ORIGINAL ARTICLE

Photodynamic therapy as salvage treatment for local failures after definitive chemoradiotherapy for esophageal cancer

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Background: Although definitive chemoradiotherapy for esophageal cancer shows a high response rate, persistent or recurrent locoregional disease remains a major problem. Salvage esophagectomy is the only curative intent treatment option; however, it carries higher morbidity and mortality rates than primary esophagectomy. Response to second-line chemotherapy is quite dismal.

Methods: From December 2002 to November 2003, we applied salvage photodynamic therapy to 13 patients with local failures after completion of chemoradiotherapy, 4 patients had local recurrence after achieving a complete response, and 9 had a persistent tumor after chemoradiotherapy. The decision to treat was based on patients' refusal of salvage surgery or chemotherapy. After the intravenous administration of 2 mg/kg of Photofrin, photoradiation treatment with an excimer dye laser was performed for 48 hours and 72 hours after the injection. Written informed consent was obtained from all patients.

Results: Eight patients (62%) achieved a complete response. After a median follow-up period of 12 months after photodynamic therapy, 6 patients were still free of disease, and the overall survival rate at 1 year was 68.4%. There were no treatment-related deaths.

Conclusions: Our results show that salvage photodynamic therapy could be a promising curative intent treatment option with low morbidity and mortality rates. (Gastrointest Endosc 2005;62:31-6.)

Although definitive chemoradiotherapy (CRT) is now commonly used for the treatment of esophageal cancer, persistent or recurrent locoregional disease occurs in more than 40% of patients and remains one of the major unsolved problems.[1] The survival of the patients who did not achieve complete response (CR) is dismal. Most of them (over 80%) would die within 1 year.[2] Esophagectomy as a salvage treatment has a curative potential; however, it is a more difficult and risky procedure than primary esophagectomy.[3] Postoperative mortality rates within 30 days of surgery also are higher.[3,4] Moreover, there are no curative chemotherapy protocols currently available for treatment of residual tumor.

Some patients with persistent or recurrent locoregional disease have truly local failures without distant metastasis. In such patients, local treatment seems to be sufficient. We have previously reported that EMR could be a salvage option.[5] In that paper, the 3-year survival rate from the initial EMR for all 16 patients was 56%, and there were no serious complications.[5] However, the application of salvage EMR is limited by its requirement for tumor recurrence that is focal in nature, and a high skill level is required for this procedure.

Photodynamic therapy (PDT) is a potential alternative, nonsurgical treatment that eliminates superficial esophageal cancer.[6,7] This method uses a photosensitizing chemical agent that is activated by light to selectively destroy the neoplastic cells.[8-10] Theoretically, PDT may cure T1 and possibly T2 tumors, as classified by the TNM classification,[11] and this procedure is relatively simple to perform. Therefore, we postulated that PDT could be a more effective salvage option than EMR. However, there have been no reports published to date that use this method to treat local failures after definitive CRT. Herein, we report our experience of esophageal cancer patients treated with salvage PDT for local failure after completion of definitive CRT.

PATIENTS AND METHODS

Between December 2002 and November 2003, 13 patients underwent salvage PDT at the National Cancer Center Hospital East, Kashiwa, Japan. All patients initially

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were treated with definitive CRT at our hospital. The CRT consisted of 60 Gy irradiation, along with two cycles of continuous infusion with 5-fluorouracil (5FU) and cisplatin (CDDP) or nedaplatin (NED). The 5FU (400 mg/m^2, 24-hour intravenous infusion) was administered on days 1 to 5 and 8 to 12. CDDP (40 mg/m^2, 2-hour intravenous infusion) was administered with hydration on day 1 and day 8. This schedule was repeated twice, every 5 weeks. Radiotherapy was initiated concurrently on the first day of the first and second course of chemotherapy and was delivered in 30 fractions of 2 Gy for a total of 60 Gy. In addition, two courses of chemotherapy were added for the patients who showed good initial response to treatment. In the cases with renal insufficiency or cardiovascular disease, we used NED instead of CDDP, because NED did not require hydration and showed a low risk of renal toxicity.[12]

Baseline staging of esophageal cancer was determined by the TNM classification of the International Union Against Cancer.[11] Clinical T stage was evaluated by endoscopy and EUS, and clinical N and M stage were evaluated mainly by CT of the neck, the chest, and the abdomen. The definition of complete response after CRT was determined as follows: (1) disappearance of tumor lesion or ulcer of primary site with confirmed cancer negative histology, and (2) disappearance of measurable or assessable metastatic lesion confirmed by CT.

