported.

To further improve the results of treatment in patients with esophageal carcinoma, IBT[4] has been proposed as a "boost" to the primary tumor, allowing potentially increasing tumor control and relative sparing of the surrounding normal tissues (11–14). In applying a similar concept, high-energy (250 MeV) proton beams have been introduced for esophageal carcinoma in our Institute (15, 16). Proton beams have a distinct physical advantage over photons. The beams produce little side scatter and stop abruptly at any prescribed depth. The pattern of energy deposition is characterized by the Bragg peak, wherein the dose is minimal on entry and reaches a maximum at the stopping region, which is planned to occur in the target volume (17). Proton beams can be shaped to deliver homogeneous radiation doses to irregular three-dimensional volumes such as those required for esophageal carcinoma. This makes it possible to deliver high doses of tumor irradiation to the target volume while simultaneously reducing the amount of photons reaching normal esophageal or adjacent normal tissues. We have administered substantially high radiation doses (>70 Gy) with a fraction size larger than 2.5 Gy. The importance of proton beam therapy to improve local disease control and survival for patients with esophageal carcinoma has been suggested in the previously

Received 12/5/02; revised 3/3/03; accepted 3/26/03.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

[1] Supported in part by a grant-in-aid for Scientific Research (No. 12670455 to S. K.) from the Ministry of Education, Science, Sports, Culture and Technology in Japan.

[2] To whom requests for reprints should be addressed, at Department of Internal Medicine, Institute of Clinical Medicine, University of Tsukuba, Tsukuba-City, Ibaraki 305-8575, Japan. Phone: 81-29-853-3210; Fax: 81-29-853-3039; E-mail: s-koyama@md.tsukuba.ac.jp.

[3] Present address: Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba 263-8555, Japan.

[4] The abbreviations used are: IBT, intraluminal brachytherapy; CR, complete response; CT, computed tomography.

*Table 1* Patient characteristics, dose of irradiation, efficacy, and toxicity in superficial esophageal carcinoma

| | | | | | Doses (Gy) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case no. | Age/ Sex | Site | Length (cm) | Stage | X-ray | Proton | Proton/ 1fr[a] | Total | Local response | Local recurrence | Survival (mo) | Ulcer | Stricture | Cause of death |
| 1 | 67/M | Im | 1.5 | I | 16.2 | 52.9 | 2.65 | 69.1 | CR | None | 72 | − | − | Respiratory failure caused by pneumonia |
| 2 | 77/M | Ei | 1.5 | I | 50.4 | 30.0 | 3.00 | 80.4 | CR | None | 66 | + | + | Ileus caused by Crohn's disease |
| 3 | 83/M | Im | 2.0 | I | 50.0 | 36.5 | 3.65 | 86.5 | CR | None | 123 | + | − | Old age |
| 4 | 69/F | Im | 2.0 | I | 40.0 | 45.0 | 3.46 | 85.0 | CR | None | 7 | + | − | Cardiac failure caused by Epstein anomaly |
| 5 | 64/M | Im | 2.0 | II | 40.0 | 45.5 | 3.50 | 85.5 | CR | None | 61 | + | − | Esophageal cancer death |
| 6 | 72/M | Im | 3.0 | I | 0 | 79.0 | 3.16 | 79.0 | CR | None | 58 | − | − | Second malignancy caused by brain tumor |
| 7 | 85/F | Ea | 2.0 | I | 0 | 75.0 | 3.13 | 75.0 | CR | None | 85 | + | + | Second malignancy caused by gastric cancer |
| 8 | 75/M | Ei | 3.0 | I | 30.6 | 50.0 | 2.78 | 80.6 | CR | None | 8 | + | + | Esophageal bleeding |
| 9 | 45/M | Im | 3.0 | I | 30.6 | 39.0 | 3.00 | 69.6 | CR | None | 66 | + | − | Respiratory failure caused by pneumonia |
| 10 | 86/M | Ei | 2.5 | I | 50.0 | 25.0 | 2.50 | 75.0 | CR | None | 9 | + | − | Respiratory failure caused by pneumonia |
| 11 | 62/M | Ei | 2.0 | I | 40.0 | 31.0 | 2.82 | 71.0 | CR | None | 114 | − | − | Respiratory failure caused by pneumonia |
| 12 | 68/M | Iu | 3.0 | I | 40.0 | 36.0 | 3.00 | 76.0 | CR | None | 101 (alive) | − | − | None (alive) |
| 13 | 70/F | Im | 2.0 | I | 41.4 | 36.0 | 3.00 | 77.4 | CR | None | 11 | + | − | Hepatic failure caused by liver cirrhosis |

[a] 1fr, fraction dose; Im, midthoracic esophagus; Ei, lower thoracic esophagus; Ea, abdominal esophagus; Iu, upper thoracic esophagus.

reported early analysis of the study (15, 16). A similar clinical approach using proton beams has been applied to five patients with esophageal carcinoma in another institution (18).

This study was undertaken to further assess the efficacy and toxicity of proton beam therapy and the first long-term survival beyond 5 years in superficial and advanced carcinomas. We describe how proton beam therapy, with a high dose of irradiation delivered by a well-defined proton field, results in excellent local control and survival.

