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Original Article

Outcome of Radiation Monotherapy for High-risk Patients with Stage I Esophageal Cancer

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Currently, chemoradiation is the most widely used nonsurgical treatment for esophageal cancer. However, some patients, particularly the very elderly or those with severe vital organ dysfunction, face difficulty with the chemotherapy component. We therefore examined the outcome of radiation therapy (RT) alone for patients with esophageal cancer at our facility. Between January 2005 and December 2014, 84 patients underwent RT at our hospital, and 78 of these patients received concomitant chemotherapy. The remaining 6 patients underwent RT alone; these patients were considered to be high-risk and to have no lymph node metastasis (stage I). Five of them received irradiation up to a curative dose: 4 showed a complete response (CR) and 1 showed a partial response (PR). Of the patients exhibiting CR, 3 are currently living recurrence-free, whereas 1 patient underwent endoscopic submucosal dissection (ESD) as salvage therapy for local recurrence, with no subsequent recurrence. High-risk stage I esophageal cancer patients can be treated radically with RT alone under certain conditions. In the future, to broaden the indications for RT monotherapy to include some degree of advanced cancers, a novel concurrent therapy should be identified.

Key words: esophageal cancer, radiation therapy, high-risk patient

Surgical resection is the current primary treatment for esophageal cancer. In Japan, the standard treatment for stage II and III esophageal cancer is preoperative chemotherapy with surgical resection [1]. Esophageal cancer surgery is one of the most invasive surgeries because it requires a procedure involving 3 regions (cervical, thoracic, and abdominal regions) and includes extensive lymph node dissection. Published reports state that esophageal cancer surgery is associated with a higher incidence of complications and perioperative mortality than any other type of cancer surgery [2,3]. In recent years, endoscopic surgery has been introduced in an attempt to reduce the invasiveness of esophageal cancer surgery, and several reports have described the effectiveness of this approach [4-7]. On the other hand, esophageal cancer often develops in elderly individuals, often among those with a significant drinking and/or smoking habit, and endoscopic surgery has been performed in such patients for safer surgical resection. Nevertheless, there are patients who require nonsurgical treatment because they are very elderly or have severe vital organ dysfunction. At the present time, chemoradiotherapy (CRT) is the standard nonsurgical treatment to preserve the esophagus in patients with a relatively good general condition.

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However, in high-risk patients, such as those mentioned above, CRT may lead to issues such as more acute adverse reactions than radiation therapy (RT) alone [8]. Therefore, in patients in whom concurrent chemotherapy is difficult, RT monotherapy has been an important treatment method. Moreover, if the indication for monotherapy is appropriately selected on the basis of accurate preoperative diagnostic imaging, then RT alone can be expected to be curative in some cases [8]. We therefore retrospectively examined the backgrounds and therapeutic outcomes of high-risk patients with esophageal cancer who were undergoing curative RT as monotherapy at our facility.

Patients and Methods

Patients. During the 10-year period from January 2005 through December 2014, 84 patients with esophageal cancer underwent curative RT at our facility. Of these, 60 patients received CRT with concurrent intravenous chemotherapy using a normal combination of 5-fluorouracil (5-FU) and cisplatin (FP therapy) or a combination of docetaxel, cisplatin, and 5-fluorouracil (DCF therapy); 18 patients showed organ failure including renal dysfunction and therefore received CRT with the concurrent oral anticancer agent TS-1 (tegafur, gimeracil, and oteracil potassium); the remaining 6 patients received RT alone because concurrent treatment with anticancer agents was difficult (Fig. 1). In the present study, we examined the background characteristics and therapeutic outcomes of these 6 patients. This retrospective study was performed in accordance with the ethical standards laid down in the Helsinki Declaration of 1975, as revised in 2000 and 2008 concerning Human and Animal Rights. The confidentiality and privacy of the patients were protected in the presentation of research results, and no information obtained from this study was used for any other purpose. This study was approved by the Ethics Committee of Okayama University Hospital (1605-512).