Although all persistent or recurrent tumors were surgically resectable, the decision to undergo nonsurgical treatment was based on the patients' refusal of surgery. All patients gave written informed consent. The criteria for salvage PDT were specific and included the following: (1) no lymph node or distant metastases was detected; (2) tumor staging by a 20-MHz US probe (UM-3R; Olympus Optical Co, Ltd, Tokyo, Japan) was limited to the following categories of uT1 or uT2, uT1 when the tumor invasion was within mucosal and/or submucosal layer, or uT2 when the tumor invaded into the muscularis propria layer; (3) other nonsurgical treatments, e.g., EMR, were not indicated for reasons of difficulty or noncurability; and (4) written informed consent was obtained from the patient.

The PDT procedure commenced with intravenous administration of 2 mg/kg of Photofrin (Wyeth K. K., Tokyo, Japan) followed by dye laser irradiation. The 630-nm-wavelength laser beam was emitted by an excimer dye laser (EDL-1; Hamamatsu Photonics, Hamamatsu, Japan). The laser treatment was performed 48 and 72 hours after injection of the drug. The excimer dye laser was delivered via a microlens fiber introduced into the operative channel of the fiberscope (GIF-Q20; Olympus) and was positioned in the esophagus. The distal tip of the fiber was maintained to keep the distance about 1 cm from the surface of the lesion. The total light density was 75 J/cm^2, with 4 mJ/pulse maximum pulse energy and 40 Hz pulse frequency.

All patients were instructed to avoid direct exposure to sunlight for 1 month after the injection of Photofrin for the purpose of protection from skin photosensitization. Patients were examined endoscopically 7 to 8 days after treatment to confirm the development of tissue necrosis. To evaluate the response and the luminal toxicity of PDT, endoscopic examination with biopsy was repeated at least every month until confirmation of the response. The response to PDT was classified as a CR if there was no macroscopic or microscopic evidence of cancer, or non-CR if a tumor was seen at endoscopy and was confirmed histologically. Recurrence was defined as a relapse after achieving CR. CT was used to evaluate the distant organ or lymph-node metastasis at 3, 6, and 12 months after PDT.

The progression-free survival was measured from the date of PDT to the date of confirmation of the recurrence or the progression of the disease. Overall survival was measured from the date of PDT to death or at last follow-up visit. Survival time was calculated by the Kaplan-Meier method. In addition, we assessed the period of hospital stay, antibiotics usage, and fasting after salvage PDT. If the toxicity occurred within 7 days after PDT, we defined it as acute toxicity. In contrast, if it occurred 8 days after PDT, it was defined as a late toxicity. All information was collected from medical records and was provided by the patient's physicians.

Capsule Summary

What is already known on this topic

- Persistent or recurrent loco-regional disease occurs in more than 40% of esophageal cancers after chemoradiotherapy.
- Photodynamic therapy (PDT) may cure T1 or T2 esophageal tumors and may be a salvage option.

What this study adds to our knowledge

- In an uncontrolled case series from Japan, salvage PDT with curative intent was used in 13 patients, achieving 62% complete response and a 68% 1-year survival.

RESULTS

Baseline patient and lesion characteristics before CRT and those before PDT are summarized in Table 1. Median age was 67 years (range 51-75 years). There were 12 men and one woman. The baseline clinical stage before CRT was as follows: T1, T2, T3, and T4 in 0, 4, 9, and 0 patients, respectively; N0 and N1 in 5 and 8 patients, respectively; and stage I, stage IIA, stage IIB, stage III, and stage IV in 0, 5, 1, 6, and 1 patients, respectively. Nine patients were treated with 5FU, CDDP, and radiation; and 4 patients were treated with 5FU, NED, and radiation. Four patients suffered local recurrence after achieving CR, and the remaining 9 patients had persistent tumor after completion of CRT. Six patients

TABLE 1. Patient and lesion characteristics

Patient	Age (y)	Gender	Baseline TNM stage*†	Tumor status after CRT	TNM stage before PDT†	Histologic confirmation of residual cancer	Tumor length before PDT (cm)
1	64	Male	T2N0M0	Recurrent	T1N0M0	Positive	1
2	59	Male	T3N1M0	Persistent	T1N0M0	Positive	2
3	74	Male	T3N0M0	Persistent	T2N0M0	Positive	4
4	51	Male	T2N0M0	Recurrent	T1N0M0	Positive	2
5	58	Male	T3N1M0	Persistent	T2N0M0	Positive	2.5
6	74	Male	T2N1M1a	Persistent	T1N0M0	Positive	4
7	68	Male	T3N1M0	Persistent	T2N0M0	Negative	7
8	75	Male	T3N1M0	Recurrent	T2N0M0	Positive	3
9	61	Female	T3N0M0	Persistent	T1N0M0	Negative	2
10	71	Male	T2N1M0	Recurrent	T1N0M0	Positive	2
11	64	Male	T3N0M0	Persistent	T2N0M0	Positive	5
12	67	Male	T3N1M0	Persistent	T2N0M0	Positive	6
13	69	Male	T3N1M0	Persistent	T2N0M0	Negative	5