## MATERIALS AND METHODS

**Patients.** From October 1985 to June 1994, 36 patients with esophageal cancer were registered to receive proton beam irradiation at the Tsukuba University Hospital. In this clinical trial, patients were selected for the following reasons: refused surgery, advanced age, medical inoperability, and technical unresectability. Patients were considered ineligible if they had a disease metastasis to distant sites, such as lung or liver; if they had a second primary malignancy simultaneously; if they had undergone previous external irradiation; if they were incapable of self-care; or if informed consent could not be fully obtained. Thirty of 36 patients entered in the analysis were treated with a curative intent for their primary tumors and were followed up until death. The clinical characteristics of these 30 patients (26 male and 4 female) are shown in Tables 1 and 2. Patients' ages ranged from 45 to 95 years with a mean of 70.2 ± 2.2 (mean ± SE) years. Thirteen patients (mean age, 71.0 years; range, 45–86 years; Table 1) had superficial carcinoma; the other 17 patients (mean age, 70.0 years; range, 50–95 years; Table 2) had advanced carcinoma. Superficial (cancerous invasion was limited to the mucosa or submucosa) and advanced (cancerous invasion reached or penetrated to proprietary muscle or adventitia) esophageal carcinoma have been defined by the guidelines for clinical and pathological studies on carcinoma of the esophagus (19). Histological assessments, made from biopsy specimens taken from the esophageal lesions, showed that 29 patients had squamous cell carcinoma and one patient (case 7) had tubular adenocarcinoma. Tumor was located in the upper third in 3 patients (10.0%), the middle third of the thoracic esophagus in 19 (63.3%), the lower third of the thoracic esophagus in 7 (23.3%), and in the abdominal esophagus in 1 (3.3%). The esophageal tumor length had been determined from the barium swallow studies and endoscopic findings, taking the longest of the two available determinations. The mean length of the superficial carcinoma was 2.3 cm (range, 1.5–3.0 cm), and of the advanced carcinoma was 6.4 cm (range, 3.0–15.0 cm). The depth of cancerous invasion of the esophageal wall ($T_1$ to $T_3$) had been evaluated by X-ray and endoscopic examinations according to the guidelines for clinical and pathological studies on carcinoma of the esophagus (19) and for radiotherapy in the treatment of esophageal carcinoma (20). Extension of the tumor to adjacent structures (T4) and the presence of regional lymph node metastasis had been assessed by CT images. Taken together with these findings, clinical staging had been defined by Union International Contre Cancer (UICC)-tumor-node-metastasis (TNM) classification of esophageal carcinoma (21). The clinical staging of all of the patients for the retrospective analysis was finally reevaluated and was confirmed. As a result, 12 of 13 patients with superficial carcinoma revealed stage I, and most (94.1%) of 17 patients with advanced carcinoma were identified as stage III.

**Radiation Therapy.** Proton beam therapy was given at the Proton Medical Research Center of the University of Tsukuba, with a 250-MeV-proton-beam generator by the booster synchrotron of the National Institute for High Energy Physics in Tsukuba City. For precise localization and identifi-

Table 2 Patient characteristics, dose of irradiation, efficacy, and toxicity in advanced esophageal carcinoma

| Case no. | Age/Sex | Site | Length (cm) | Stage | Doses (Gy) X-ray | Proton | Proton/1fr[a] | Total | Local response | Local recurrence | Survival (mo) | Ulcer | Stricture | Cause of death |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 14 | 77/M | Im | 8.5 | III | 30.6 | 53.0 | 2.94 | 83.6 | CR | None | 19 | + | + | Respiratory failure caused by lung tuberculosis |
| 15 | 60/M | Im | 6.0 | III | 0 | 86.5 | 3.09 | 86.5 | CR | None | 10 | + | − | Esophageal bleeding |
| 16 | 62/M | Im | 6.0 | II | 0 | 89.5 | 3.09 | 89.5 | CR | None | 6 | + | + | Hepatic failure caused by liver cirrhosis |
| 17 | 50/M | Im | 9.0 | III | 0 | 85.0 | 3.27 | 85.0 | Failure | Failure | 5 | − | − | Esophageal cancer death (local failure) with esophageal bleeding |
| 18 | 84/M | Iu | 15.0 | III | 50.4 | 33.0 | 3.67 | 83.4 | CR | None | 32 | − | − | Respiratory failure caused by pneumonia |
| 19 | 51/M | Im | 7.0 | III | 50.4 | 32.4 | 2.95 | 82.8 | CR | Yes (44)[b] | 132 | − | − | Hepatic failure caused by hepatoma |
| 20 | 73/M | Im | 7.0 | III | 50.4 | 35.0 | 2.92 | 85.4 | CR | Yes (8)[b] | 18 | − | − | Esophageal cancer death |
| 21 | 85/M | Im | 3.0 | III | 0 | 75.5 | 3.60 | 75.5 | CR | None | 11 | + | + | Respiratory failure caused by pneumonia |
| 22 | 69/M | Im | 7.5 | III | 30.6 | 54.5 | 3.41 | 85.1 | CR | None | 7 | + | − | Cardiac failure caused by ischemic heart disease |
| 23 | 82/F | Im | 4.0 | III | 41.4 | 39.0 | 3.00 | 80.4 | CR | Yes (16)[b] | 35 | + | + | Esophageal cancer death |
| 24 | 63/M | Iu | 5.0 | III | 51.6 | 34.0 | 2.61 | 85.6 | CR | None | 128 (alive) | − | − | None (alive) |
| 25 | 59/M | Im | 8.0 | III | 37.8 | 33.0 | 3.00 | 70.8 | CR | Yes (75)[b] | 96 | − | − | Esophageal cancer death |
| 26 | 95/M | Ei | 3.0 | III | 40.0 | 37.0 | 3.36 | 77.0 | CR | None | 48 | + | + | Old age |
| 27 | 66/M | Ei | 6.0 | III | 40.0 | 37.0 | 3.70 | 77.0 | CR | Yes (25)[b] | 29 | + | − | Esophageal cancer death |
| 28 | 67/M | Ei | 4.0 | III | 48.0 | 27.0 | 3.00 | 75.0 | CR | Yes (27)[b] | 49 | + | − | Esophageal cancer death |
| 29 | 65/M | Im | 5.0 | III | 50.0 | 25.0 | 2.50 | 75.0 | CR | Yes (9)[b] | 11 | + | − | Esophageal cancer death |
| 30 | 76/M | Im | 3.0 | III | 50.0 | 25.0 | 2.50 | 75.0 | CR | Yes (21)[b] | 21 | + | − | Respiratory failure caused by pneumonia |