Treatment. Three-dimensional conformal RT based on computed tomography (CT) images using 6-10 MV X-rays was administered at a dose of 54-66 Gy in 27-33 fractions over 6-7 weeks. Clinical target volume (CTV) 1 was defined as the region covering the primary lesion with a 3-cm margin in a craniocaudal direction and the regional lymph node area detected using endoscopy, CT, and 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT. CTV2 was defined as the region covering the primary lesion with 2-cm and 0.5-cm margins in the craniocaudal and lateral directions, respectively, and the involved lymph nodes. Planning target volume (PTV) 1 and PTV2 were defined as the regions covering CTV1 and CTV2, respectively, with an adequate margin to facilitate respiratory movements and error in reproducing patient fixation. In PTV1, irradiation was performed up to 40 Gy with anterior/posterior opposed portals. In PTV2, irradiation was performed up to the planned radiation dose with bilateral oblique (off-cord) portals.

Follow-up. After treatment, follow-up was conducted on an outpatient basis once every 3 months, including a physical examination and blood tests, including those for tumor markers. Alternating 3-month periods of contrast-enhanced CT and FDG-

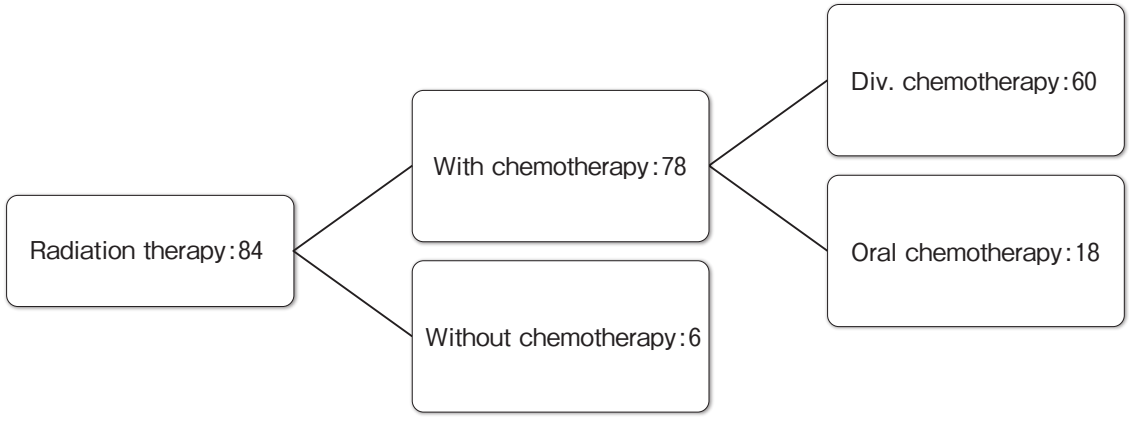

Fig. 1 Eighty-four patients who underwent radiation therapy at our facility.

PET/CT were performed during the first year. In the second and subsequent years, either contrast-enhanced CT or FDG-PET/CT was performed every 6 months. In addition, endoscopy was performed every 6 months.

Description and statistical analysis. Clinicopathological factors were noted according to the Union for International Cancer Control (UICC) Tumor Nodes Metastasis (TNM) Classification of Malignant Tumors, 7th edition [9]. Postoperative complications were categorized according to the Clavien–Dindo classification [10]. All analyses were performed using JMP version 11 statistical analysis software (SAS Institute, Cary, NC, USA).

Results

All 6 patients undergoing RT alone were male, with a mean age of 69.8 years (range: 39-82 years). All patients had squamous cell carcinoma, with stage IA in 3 patients and stage IB in 3 patients. No patients had lymph node metastasis. RT monotherapy was used in 2 patients due to renal dysfunction, in 2 patients due to liver dysfunction, and in 3 patients due to very advanced age. Treatment was discontinued in 1 patient because of complications during treatment that exacerbated the underlying disease, chronic obstructive pulmonary disease. The remaining 5 patients received irradiation up to the scheduled curative dose (Table 1). There were no RT-related complications during the acute phase or the last stage. Treatment was successful in all 5 patients who received irradiation up to the scheduled curative dose (CR: 4 patients; PR: 1 patient). Of the 4 patients with CR, 3 patients did not develop recurrence, but another patient developed local recurrence and consequently underwent ESD as salvage therapy. Thereafter, no evidence of recurrence was observed. The patient with PR developed regrowth of the primary lesion, and lymph node metastasis appeared outside the irradiation range. The primary lesion was treated with repeated argon plasma coagulation (APC) but without adjuvant chemotherapy.