CRT, Chemoradiotherapy; *PDT*, photodynamic therapy.
*Based on the criteria of the TNM classification of malignant tumors by the International Union Against Cancer.
†The tumor stage was evaluated by EUS.

had uT1 tumors (all of them were assessed as having massive submucosal invasion), and 7 patients had uT2 tumors. Three patients were judged to have persistent tumor without histologic confirmation of carcinoma according to the endoscopic and EUS findings of submucosal tumor-like lesions. The median length of tumor before salvage PDT was 3 cm (range 1-7 cm). Seven patients had ulceration on the lesions before PDT.

Clinical outcomes after salvage PDT are summarized in Table 2. The median total delivered light dose was 750 J (range 300-1000 J). A response of the tumors to salvage PDT was seen in all patients. CR was attained in 8 (62%) of the 13 patients. Among the cases with histologically confirmed residual cancer, the CR rate was 60% (6/10). We show the representative case of a patient who achieved CR after salvage PDT in Figure 1. All patients with uT1 tumors achieved CR, whereas two of 7 patients with uT2 also achieved CR. The median time to confirm CR was 3 months (range 1-4 months). Two patients experienced local recurrence after salvage PDT and were re-treated with PDT; however, their recurrent lesions did not disappear. They died of esophageal cancer progression. Of the 5 patients who did not achieve CR, 3 patients were re-treated with PDT, and the remaining two were followed with appropriate best-supportive care. At a median follow-up period of 12 months (range 6-19 months) after application of salvage PDT, 9 patients were still alive and 6 of them were free of disease. The overall survival rate after salvage PDT after 1 year was 68.4% (Fig. 2).

In all cases, intravenous injection of the Photofrin was well tolerated. There were no allergic reactions or injection site irritation. For all 13 patients, the median hospital stay was 13 days (range 6-20 days), the fasting period was 1 day (range 0-6 days), and the antibiotics-required period was 4 days (range 0-10 days). As for acute complication within the 7 days after salvage PDT, high fever (>38.5°C), and chest pain that needed pain killers was observed in 4 and 7 patients, respectively. White blood count (WBC) and C-reactive protein (CRP) were elevated after initial salvage PDT. Median WBC and CRP at 2 days after salvage PDT were 9400/mm^3 (range 5300-15900/mm^3) (normal 4500-8500/mm^3) and 11.2 mg/dL (range 2.3-18.8 mg/dL); (<0.5 mg/dL), respectively. Six patients experienced significant complications: one mediastinitis, one esophagotracheal fistula, 3 stenosis that required repeated balloon dilation, one cutaneous phototoxicity, and one increase of radiation-induced pericardial effusion that required drainage. The patient who developed mediastinitis was cured by intravenous administration of antibiotics and fasting for 1 week. The patient who developed a fistula died of the progression of esophageal cancer. There were no occurrences of treatment-related death.

DISCUSSION

Definitive CRT is considered the standard non-surgical treatment for esophageal cancer, because it shows

TABLE 2. Clinical outcome after salvage PDT

Patient	Total light dose (J)	Best response for PDT	Time to confirm CR (mo)	Recurrence after PDT (site)	Treatment to persistent or recurrent tumor	Major complications	Outcome	Tumor status	Survival from PDT (mo)
1	600	CR	1	No	—	—	Alive	Disease free	19
2	1000	CR	4	Yes (primary)	PDT	—	Dead	With disease	14
3	840	Non-CR	—	—	Palliation	Fistula	Dead	With disease	3
4	750	CR	3	No	—	Stenosis	Alive	Disease free	15
5	750	Non-CR	—	—	Palliation	Mediastinitis	Dead	With disease	8
6	450	CR	3	No	—	Increase of PE	Alive	Disease free	15
7	900	CR	2	Yes (primary)	PDT	—	Dead	With disease	5
8	525	Non-CR	—	Yes (brain)	PDT	—	Dead	With disease	6
9	300	CR	2	No	—	—	Alive	Disease free	13
10	450	CR	2	No	—	—	Alive	Disease free	11
11	825	Non-CR	—	Yes (primary)	PDT	Stenosis	Alive	With disease	6
12	900	Non-CR	—	Yes (primary)	PDT	—	Alive	With disease	9
13	625	CR	3	No	—	Stenosis, phototoxicity	Alive	Disease free	8

PDT, Photodynamic therapy; *CR,* complete response; *NON-CR,* non-complete response; *PE,* pericardial effusion.