[a] 1fr, fraction dose; Im, midthoracic esophagus; Ei, lower thoracic esophagus; Ea, abdominal esophagus; Iu, upper thoracic esophagus.
[b] Values in parentheses represent onset of local recurrence (months).

cation of the irradiation field, radiopaque markers (iridium chips of 0.5 mm in diameter and 3.0 mm in length) were implanted at the proximal and distal edges of the primary tumor using an endoscopic technique. As shown in Fig. 1, proton radiation was delivered through an anterior approach. The exact method for proton beam irradiation has been described previously in detail (15–17, 22). Briefly, set-up accuracy was noted immediately using a real-time field verification system, and the patient positioning was corrected accordingly. Respiration-gated irradiation was made if the respiration-induced movement of the esophagus had exceeded 5 mm in the cranial-caudal direction. Finally, the design of a beam-shaping compensator (bolus) and isodose distributions were presented on the CT image of the representative patient with advanced esophageal carcinoma (Fig. 1). The method had insured accurate localization of the proton beam with respect to the tumor volume in this study. Thus, the target volume had been determined by setting margins around the tumor boundary as small as practical. Namely, the treatment field for proton beam included the primary tumor with an additional 1-cm margin in proximal and distal directions. The rationale of the treatment had been explained to the patients, who signed a consent form before the therapy was begun.

It was initially planned that irradiation in this clinical trial would consist of proton beam only. However, it was difficult to enroll patients effectively because of limited availability of the accelerator or a shortage of machine time (27–30 weeks/year; 3–3.5 h/day), as described previously (15, 16). Thus, proton beam therapy had been given either alone or in combination with photons. In photon therapy, five-times-a-week treatment was delivered using 10-MV X rays. Consequently, two patients with superficial carcinoma and four patients with advanced carcinoma had been treated with proton beam alone to the primary lesion. The other 11 patients with superficial carcinoma and 13 patients with advanced carcinoma had been treated with combined photon and proton beam irradiation. In the combination therapy, the patients initially received photon radiation, followed by irradiation with proton beam. Initial AP-PA portals for photon therapy were extended at least 3 cm above and below the primary tumor, with at least a 2-cm lateral margin. The treatment field included the supraclavicular fossae if the tumor originated above the level of the carina. When mediastinal nodal disease was suspected, the suspected nodes were included with an additional 1–2-cm margin. The daily fraction size ranged from 1.8 to 2.0 Gy in photon therapy, and from 2.5 to 3.7 Gy in proton therapy. The daily fraction size of the proton beam could be increased, because the proton beam has the advantage of producing a homogeneous dose distribution with a well-defined field to deeply seated tumors. Practical doses of photon and/or proton in individual patients with superficial and advanced carcinomas are summarized in Table 1 and 2, respectively. Mean total dose of irradiation for 30 esophageal cancer patients was 79.4 Gy. All of the patients were able to complete the planned irradiation without interruption; even if most patients were irradiated with substantially higher doses compared with those traditionally used (1–7). None of the patients received chemotherapy for tumor during the clinical trial; this allowed us

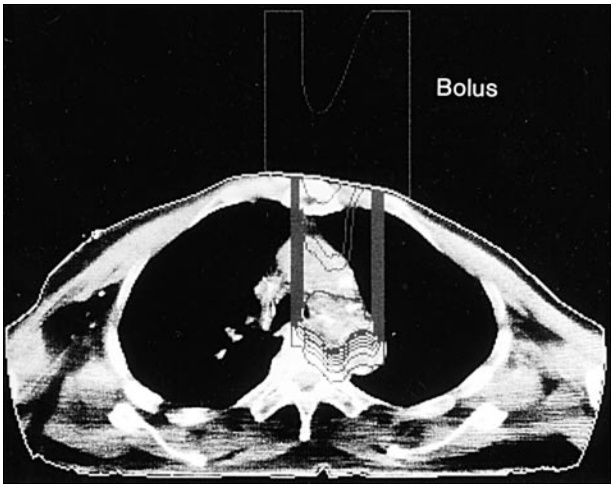


*Fig. 1* Illustration of isodose distribution curve shapes of 95, 90, 80, 50, and 10% level, and bolus shape on CT slice of patient with advanced esophageal carcinoma (single ventral field). Proton beam produced little side scatter and stopped abruptly at tumor depth. The radiation field of the proton beam avoids the spinal cord.

to precisely evaluate the efficacy and toxicity of proton beam therapy with high-dose of irradiation.