Case presentation. A patient who, despite achieving CR by RT alone, developed localized recurrence 13 months later and underwent ESD as salvage therapy is presented. The patient was an 81-year-old man who was examined at a local clinic with a chief complaint of bloody stool. Therefore, upper and lower gastrointestinal endoscopy was performed, revealing an irregular, protruding tumor (type 1) in the lower intrathoracic esophagus, which was confirmed to be squamous cell carcinoma on biopsy (Fig. 2A, B, and C). Advanced cancer was observed in the sigmoid colon, which was diagnosed as adenocarcinoma on biopsy. FDG-PET/CT revealed uptake in the tumor area. Laparoscopic curative resection was performed for the sigmoid colon cancer, but the patient refused surgery for the esophageal cancer. Therefore, considering the patient's age, RT alone at a dose of 60 Gy was administered to the intrathoracic esophagus only (Fig. 2D and E). The patient progressed with no particular complications, and irradiation was completed up to the scheduled curative dose. Therefore, CR was confirmed (Fig. 2F, G, and H). Thereafter, regular endoscopic tests were performed, but endoscopy performed 13 months after RT revealed localized recurrence (Fig. 3A, B, and C). The lesion was diagnosed to be confined to the mucosa and was removed *en bloc* by ESD as salvage therapy (Fig. 3D, E, and F). Pathological examination of the resected specimen revealed curative resection of intramucosal cancer. There was no subsequent recurrence.

Table 1 Five cases that have completed radiation therapy alone

Case No.	Age/Sex	TNM Stage	RT dose (Gy)	Response	Recurrence	Time to PD (Recurrent site)	Additional treatment	Prognosis	Residual tumor
1	64/M	T1N0M0 Stage IA	54	CR	−	−	None	12 M alive	−
2	76/M	T1N0M0 Stage IA	66	CR	−	−	None	58 M dead	−
3	39/M	T2N0M0 Stage IB	60	PR	+	3 M (local & distant)	APC	60 M alive	+
4	82/M	T1N0M0 Stage IA	66	CR	−	−	None	48 M alive	−
5	81/M	T2N0M0 Stage IB	60	CR	+	13 M (local)	ESD	24 M alive	−

RT, radiation therapy; CR, complete response; PR, partial response; PD, progressive disease; M, months; APC, argon plasma coagulation; ESD, endoscopic submucosal dissection.