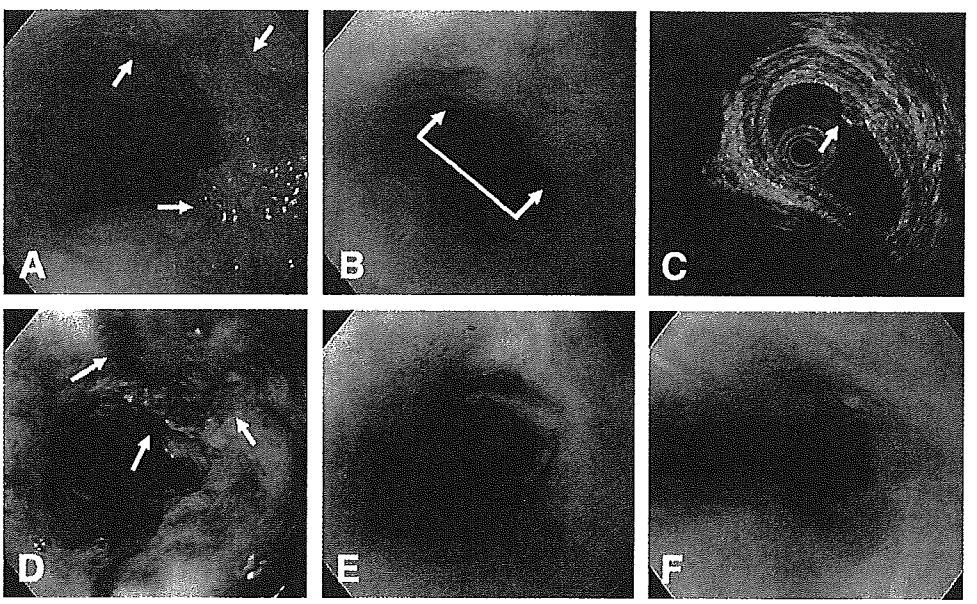

Figure 1. Endoscopic pictures of the patient with esophageal cancer. Baseline clinical stage was assessed as cT2N0M0. **A,** Depressed tumor with surrounding mound *(arrows)* is seen before definitive CRT. **B,** After completion of CRT, a submucosal tumor-like elevation *(arrows)* was persistent at the primary site, and residual cancer was confirmed by biopsy specimen. **C,** EUS image showed a hypoechoic lesion both in the mucosal and submucosal layer *(arrow)*; then, the depth of the residual tumor was assessed as uT1. **D,** At the primary site, tumor necrosis can be recognized by ischemic changes in color *(arrows)*; ulcerative change also can be seen in the background mucosa at 3 days after salvage PDT. **E,** Primary site still shows deep ulceration at 1 month after salvage PDT; however, no cancerous tissue was found by biopsy specimen. **F,** Primary site showed a scar of ulceration at 3 months after salvage PDT; no residual cancer could be found in the biopsy specimen.

comparable survival results to esophagectomy. However, the long-term follow-up results of the prospective randomized trial (Radiation Therapy Oncology Group 85-01) showed that persistence of disease and locoregional failure after definitive CRT were 25% and 13%, respectively.[13] In our previous report, local failure occurred in 34% (18/53)

of the patients treated with definitive CRT.[14] Therefore, improvement of local control is one of the major factors in producing better survival for patients who are treated with definitive CRT.

In our case series, 8 of 13 patients (62%) achieved CR by salvage PDT. Furthermore, the overall survival rate after salvage PDT at 1 year was 68.4%, whereas our previous report showed that overall survival data for patients with non-CR at 3 years was 6%.[2] While, all tumors were assessed as having massive invasion to the submucosal layer or invasion to the muscularis propria layer in this study, salvage PDT showed a relatively high CR rate and excellent short-term survival. These results indicate that carefully selected patients might have a chance of cure by salvage PDT even though they had persistent or recurrent tumor after definitive CRT.

We also previously reported that the overall survival rate of the patients treated by salvage EMR for locoregional failure after definitive CRT was 56% at 3 years.[5] These results might suggest that local treatment by endoscopic modalities such as EMR and PDT could be a treatment option for selected patients.

From a technical point of view, PDT seems to be superior to EMR. If the persistent or the recurrent lesion has an ulceration or severe fibrosis or stenosis, salvage EMR is quite difficult or impossible to perform. If the depth of the residual tumor is limited within the submucosal layer, salvage EMR is relatively difficult and has a risk of being incomplete. Even in such cases, salvage PDT could be indicated in addition to the primary treatment.

Generally, most locoregional failures after definitive CRT are detected at an advanced stage. Endoscopic treatment may not be indicated in such cases because it lacks curative potential. To date, surgical resection is considered to be the only curative treatment in these cases. However, Swisher et al[3] reported that the patients treated by salvage esophagectomy had a significantly higher incidence of anastomotic leaks (39% vs. 7%) and a longer hospital stay (29 days vs. 18 days) than those treated with planned esophagectomy. To treat malignant neoplasms, early detection is very important to cure the patient. Indeed, in our experience, all of the uT1 cases achieved CR. To detect the locoregional failure at earlier stage, the appropriate follow-up schedule after definitive CRT needs to be clarified.