**Follow-Up.** After completion of the radiation therapy, barium swallow studies and endoscopic examinations were carried out at regular intervals, and the clinical radiation effect was evaluated according to the criteria for evaluating the therapeutic effect in the guidelines (19, 20). Briefly, local control was defined as a lack of either clinical or pathological evidence of tumor recurrence in the esophagus. Indeed, the onset of local recurrence was determined by the disease relapse confirmed by regular endoscopic and/or X-ray examinations. The duration of follow-up ranged from 5 to 132 months (median, 47.8 months). Eleven of 30 treated patients were followed up for more than 60 months, and 3 of the 11 patients were followed up for over 10 years. The survival time was judged on September 30, 2002.

**Statistical Analysis.** Overall survival, disease-specific survival, and local recurrence rates were calculated from the first date of external irradiation. Probability of disease-specific survival and local recurrence rates for patients with superficial and advanced esophageal carcinomas was calculated by using the Kaplan-Meier method (23). The statistical differences in local recurrence and survival curves during the entire follow-up period were evaluated by the log-rank test, and a $P$ of $<0.05$ was regarded as significant. The statistical analysis was performed with StatView software (SAS Institute Inc., Cary, NC).

## RESULTS

Table 1 shows the summary of irradiation doses of practical photon and proton beam, and results of their therapy in each patient with superficial esophageal carcinoma. Two patients were treated with proton beam alone with total dose of 79 Gy and 75 Gy in 25 and 24 fractions, respectively. The other 11 cases were initially treated with X rays with doses of 16.2–50.4 Gy (mean, 39.0 Gy) in 9–28 fractions, followed by proton irradiation with doses of 30.0–52.9 Gy (mean, 39.5 Gy) in 10–20 fractions (mean, 12.9 fractions), thus total combined doses were 69.1–86.5 Gy (mean, 77.8 Gy). The one-fraction dose of proton beam was 2.5–3.7 Gy (mean, 3.1 Gy). Overall mean total doses of the irradiation were 77.7 Gy in 13 patients with superficial esophageal carcinoma.

Cancerous lesions of all 13 patients with superficial carcinoma completely disappeared by the end of the proton beam therapy, and a CR was obtained in all cases (100%). CR criteria used in the study have been defined by the Japanese Society of Esophageal Disease (19). Briefly, all measurable, evaluated primary tumor lesions disappear at the end of the treatment, and no new lesions appear for at least four weeks. In all 13 cases of superficial carcinoma, there was no local recurrence throughout the long-term follow-up. One patient (case 12), however, relapsed with a small cancerous lesion outside of the upper part of the radiation field in the esophagus at 6 months after the treatment. Salvage surgery was carried out, and the patient is now alive and well. Regional lymph node metastasis (right peritracheal lymph node) occurred in one patient (case 5) 20 months after the treatment without local recurrence in the esophagus. The lymph node swelling involved in cancer was outside the area of the radiation field. He died of pleural dissemination of esophageal carcinoma. At autopsy, any local recurrent cancerous lesion could not histologically be observed in the esophageal mucosa. Eleven of 13 patients died of intercurrent diseases, as shown in Table 1. Mean overall actuarial survival for patients with superficial carcinoma was 60.1 months.

Table 2 shows the summary of practical irradiation doses of photon and proton beam, and the results of this therapy in each patient with advanced esophageal carcinoma. Four patients were treated with proton beam alone with a total dose of 75.5–89.5 Gy (mean, 84.1 Gy) in 25–29 fractions (mean, 27.5 fractions). The other 13 cases were treated with X rays with doses of 30.6–51.6 Gy (mean, 43.9 Gy) in 17–26 fractions, followed by proton beam with doses of 25.0–54.5 Gy (mean, 35.8 Gy) in 9–16 fractions (mean, 11.9 fractions); thus, total combined doses were 70.8–89.5 Gy (mean, 79.7 Gy). The one-fraction dose of proton beam was 2.5–3.7 Gy (mean, 3.1 Gy). Overall mean total doses of irradiation were 80.7 Gy in 17 patients with advanced esophageal carcinoma.

CR was obtained in 16 (94.1%) of 17 patients with advanced carcinoma; local failure occurred in one patient (5.9%; case 17). Among 16 patients who have had local control, local recurrence had been observed in 8 patients. The recurrent time from the end of the proton beam therapy was different in each case, ranging from 8 to 75 months. The mean time to recurrent progression of treated local control region was 28 months. The cumulative monthly incidental curves of local recurrence have been plotted in Fig. 2. The 5-year local-recurrence rates for patients with superficial carcinoma, advanced carcinoma, and for whole populations were 0, 56.6, and 28.9%, respectively; the 10-year rates were 0, 78.3, and 40.7%, respectively. The local recurrence rate in patients with advanced carcinoma was significantly higher than those with superficial carcinoma ($P <$ 0.0001). Concerning the pattern of local recurrence, four of eight patients showed recurrence in the middle of the tumor site treated with high-dose irradiation, but the other 4 patients (cases 19, 27, 28, and 29) revealed marginal recurrence in the field of proton beam therapy. The marginal recurrent lesion could be