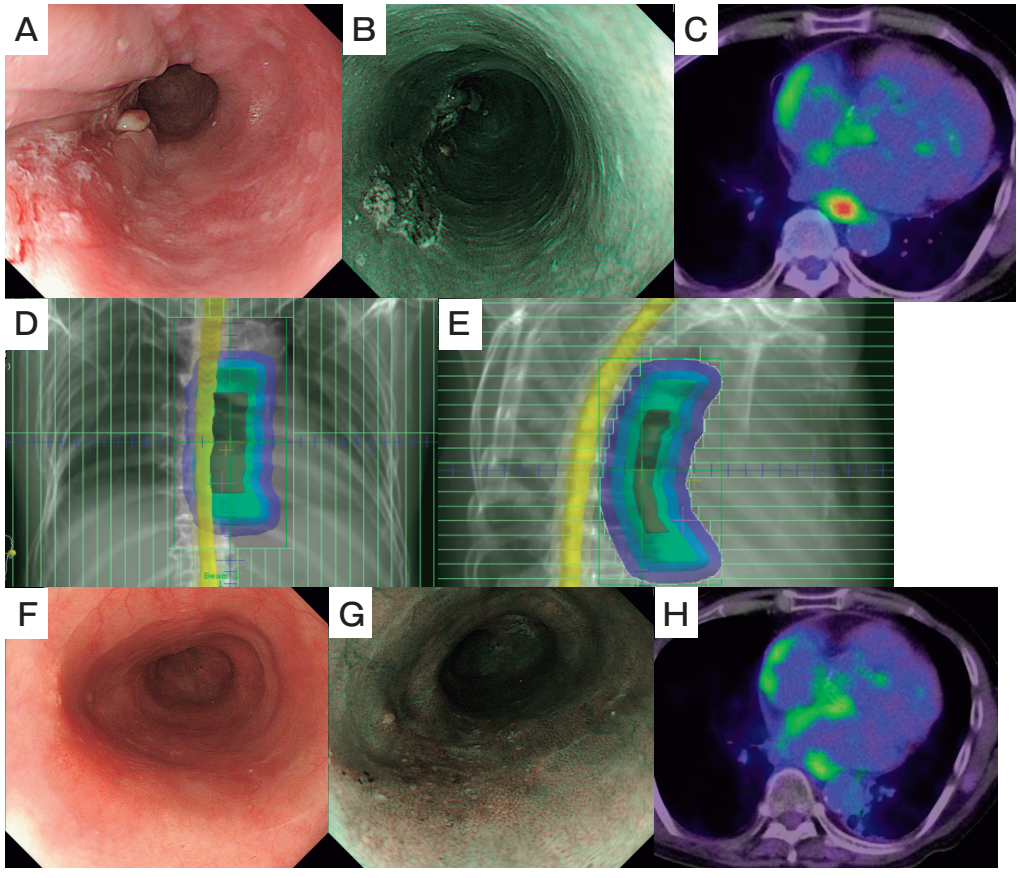

Fig. 2 Endoscopy, PET-CT findings before and after RT, and irradiation field of Case 5.
A, B, and C, Pre-treatment findings; F, G, and H, Post-treatment findings; A and F, Normal white-light endoscopic findings; B and G, NBI findings; D and E, Irradiation field configuration.

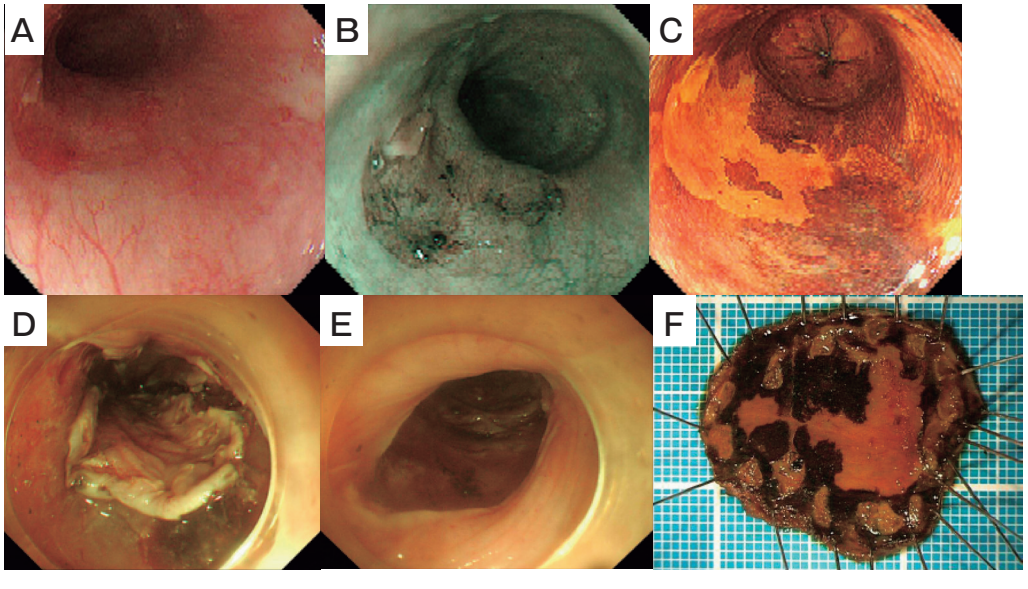

Fig. 3 Endoscopic findings at the time of recurrence and at the time of ESD of Case 5.
A, Normal white-light endoscopic findings; B, NBI findings; C, Iodine staining findings; D and E, Findings at the time of the ESD; F, Resected specimen findings.