As for the complications of salvage PDT, most of them were manageable with medical treatments. However, one patient developed an esophagotracheal fistula. It is unknown whether the fistula was PDT related or because of the natural progression of disease. Because the tumor in this case was non-CR, we could not deny the possibility of the latter. An esophagotracheal fistula could develop by PDT even for naïve early esophageal cancer cases, and an incidence of 6.5% has been previously reported.[7] Sanfilippo et al[15] reported two patients with esophageal cancer who had developed a fistula after PDT. One received prior external beam irradiation, and the other had intraluminal brachytherapy.[15] Similarly, the reason for mediastinitis or the increase in pericardial effusion occurring after salvage PDT is unknown. One possibility is that radiation-induced esophageal damage and heart disease,[16,17] are potentiated by PDT and that structural damage occurs by transmural necrosis. Nevertheless, it is important to elucidate their mechanism to prevent the potential complications of PDT.

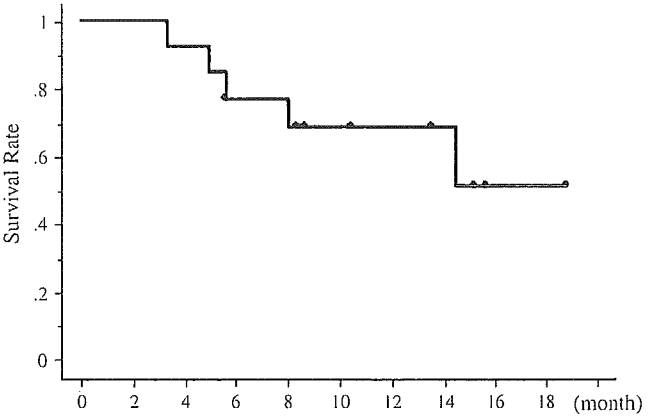

Figure 2. Overall survival of all patients from initiation of salvage PDT.

We have shown the acceptable short-term safety and worthwhile curative properties of salvage PDT when applied to the local failures after definitive CRT. Although further long-term follow-up studies will be required, salvage PDT represents a potentially new and promising treatment option. Large studies will be necessary to define the population of patients who are most likely to benefit from this treatment. Furthermore, we should confirm the efficacy of PDT as a salvage treatment for local failure after definitive CRT.

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ELSEVIER

Seminars in Oncology

Overview of Adjuvant Therapy for Resected Gastric Cancer: Differences in Japan and the United States

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Survival in adjuvant chemotherapy following resected gastric cancer has been studied by both Japanese and Western investigators using varied chemotherapy regimens in different target patients. Gastrectomy with D2 lymphadenectomy is the standard in Japan, and trials of adjuvant therapy in these patients have shown no survival advantages over surgery alone. In the United States, where 5-year survival rates in patients with gastric cancer are much lower following potentially curative surgery, adjuvant therapy has shown a survival benefit. The differences observed in these trials may result from the additional experience that Japanese surgeons have gained because of the higher incidence of gastric cancer there, or because of this increased incidence, there are more stringent screening guidelines in place and these cancers are possibly being diagnosed at an earlier stage. The Japanese viewpoint on the use of adjuvant therapy in patients with gastric cancer following potentially curative resection is that the quality of surgery, including diagnostic and pathologic procedures, is a more important prognostic factor than adjuvant chemotherapy. Also, they have determined from previously conducted clinical trials that patients with stage 1–2 tumors should be excluded from the target populations of randomized trials. Until the results of INT-0116 became available, there had been no improvement, or only marginal improvement, in overall or disease-free survival for patients receiving adjuvant chemotherapy following gastric cancer resection in the United States and Europe.
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Gastric cancer is the fourth most common cancer worldwide and the second leading cause of cancer death, accounting for 10.4% of cancer deaths globally. In 2000, there were an estimated 865,000 new cases of gastric cancer.[1] Approximately 50% of patients with gastric cancer have metastasis at diagnosis, and of those without metastasis at diagnosis, only 50% are eligible for gastric resection. In fact, gastric cancer resection typically occurs in late-stage cancer, when the cancer has already spread to the peritoneal cavity, lymph nodes, or blood vessels.[2] The 5-year survival rate in the United States and most Western countries is between 5% and 15%.[3] Age-standardized incidence rates of gastric cancer are highest in Japan; however, because of mass screening that leads to earlier disease stage at diagnosis, the 5-year survival rate is approximately 52%.[1] Adjuvant therapy for gastric cancer after surgical resection has been investigated for many years. Its efficacy in gastric cancer remains questionable because no concrete evidence exists to show that adjuvant therapy for resected gastric cancer improves survival. Questions exist regarding the necessity, most useful chemotherapy combinations, worldwide standardization of lymph node dissection grade, eligibility for surgery based on tumor stage, and the benefit of individualization of therapy for adjuvant chemotherapy for gastric cancer.