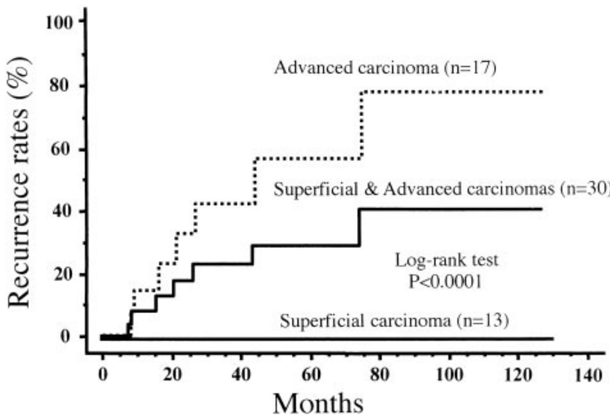


*Fig. 2* The cumulative incidental local recurrence curves for patients with superficial and advanced esophageal carcinomas. The patients with advanced esophageal carcinoma showed a significantly higher local recurrence rate compared with those of patients with superficial esophageal carcinoma ($P < 0.0001$).

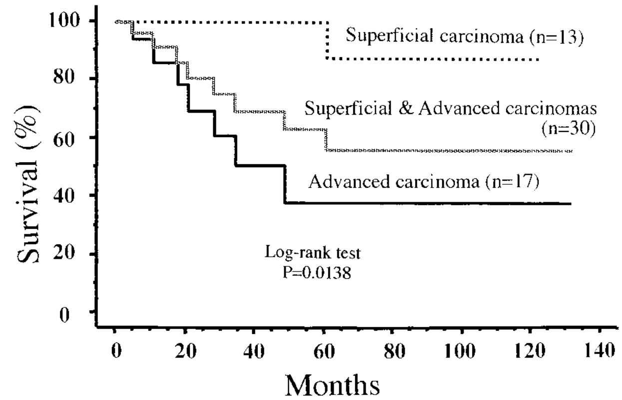


*Fig. 3* The disease-specific survival curves for patients with superficial and advanced esophageal carcinomas. The patients with superficial esophageal carcinoma showed a significantly more favorable survival rate compared with that of patients with advanced esophageal carcinoma ($P < 0.02$).

observed in the superior (cases 19 and 29) and inferior (cases 27 and 28) margins in the field of the irradiated tumor.

Six of eight patients with local recurrence were considered to have suffered disease-specific death. One patient (case 19) showed local recurrence (0-IIc type carcinoma) in the posterior wall at the oral margin of the treated tumor at 44 months after radiotherapy, as previously described in detail (16). After receiving salvage surgery, he had maintained his health, but died of hepatoma at 132 months after the irradiation. Only one patient (case 24) is still alive, and he has survived for more than 10 years without tumor recurrence. Mean overall actuarial survival for patients with advanced carcinoma was 38.6 months, but 9 of 17 patients with advanced carcinoma died of intercurrent diseases, as shown in Table 2. The disease-specific survival curves for esophageal carcinoma are plotted in Fig. 3. The survival rate at 5 years for patients with superficial carcinoma, advanced carcinoma, and for whole populations was 100, 49.0, and 67.1%, respectively; the 10-year survival rates were 87.5, 38.1, and 61.0%, respectively. The disease-specific survival rate in patients with superficial carcinoma was significantly higher than in those with advanced carcinoma ($P < 0.02$).

Acute toxicity including mucositis was minimal, followed by complete healing in 1–1.5 months. Severe late injury, esophageal ulceration, was documented in 9 (69.2%) of 13 and 11 (64.7%) of 17 patients with superficial and advanced carcinoma, respectively (Tables 1 and 2). Additional detailed findings about radiation-induced ulceration were summarized in Table 3. Onset of ulcer was variable in each case, ranging from 3 to 11 months (mean, 5.6 months) in the field of proton beam after the radiation therapy. Eleven (55%) of 20 ulcer patients were eventually healed by appropriate conservative management, such as liquid or soft food and/or i.v. hyperalimentation. Resolving time required for healed state was ranged from 0.5 to 8 months (mean, 4.4 months). Although 6 of completely healed 11 patients had been cured without any clinical sequelae, the other 5 patients had developed esophageal stricture with clinical symptoms, dysphagia. To easily swallow a food, two (cases 2 and 26) of the patients with fibrotic stricture were further treated with endoscopic balloon-dilated method. There was no case that required surgery to manage the stricture. In 7 (cases 4, 10, 13, 16, 21, 22, and 29) of 20 patients with ulceration, a healed state could not be confirmed, because the shorter survival of these patients did not allow enough observation time to evaluate the healing process of ulceration. Treatment-induced esophageal bleeding was observed in two patients (cases 8 and 15). However, there was no life-threatening esophageal perforation or fistula. The spinal cord, heart, and lung, which are the dose-limiting organs at risk, did not reveal any symptomatic late complications.

## DISCUSSION

The present study clearly demonstrates that the proton beam therapy with high-dose irradiation for superficial and advanced esophageal carcinomas has improved local control and 5- and 10-year disease-specific survival rates. These indicate that the therapy for esophageal carcinoma has potential advantages over external conventional photons. The magnitude of the advantage is an improved control of local tumors, resulting in diminishing local failure and recurrence, and lengthening survival.