Discussion

Esophageal cancer includes squamous cell carcinoma, which is highly responsive to chemotherapy and RT. Consequently, RT and CRT have been developed as nonsurgical treatments. The Radiation Therapy Oncology Group (RTOG) of Europe and America has reported a well-known controlled trial of curative RT monotherapy and CRT (RTOG85-01). This trial included patients with clinical stage T1-3, N0-1, M0 intrathoracic esophageal cancer, for whom treatment included a total radiation dose of 64 Gy for the RT monotherapy group and 4 courses of 5-FU + cis-diamminedichloroplatinum (II) (CDDP) chemotherapy concurrent with a total radiation dose of 50 Gy for the CRT group. The 5-year survival rate for the RT monotherapy group was 0%, whereas that for the CRT group was significantly higher, at 27%. On the basis of these results, CRT has gained increasing popularity as a nonsurgical treatment method for esophageal cancer [11-13]. However, CRT of 50 Gy has been shown to achieve only a low local tumor control rate, and thus the irradiation method was subsequently amended from 2.0 Gy to 1.8 Gy per fraction. Thus, based on RTOG85-01, the CRT outcomes at radiation doses of 64.8 Gy (1.8 Gy×36 fractions) and 50.4 Gy (1.8 Gy×28 fractions) were examined (RTOG94-05). There was no difference in therapeutic outcomes between these 2 groups of patients [14]. Therefore, the standard curative radiation dose for CRT in Europe and America is currently set at 50.4 Gy. In Japan, on the other hand several reports indicate that irradiation at a dose of 60 Gy in 30 fractions over 6-8 weeks is still being administered [15]. Furthermore, in cases with RT alone, it is standard practice to administer 60-70 Gy in 30-35 fractions over 6-7 weeks.

At all these doses, the incidence of complications in the acute phase is higher when RT is combined with chemotherapy than when RT is used alone [17]. In particular, with CDDP, a key drug in chemotherapy for esophageal cancer, nephrotoxicity and myelosuppression can easily cause issues. Therefore, when administering CRT to elderly patients and patients with severe vital organ dysfunction, we decided to administer concurrent oral anticancer agents associated with relatively few side effects, such as TS-1. In addition, we selected RT monotherapy to treat patients with relatively early cancer up to stage II without lymph node metastasis, in whom TS-1 use was still considered to be a risk. Our data showed that, among relatively early-stage patients, including high-risk patients, most (5/6) received the standard curative dose with RT alone. In all patients who received the curative dose, the treatment was successful: 4 patients with CR and 1 patient with PR. Of the patients with CR, 3 patients with stage IA are currently living recurrence-free, whereas 1 patient with stage IB underwent endoscopic submucosal dissection (ESD) as salvage therapy for local recurrence, with no subsequent recurrence. Recently, there have been some reports about the benefit of salvage endoscopic therapies including ESD for esophageal recurrent cancer after definitive RT [15-18]. However, the patient with PR was unable to undergo adjuvant treatment; therefore, regrowth and distant lymph node metastasis were detected during the observation period. We therefore consider that stage I esophageal cancer patients can be treated radically with RT monotherapy under certain conditions, and that the keys to a radical cure are the absence of lymph node metastasis and the achievement of CR.

In the future, to improve the effectiveness of RT in high-risk patients with some degree of advanced esophageal cancer, we propose the use of a concurrent therapy with few side effects to enhance the effectiveness of RT and to achieve CR. An alternative to anticancer agents is gene therapy using viral vectors. Among these, the most well known is a treatment using the p53 tumor suppressor gene, which enhances radiation sensitivity [19]. For several years, our department has conducted research and development on p53 gene therapy using adenovirus type 5, and we have experimented with its clinical use for advanced lung cancer patients [20,21]. In addition, other reports have indicated that p53 gene therapy is effective for esophageal cancer [22,23]. We have developed a new gene therapy drug termed Telomelysin, a tumor-selective oncolytic adenovirus. Telomelysin is a type 5 adenovirus that has been modified to proliferate in tumors with high telomerase activity. Although the agent has exhibited an antitumor effect even when used alone [24-26], it has been demonstrated on an experimental level that the anti-tumor effect is further increased when combined with radiation [27]. The clinical application of Telomelysin combined with RT is eagerly awaited, and we believe that esophageal cancer would be a promising candidate disease for this purpose, since it has essentially high

sensitivity to radiation and since more than 80% of esophageal cancer patients exhibit enhanced telomerase activity. Moreover, we believe that the most benefit will be gained in high-risk patients with esophageal cancer in whom concurrent chemotherapy is difficult.