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Adjuvant Therapy for Resected Gastric Cancer

Early trials of adjuvant therapy for gastric cancer in Japan evaluated the use of mitomycin-C (MMC), and later, a combination of MMC and oral fluoropyrimidines. These studies showed a small survival benefit compared with surgery alone. Re-examination of these data led to additional studies of these agents. Pooled data showed borderline survival benefit for oral fluoropyrimidines compared with surgery alone.

Recent studies have shown either no differences or marginal improvement in overall survival (OS) with adjuvant chemotherapy compared with surgery alone.[4–6] Three meta-analyses of randomized, controlled clinical trials comparing surgery alone with adjuvant chemotherapy showed only

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Table 1 Meta-Analyses Randomized Clinical Trials in Patients With Resected Gastric Cancer (Adjuvant Chemotherapy *v* Surgery Alone)

Study	Trials Analyzed (No.)	HR	95% CI
Hermans et al (1993)[7]	11	0.82	0.68–0.97
Earle and Maroun (1999)[8]	13	0.80	0.66–0.97
Mari et al (2000)[6]	20	0.82	0.75–0.89

Abbreviations: CI, confidence interval; HR, hazard ratio.

marginal advantages of adjuvant chemotherapy (Table 1).[6–8] As a result of these meta-analyses, adjuvant chemotherapy following curative surgery for gastric cancer continues to be an investigational approach.[6] The use of meta-analysis has been the trend in determining benefits of adjuvant chemotherapy for resected gastric cancer, but recent studies suggest standardization of lymph node dissection protocols worldwide, tumor stage qualification for target populations of randomized trials, and surgery quality along with diagnostic procedures are all needed to qualify the results of these meta-analyses.

Adjuvant Therapy for Resected Gastric Cancer in Japan

Three randomized controlled clinical trials have been conducted or are currently underway in Japan comparing surgery with or without adjuvant chemotherapy (Table 2).[9,10]

Nashimoto et al[9] conducted a randomized, multicenter, phase III study ([Japan Clinical Oncology Group] JCOG-9206-1) to evaluate the survival benefit of adjuvant chemotherapy in patients with serosa-negative gastric cancer following curative resection. Patients were randomly assigned to observation or chemotherapy with MMC 1.33 mg/m^2, 5-fluorouracil (5-FU) 166.7 mg/m^2, and cytarabine 13.3 mg/m^2 twice weekly for the first 3 weeks after surgery, and oral 5-FU 134 mg/m^2 daily for the next 18 months. The primary endpoint was relapse-free survival. The 5-year relapse-free survival among patients who received chemotherapy in addition to surgery was 88.8% versus 83.7% in patients who underwent surgery alone; these differences were not statistically significant ($P = .14$). The 5-year survival in the chemotherapy plus surgery group was 91.2% versus 86.1% in patients who had surgery alone ($P = .13$). Fewer patients who received the combination of chemotherapy plus surgery experienced cancer recurrence (7.1%) than did patients who received surgery alone (13.8%). Because there was no relapse-free or OS benefit with this adjuvant chemotherapy regimen in patients with macroscopically serosa-negative gastric cancer after curative resection, and there were no remarkable differences in modes of cancer recurrence between the arms, the investigators concluded that adjuvant chemotherapy with this regimen is not recommended for this patient population in clinical practice.

Nakajima et al[10] conducted a randomized, phase III trial (JCOG-8801) in patients with T1 and T2 gastric tumors, who were either observed or received chemotherapy following resection to assess the survival benefit of adjuvant chemotherapy after curative gastrectomy for macroscopically serosa-negative gastric cancer. Patients who were randomly assigned to the chemotherapy group received MMC 1.4 mg/m^2 and 5-FU 166.7 mg/m^2 twice weekly for 3 weeks and oral uracil-tegafur (UFT) 300 mg daily for 18 months following surgery. At the median follow-up time of 72 months, 5-year survival was 82.9% for the observation group versus 85.8% for patients receiving chemotherapy. This difference in survival was not significant (log-rank test, $P = .17$; hazard ratio, 0.738; 95% confidence interval, 0.498–1.093). Toxic effects were generally mild. For patients with T1 (mucosal or submucosal) gastric tumors, 5-year survival was 94.9% in the observation group and 92.0% in the chemotherapy-treated group. Survival for T2 (muscularis propria or subserosa) was 76.9% and 83.0% for the observation and chemotherapy treated groups, respectively; the differences observed between the two groups were not statistically significant. The respective cancer recurrence rate was 13.7% versus 10.1% of the observation and chemotherapy-treated groups. Death from cancer occurred in 0.4% versus 1.0% of the observation and chemotherapy groups, respectively. The investigators concluded that there was no survival benefit with this adjuvant chemotherapy regimen for patients with macroscopically serosa-negative gastric cancer (T1 and T2) after surgery. They also recommended that T1 cancer patients be excluded