In studies of superficial carcinoma treated with definitive radiation, total dose ranged from 60 to 70 Gy (mean, 65.5 Gy; Refs. 9, 10). Favorable therapeutic results have been obtained with disease-specific 5-year survival rate of 62~71%. These results reflect the fact that appropriate radiotherapy is generally more effective against tumors with a small tumor volume. In our study, proton beam therapy showed no local recurrence and 100% 5-year disease-specific survival in patients with superficial carcinoma, strongly suggesting the more improved local control and long-term survival rates. In Japan, the 5-year survival rate in patients with surgically treated superficial esophageal carcinoma has been shown to be more than 60 to 90% (24, 25). The treatment outcome in our study is approximately equal to the result of surgery. Thus, proton beam therapy with the high dose of radiation presented here for superficial carcinoma might be used as an alternative to surgery.

In conventional radiation therapy alone for advanced esoph-

*Table 3* Summary of radiation-induced ulceration

| | Ulcer, no. of cases[a] | | | | | Mean time required, mo[b] | | |
|---|---|---|---|---|---|---|---|---|
| | Incidence | Healed | Healed-unknown | Not healed | Stricture | Onset of ulcer | Resolving time for healing | Observation time in healed-unknown |
| Superficial carcinoma (13 cases) | 9 | 5 (2) | 3 (1) | 1 (0) | 3 | 5.9 (3–11) | 3.4 (0.5–7) | 2.4 (0.07–4) |
| Advanced carcinoma (17 cases) | 11 | 6 (3) | 4 (2) | 1 (0) | 5 | 5.4 (3–11) | 5.1 (0.8–8) | 3.7 (2–5) |
| Total (30 cases) | 20 | 11 (5) | 7 (3) | 2 (0) | 8 | 5.6 (3–11) | 4.4 (0.5–8) | 3.2 (0.07–5) |

[a] Values in parentheses represent numbers of patient with esophageal stricture.
[b] Values in parentheses represent range of time required (months).

ageal carcinoma, however, the total irradiation dose was 50–60 Gy in most studies (1–7). These works revealed high local-failure rates, ranging from 42 to 52% at the end of the irradiation. Indeed, in locally advanced esophageal carcinoma, Al-Sarraf *et al.* (5) have reported that the 2-year local recurrence rate is 59%, and all patients were dead by the end of 3 years in external radiation therapy (total dose of 64 Gy). This implies the persistence of cancer disease in many patients. High frequent local failure and local recurrence are the main causes of lower survival rates in the treatment with radiation alone. Hence, the key to improve the therapeutic result is the extent to which the rate of local control can be improved. As a result, there have been various recent attempts at combined therapy, such as chemoradiotherapy (4–7). The treatment delays the local recurrence, and reduces incidence of distant metastases to some degree. However, the survival could not always be lengthened. To solve the problem, high-dose-rate IBT has been investigated because IBT can distribute a large dose of radiation to the primary esophageal carcinoma. Some studies using IBT have showed improved local control and survival with increasing tumor doses in patients with superficial carcinoma (11, 12). However, unfavorable results have been obtained in patients with advanced carcinoma (13, 14). These have suggested that IBT is applicable to the small tumor with shallow invasion, but not to large tumor with deep invasion, perhaps because IBT merely enables a uniform irradiation of the former tumor, but not of the latter tumor.

In our series of proton beam therapy with high-dose irradiation, excellent local control and survival was also obtained in advanced carcinoma. It has been shown that improvement of both local control and survival can be achieved by escalating a dose of radiation to the primary tumor (26). Indeed, among 16 advanced carcinoma patients who obtained a CR, local recurrence rates were 5 (71.4%) of 7 patients irradiated with total dose of 70–80 Gy range but merely 3 (33.3%) of 9 patients with total irradiation dose of over 80 Gy, respectively. The results suggest that higher radiation dose (>80 Gy) reduces local recurrence in advanced esophageal carcinoma. In an analysis of the depth of cancerous invasion of the 17 patients with advanced carcinoma, there were 2 with $T_2$, 12 with $T_3$, and 3 with $T_4$. Also, 12 (70.6%) of 17 patients with tumor length of >5 cm was noted. Therefore, we are dealing with rather advanced large and deep tumors for the current treatment, because tumor length of >5 cm and class $T_3$ or $T_4$ has been considered as a large and deep tumor (13). Nevertheless, 5-year local recurrence rate in our cases with advanced carcinoma was lower than that of other studies of therapy with irradiation alone, chemoradiation therapy, or high-dose-rate IBT (4, 5, 7, 14). It is likely that the beneficial effect of the proton beam irradiation is attributable to the capability of delivering homogeneous dose distribution with well-defined fields to deeply seated irregular large tumor masses with deep invasion. In addition, the biological effectiveness of irradiation would be greater than that of the physical dose actually given, when large daily radiation doses (>2.5 Gy) for the therapy were administered at the tumor site. These factors may also have contributed to the favorable results obtained at Tsukuba.

The 5- and 10-year survival rates with treatment by surgery in esophageal cancer with a length 5–7 cm were shown to be 21.9% and 17.9%, respectively, and were 22.4% and 17.8% for class $T_3$-cancer, respectively, in a study of Iizuka *et al*. (27). In particular, the 5- and 10-year survival rates of patients with stage III were 17.2% and 13.8%, respectively (27). Thus, the treatment outcome of proton beam therapy in advanced carcinoma presented here is comparable with that of surgery, although the number of patients treated with proton beam is small. These findings are distinctly different from those of patients with advanced carcinoma treated by high-dose-rate IBT (13, 14). It is reasonable to conclude that proton beam therapy with high-dose of irradiation provides an effective treatment modality even in patients with advanced esophageal carcinoma.