In conclusion, when performed in appropriately selected patients with relatively early esophageal cancer, RT monotherapy can be expected to achieve a satisfactory cure. Moreover, to expand the indications to include some degree of advanced cancers, a novel concurrent therapy should be identified in the near future.

References

1. Ando N, Kato H, Igaki H, Shinoda M, Ozawa S, Shimizu H, Nakamura T, Yabusaki H, Aoyama N, Kurita A, Ikeda K, Kanda T, Tsujinaka T, Nakamura K and Fukuda H: A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol (2012) 19: 68–74.
2. Allareddy V, Ward MM, Allareddy V and Konety BR: Effect of meeting Leapfrog volume thresholds on complication rates following complex surgical procedures. Ann Surg (2010) 251: 377–383.
3. Takeuchi H, Miyata H, Gotoh M, Kitagawa Y, Baba H, Kimura W, Tomita N, Nakagoe T, Shimada M, Sugihara K and Mori M: A risk model for esophagectomy using data of 5354 patients included in a Japanese nationwide web-based database. Ann Surg (2014) 260: 259–266.
4. Tsujimoto H, Takahata R, Nomura S, Yaguchi Y, Kumano I, Matsumoto Y, Yoshida K, Horiguchi H, Hiraki S, Ono S, Yamamoto J and Hase K: Video-assisted thoracoscopic surgery for esophageal cancer attenuates postoperative systemic responses and pulmonary complications. Surgery (2012) 151: 667–673.
5. Petri R, Zuccolo M, Brizzolari M, Rossit L, Rosignoli A, Durastante V, Petrin G, De Cecchis L and Sorrentino M: Minimally invasive esophagectomy: thoracoscopic esophageal mobilization for esophageal cancer with the patient in prone position. Surg Endosc (2012) 26: 1102–1107.
6. Ozawa S, Ito E, Kazuno A, Chino O, Nakui M, Yamamoto S, Shimada H and Makuuchi H: Thoracoscopic esophagectomy while in a prone position for esophageal cancer: a preceding anterior approach method. Surg Endosc (2013) 27: 40–47.
7. Palanivelu C, Prakash A, Senthilkumar R, Senthilnathan P, Parthasarathi R, Rajan PS and Venkatachlam S: Minimally invasive esophagectomy: thoracoscopic mobilization of the esophagus and mediastinal lymphadenectomy in prone position--experience of 130 patients. J Am Coll Surg (2006) 203: 7–16.
8. Okawa T, Dokiya T, Nishio M, Hishikawa Y and Morita K: Multiinstitutional randomized trial of external radiotherapy with and without intraluminal brachytherapy for esophageal cancer in Japan. Japanese Society of Therapeutic Radiology and Oncology (JASTRO) Study Group. Int J Radiat Oncol Biol Phys (1999) 45: 623–628.
9. Sobin LH, Gospodarowicz MK and Wittekind C: TNM classification of malignant tumors (UICC international union against cancer), 7th Ed. Wiley-Blackwell, Oxford (2009).
10. Dindo D, Demartines N and Clavien PA: Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg (2004) 240: 205–213.
11. 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 (1992) 326: 1593–1598.
12. Al-Sarraf M, Martz K, Herskovic A, Leichman L, Brindle JS, Vaitkevicius VK, Cooper J, Byhardt R, Davis L and Emami B: Progress report of combinedchemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. J Clin Oncol (1997) 15: 277–284.
13. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA Jr, Al-Sarraf M, Byhardt R, Russell AH, Beitler JJ, Spencer S, Asbell SO, Graham MV and Leichman LL: 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: 1623–1627.
14. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, Okawara G, Rosenthal SA and Kelsen DP: 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: 1167–1174.
15. Ishii N, Suzuki K and Fujita Y: Salvage endoscopic submucosal dissection for recurrent esophageal squamous-cell carcinoma after definitive chemoradiotherapy. Clin J Gastroenterol (2011) 4: 85–88.
16. Takeuchi M, Kobayashi M, Hashimoto S, Mizuno K, Kawaguchi G, Sasamoto R, Aoyama H and Aoyagi Y: Salvage endoscopic submucosal dissection in patients with local failure after chemoradiotherapy for esophageal squamous cell carcinoma. Scand J Gastroenterol (2013) 8: 1095–1101.
17. Koizumi S, Jin M, Matsuhashi T, Tawaraya S, Watanabe N, Sawaguchi M, Kanazawa N, Yamada Y, Onochi K, Kimura Y, Ohba R, Kataoka J, Hatakeyma N, Mashima H and Ohnishi H: Salvage endoscopic submucosal dissection for the esophagus-localized recurrence of esophageal squamous cell cancer after definitive chemoradiotherapy. Gastrointest Endosc (2014) 79: 348–353.
18. Makazu M, Kato K, Takisawa H, Yoshinaga S, Oda I, Saito Y, Mayahara H, Ito Y, Itami J, Hamaguchi T, Yamada Y and Shimada Y: Feasibility of endoscopic mucosal resection as salvage treatment for patients with local failure after definitive chemoradiotherapy for stage IB, II, and III esophageal squamous cell cancer. Dis Esophagus (2014) 27: 42–49.
19. Roth JA, Grammer SF, Swisher SG, Komaki R, Nemunaitis J, Merritt J, Fujiwara T and Meyn RE Jr: Gene therapy approaches for the management of non-small cell lung cancer. Semin Oncol (2001) 28: 50–56.
20. Fujiwara T, Kataoka M and Tanaka N: Adenovirus-mediated p53 gene therapy for human cancer. Mol Urol (2000) 4: 51–54.
21. Fujiwara T, Tanaka N, Kanazawa S, Ohtani S, Saijo Y, Nukiwa T, Yoshimura K, Sato T, Eto Y, Chada S, Nakamura H and Kato H: Multicenter phase I study of repeatedintratumoral delivery of adenoviral p53 in patients with advanced non-small-cell lung cancer. J Clin Oncol (2006) 24: 1689–1699.
22. Shimada H, Matsubara H, Shiratori T, Shimizu T, Miyazaki S, Okazumi S, Nabeya Y, Shuto K, Hayashi H, Tanizawa T, Nakatani Y, Nakasa H, Kitada M and Ochiai T: Phase I/II adenoviral p53 gene therapy for chemoradiation resistant advanced esophageal squamous cell carcinoma. Cancer Sci (2006) 97: 554–