Table 2 Japanese Studies of Adjuvant Chemotherapy Versus Surgery Alone in Patients With Resected Gastric Cancer

Study/Trial	Target Patients	Treatment	No. of Patients	5-Year Survival (%)	*P* Value
Nashimoto et al/JCOG-9206-1[9]	T1-T2	5-FU plus MMC plus cytarabine followed by oral 5-FU	127	91.2	.13
	T1-T2	Observation	123	86.1	
Nakajima et al/JCOG-8801[10]	T1-T2	5-FU plus MMC followed by UFT	288	85.8	.17
	T1-T2	Observation	285	82.9	
JCOG 9206-2	T3-T4	5-FU plus cisplatin followed by UFT	135	*	*
	T3-T4	Observation	133	*	

Abbreviations: 5-FU, 5-fluorouracil; JCOG, Japan Clinical Oncology Group; MMC, mitomycin-C; UFT, uracil-tegafur.
*Not yet available: data will be available in 2005.

from future trials because surgery alone resulted in a good survival rate.

Results of a randomized phase III clinical trial evaluating patients with T3 and T4 gastric tumors in Japan will be available in 2005. This ongoing study has enrolled 133 patients who are being observed post-surgery and 135 patients who are receiving 5-FU plus cisplatin followed by UFT.

Another phase III study of adjuvant chemotherapy for gastric cancer in Japan (Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer [ACTS-GC])[11] began accruing patients with stage II, IIIA, or IIIB gastric cancer in October 2001. Anticipated accrual is 1,000 patients (500 patients per arm), and the primary objective is to assess OS. Expected 5-year survival of the control arm compared with the test arm is 70% versus 78%, respectively. There are 108 institutions involved in the study, 825 patients have been accrued, and the expected final accrual was completed in the third quarter of 2004. Table 2 summarizes the results of these studies.

Adjuvant Therapy for Resected Gastric Cancer in the United States

The development of adjuvant chemotherapy for gastric cancer in the West was not based on combinations with MMC, but rather 5-FU. While sometimes showing a survival benefit compared with surgery alone, these 5-FU–containing regimens have been criticized for lack of regimen standardization as adjuvant chemotherapy.

Macdonald et al[12] conducted the randomized, multicenter, phase III intergroup INT-0116 study that evaluated survival at 3 and 5 years following adjuvant chemoradiotherapy (chemoRT) in patients with adenocarcinoma of the stomach or gastroesophageal junction after curative resection. A total of 556 patients were enrolled in the trial; 275 patients were randomly assigned to receive surgery only, and 281 patients received surgery plus chemoRT. Patient tumor stage was 1 (n = 14), 2 (n = 74), 3 (n = 175), and 4 (n = 18). Of the 552 patients whose surgical records were reviewed, 10% had undergone a formal D2 lymph node dissection, 36% a D1 dissection, and most patients (54%) a D0 dissection. Adjuvant chemotherapy consisted of 5-FU 425 mg/m^2 plus leucovorin 20 mg/m^2 per day, for 5 days, followed by 4,500 cGy of radiation therapy (RT) (180 cGy/day), given 5 days per week for 5 weeks. Modified doses of 5-FU and leucovorin were given on the first 4 and the last 3 days of RT. One month after the completion of RT, two 5-day cycles of 5-FU (at 425 mg/m^2/day) plus leucovorin (20 mg/m^2/day) were given 1 month apart. The median 5-year survival was 36 months in patients who received chemoRT plus surgery versus 27 months in patients who received surgery alone. The 3-year survival rates were 50% versus 41% in the chemoRT plus surgery groups and surgery-only groups, respectively. The median duration of relapse-free survival was significantly longer in patients who received chemoRT plus surgery versus those receiving surgery only (30 *v* 19 months; $P < .001$, log-rank test). Relapses were reported in 64% of patients who received surgery only versus 43% of patients who received surgery plus chemoRT. The investigators concluded that local-regional RT plus fluoropyrimidine-based chemotherapy as adjuvant treatment significantly improves OS and relapse-free survival in patients with gastric cancer. This study also showed that the most frequently performed lymph node dissection in the United States was a D0 lymphadenectomy.