An improvement in local control in the study could certainly lead to improved survival rates. To improve local control and survival rate, a radiation dose to primary tumor should be increased, as has been described by Suit and Westgate (26). However, the increased irradiation dose in proton beam therapy simultaneously caused higher incidence of esophageal ulcer or bleeding, as compared with that of conventional radiation therapy. The higher complication rates might also be related to the large fraction size (>2.5 Gy) of irradiation. Similar severe late complications of the esophagus, such as ulceration or fistula have been reported in high-dose-rate IBT after external irradiation (11–14). Whereas, there seems to be no definite correlation between delivered dosage for the present treatment and the incidence of ulcer formation, because mean external total dose, mean total proton dose, and mean one fraction size of proton beam in 20 patients with esophageal ulceration was 79.7, 46.6, and 3.11 Gy, respectively, but those in 10 patients without late complication were also similar values, showing 78.9, 45.1, and 3.01 Gy, respectively. Thus, high-dose of irradiation plus unknown individual factors might contribute to the incidental formation of esophageal ulcer. The unknown individual factors include how meals are consumed: the type of food (soft or solid); the amount (light or heavy); and the timing (when and how often).

We would like to emphasize that local failure and recurrences play a significant role in patient death, but a higher incidence of esophageal ulcer does not appear to be related to the survival rate in the present study. The coexistence of long-term survival rate with local control, and of increased incidence of late complications may certainly be a major paradox in the proton beam therapy with high-dose irradiation. Thus, more exact studies are needed to confirm an optimal total dose or ideal dose-fractionation schemes that will contribute local tumor control and survival rate with a decreased incidence of late complications.

Suitable conservative management has gradually relieved severe ulceration of the esophagus. In particular, i.v. hyperalimentation therapy without oral intake can be recommended in severe late complications, because the friction of solid food may injure the ulcer or the recently healed wound, and the therapy alone would accelerate wound healing to avoid development of additional ulceration and/or stenosis. Hereafter, when the patients survive longer, fibrotic stricture rather than esophageal ulcer will become a major problem. The difficulty for the patients would be managed by endoscopic balloon-dilated method or application of expandable metallic stent without surgery. These methods can contribute to maintaining the quality of life of survivors.

In conclusion, our clinical study shows that the patients with superficial and advanced carcinomas could successfully receive a high dose of proton beam therapy and tolerate it well. The study has demonstrated encouraging results in local tumor control and long-term survival that compare favorably with previously reported data using conventional external radiotherapy and/or IBT in esophageal carcinoma.

## REFERENCES


1. Earlam, R., and Cuhana-Melo, J. R. Oesophageal squamous cell carcinoma. II. A critical review of radiotherapy. Br. J. Surg., *67:* 457–461, 1980.

2. Okawa, T., Kita, M., Tanaka, M., and Ikeda, M. Results of radiotherapy for inoperable locally advanced esophageal cancer. Int. J. Radiat. Oncol. Biol. Phys., *17:* 49–54, 1989.

3. Smalley, S. R., Gunderson, L. L., Reddy, E. K., and Williamson, S. Radiotherapy alone in esophageal carcinoma: current management and future directions of adjuvant, curative and palliative approaches. Semin. Oncol., *21:* 467–473, 1994.

4. Herskovic, A., Martz, K., Al-Sarraf, M., Leichman, L., Brindle, J., Vaitkevicius, V., Cooper, J., Byhardt, R., Davis, L., and Emami, B. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N. Engl. J. Med., *326:* 1593–1598, 1992.

5. Al-Sarraf, M., Martz. K., Herskovic, A., Leichman, L., Brindle, J. S., Vaitkevicius, V. K., Cooper, J., Byhardt, R., Davis, L., and Emami, B. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. J. Clin. Oncol., *15:* 277–284, 1997.

6. Chan, A., and Wong, A. Is combined chemotherapy and radiation therapy equally effective as surgical resection in localized esophageal carcinoma? Int. J. Radiat. Oncol. Biol. Phys., *45:* 265–270, 1999.

7. Cooper, J. S., Guo, M. D., Herskovic, A., Macdonald, J. S., and Al-Sarraf, M. Chemoradiotherapy of locally advanced esophageal cancer. Long-term follow-up of a prospective randomized trial (RTOG 85-01). JAMA, *281:* 1623–1627, 1999.

8. Sugimachi, K., Ohno, S., Matsuda. H., Mori, M., and Kuwano, H. Lugol-combined endoscopic detection of minute malignant lesions of the thoracic esophagus. Ann. Surg., *208:* 179–183, 1988.

9. Okawa, T., Tanaka, M., Kita-Okawa, M., Nishio, M., Kikuchi, Y., Shirato, H., Yamada, S., Asakawa, H., Niibe, H., Dokiya, T., Tanaka, Y., Hishikawa, Y., Hirota, S., Imajo, Y., Hirokawa, Y., Hayabuchi, N., and Miyajima, N. Superficial esophageal cancer: multicenter analysis of results of definitive radiation therapy in Japan. Radiology, *196:* 271–274, 1995.