561.
23. Shimada H and Ochiai T: Gene therapy for esophageal squamous cell carcinoma. Front Biosci (2008) 13: 3364–3732.
24. Nakajima O, Matsunaga A, Ichimaru D, Urata Y, Fujiwara T and Kawakami K: Telomerase-specific virotherapy in an animal model of human head and neck cancer. Mol Cancer Ther (2009) 8: 171–177.
25. Kurihara Y, Watanabe Y, Onimatsu H, Kojima T, Shirota T, Hatori M, Liu D, Kyo S, Mizuguchi H, Urata Y, Shintani S and Fujiwara T: Telomerase-specific virotheranostics for human head and neck cancer. Clin Cancer Res (2009) 15: 2335–1343.
26. Liu D, Kojima T, Ouchi M, Kuroda S, Watanabe Y, Hashimoto Y, Onimatsu H, Urata Y and Fujiwara T: Preclinical evaluation of synergistic effect of telomerase-specific oncolytic virotherapy and gemcitabine for human lung cancer. Mol Cancer Ther (2009) 8: 980–987.
27. Kuroda S, Fujiwara T, Shirakawa Y, Yamasaki Y, Yano S, Uno F, Tazawa H, Hashimoto Y, Watanabe Y, Noma K, Urata Y, Kagawa S and Fujiwara T: Telomerase-dependent oncolytic adenovirus sensitizes human cancer cells to ionizing radiation via inhibition of DNA repair machinery. Cancer Res (2010) 70: 9339–9348.