10. Nemoto, K., Matumoto, Y., Yamakawa, M., Jo, S., Ito, Y., Oguchi, M., Kokubo, N., Nishimura, Y., Yamada, S., and Okawa, T. Treatment of superficial esophageal cancer by external radiation therapy alone: results of a multi-institutional experience. Int. J. Radiat. Oncol. Biol. Phys., *46:* 921–925, 2000.

11. Akagi, Y., Hirokawa, Y., Kagemoto, M., Matuura, K., Ito, A., Fujita, K., Kenjo, M., Kiriu, H., and Ito, K. Optimum fractionation for high-dose-rate endoesophageal brachytherapy following external irradiation of early stage esophageal cancer. Int. J. Radiat. Oncol. Biol. Phys., *43:* 525–530, 1999.

12. Nishimura, Y., Okuno, Y., Ono, K., Mitsumori, M., Nagata, Y., and Hiraoka, M. External beam radiation therapy with or without high-dose-rate intraluminal brachytherapy for patients with superficial esophageal carcinoma. Cancer (Phila.), *86:* 220–228, 1999.

13. Okawa, T., Dokiya, T., Nishio, M., Hishikawa, Y., Morita, K., and Japanese Society of Therapeutic Radiology and Oncology (JASTRO) Study Group. Multi-institutional randomized trial of external radiotherapy with and without intraluminal brachytherapy for esophageal cancer in Japan. Int. J. Radiat. Oncol. Biol. Phys., *45:* 623–628, 1999.

14. Gasper, L. E., Winter, K., Kocha, W. I., Coia, L. R., Herskovic, A., and Graham, M. A. Phase I/II study of external beam radiation, brachytherapy, and concurrent chemotherapy for patients with localized carcinoma of the esophagus (radiation therapy oncology group study 9207). Cancer (Phila.), *88:* 988–996, 2000.

15. Tsujii, H., Tsuji, H., Inada, T., Maruhashi, A., Hayakawa, Y., Takada, Y., Tada, J., Fukumoto, S., Tatuzaki, H., Ohara, K., and Kitagawa, T. Clinical results of fractionated proton therapy. Int. J. Radiat. Oncol. Biol. Phys., *25:* 49–60, 1993.

16. Koyama, S., Tsujii, H., Yokota, H., Hotta, S., Miyo, Y., Fukutomi, S., Osuga, T., Tsuji, H., Okumura, H., Ohara, K., and Kikuchi, M. Proton beam therapy for patients with esophageal carcinoma. Jpn. J. Clin. Oncol., *24:* 144–153, 1994.

17. Tsujii, H., Inada, T., Maruhashi, A., Hayakawa, Y., Tsuji, H., Ohara, K., and Kitagawa, T. Field localization and verification system for proton beam radiotherapy in deep-seated tumors. Nippon Acta Radiol., *49:* 622–629, 1989.

18. Isacsson, U., Lennernas, B., Grusell, E., Jung, B., and Montelius, A. C. B. Comparative treatment planning between proton and X-ray therapy in esophageal cancer. Int. J. Radiat. Oncol. Biol. Phys., *41:* 441–450, 1998.

19. Japanese Society for Esophageal Diseases: Guide lines for the clinical and pathological studies on carcinoma of the esophagus. Jpn. J. Surg., *6:* 69–78, 1976.

20. Ikeda, M., Ando, N., Ishikawa, T., Iwata, T., Uematsu, S., Okawa, T., Kakegawa, T., Kaneda, K., Tanaka, Y., Miyakomaru, T., Nabeya, K., Nishio, M., Matsuda, T., Morita, K., and Yamashita, T. Guideline for radiotherapy in the treatment of esophageal cancer (in Japanese). Jpn. J. Cancer Clin., *33:* 1001–1019, 1987.

21. Sobin, L. H., and Wittekind, C. H. UICC-TNM classification of malignant tumours, Ed. 5. New York: John Wiley & Sons, Inc. 1997.

22. Koyama, S., Kawanishi, N., Fukutomi, H., Osuga, T., Iijima, T., Tsujii, H., and Kitagawa, T. Advanced carcinoma of the stomach treated with definitive proton therapy. Am. J. Gastroenterol., *85:* 443–447, 1990.

23. Kaplan, E. L., and Meier, P. Nonparametric estimation from incomplete observation. J. Am. Stat. Assoc., *53:* 457–481, 1958.

24. Endo, M. Early-stage esophageal cancer: the report of nationwide survey (in Japanese). Gastroenterol. Endosc., *32:* 2466–2470, 1990.

25. Kato, H., Tachimori, Y., Watanabe, H., Yamaguchi, H., Ishikawa, T., and Itabashi, M. Superficial esophageal carcinoma: surgical treatment and the results. Cancer (Phila.), *66:* 2319–2323, 1990.

26. Suit, H. D., and Westgate, S. J. Impact of improved local control on survival. Int. J. Radiat. Oncol. Biol. Phys., *12:* 453–458, 1986.

27. Iizuka, T., Isono, K., Kakegawa, T., and Watanabe, H. Parameters linked to ten-year survival in Japan of resected esophageal carcinoma. Chest, *96:* 1005–1011, 1989.

# Proton Beam Therapy with High-Dose Irradiation for Superficial and Advanced Esophageal Carcinomas

Shohei Koyama and Hirohiko Tsujii

*Clin Cancer Res* 2003;9:3571-3577.