Table 3 Comparison of Results of INT-0116 and JCOG-9501[16]

	INT-0116	JCOG-9501
Surgery (%)	D0: 54 D1: 36 D2: 10	D2: 50 D3: 50
Adjuvant therapy	CT: 5-FU and LV RT: 45 Gy	None
No. of patients	281 (CT arm)	523
Tumor location (%)	Antrum: 53 Gastric body: 24 Cardia: 21 Multiple lesions: 2	Lower-third: 41 Middle-third: 39 Upper-third: 19
pT stage (1:2:3:4)	1: 14 pts 2: 74 pts 3: 175 pts 4: 18 pts	1: 23 pts 2: 257 pts 3: 230 pts 4: 13 pts
Survival (%)	3-yr: 50 5-yr: 42	5-yr: 71.4

Abbreviations: CT, chemotherapy; 5-FU, 5-fluorouracil; LV, leucovorin; pT, pathologic tumor stage; RT, radiation therapy; pts, patients.

Future Directions

Individualizing chemotherapy in various types of cancers has recently received much focused interest. In gastric cancer, individualized chemotherapy is based on subgroups of patients who are evaluated through molecular targeting that includes the use of the epidermal growth factor and vascular endothelial growth factor receptors. Recent studies have confirmed that: (1) the use of cDNA microarray analysis to detect expression files of cancer tissues improves the understanding of molecular changes during the development of gastric cancers, and (2) the expression of the S100A11 gene was useful to distinguish lymph node metastases of gastric cancers.[13–15] The evaluation of individual genetic information may prompt the future development of more personalized adjuvant chemotherapy regimens.

Discussion

In the United States, adjuvant chemoRT is considered a standard treatment and is based largely on the results of INT-0116, whereas in Japan the use of adjuvant therapy is the standard. Sasako[16] compared the results of INT-0116 with those of JCOG-9501 (Table 3).[16] INT-0116 showed a survival advantage with chemoRT plus surgery in patients with gastric cancer following curative resection; however, the 3-year survival rate in INT-0116 was only 50% which, when compared with Japanese studies, is lower than the 3-year

survival rate in patients who received surgery alone. The JCOG-9501 trial was designed to compare survival in patients with D2 versus D3 lymph node dissection without adjuvant chemotherapy or RT, while in INT-0116 the majority of patients had a D0 or D1 lymph node dissection and also received chemoRT. In the Japanese trial JCOG-9501 there was a higher proportion of patients with T2 disease than in the INT-0116 trial (49% *v* 26%) and also a lower proportion of patients with T3 disease (44% *v* 62%), respectively. Five-year survival rates were considerably higher (71%) in patients who received surgery only in the Japanese trial versus 42% in patients who received surgery plus chemoRT in the US trial. The Japanese interpretation of these results are that D0 or D1 lymph node dissection plus chemoRT is better than D0 or D1 lymph node dissection alone, but may be worse than D2 surgery alone. Determining whether a D0 or D1 lymph node dissection can replace a D2 lymph node dissection should be evaluated in a randomized, controlled clinical trial; however, D2 lymph node dissection in the United States appears difficult to achieve. Also, whether chemoRT after D2 surgery can improve the results of surgery alone is another unresolved issue.

Several factors should be considered when interpreting the differences in the results of these trials. Because the incidence of gastric cancer is several times higher in Japan than in the United States there are more stringent screening programs in place that may affect the baseline condition of patients accrued onto clinical trials. Moreover, the standard curative resection in the United States is gastrectomy plus D0 or D1 lymphadenectomy, whereas in Japan gastrectomy plus D2 lymphadenectomy with en bloc dissection of the lymph nodes around the common hepatic artery and the splenic artery is used. Japanese surgeons believe that these differences may be because of the additional experience they have acquired due to the higher incidence of gastric cancer in Japan.

The Japanese viewpoint on the use of adjuvant therapy in patients with gastric cancer following curative resection is that the quality of surgery, including diagnostic procedures or pathologic procedures, will be a more important prognostic factor than adjuvant chemotherapy because no survival advantages have been shown in patients with gastrectomy and D2 lymph node dissection in clinical trials. However, standard adjuvant chemotherapy after good local control by surgery (D2 or more) has yet to be established and remains an urgent issue. Also, data from clinical trials indicate that patients with stage 1–2 tumors should be excluded from the target populations of randomized, controlled clinical trials. In the United States and Europe there had been either no or only marginal improvement in OS or disease-free survival for patients receiving adjuvant chemotherapy following gastric cancer resection, until the results of INT-0116 became available, at which time the issue of postoperative chemoRT became the standard treatment for patients with gastric carcinoma. The question as to whether or not chemoRT can improve the results of D2 surgery alone remains unsolved.

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Pilot Study of Concurrent Etoposide and Cisplatin Plus Accelerated Hyperfractionated Thoracic Radiotherapy Followed by Irinotecan and Cisplatin for Limited-Stage Small Cell Lung Cancer: Japan Clinical Oncology Group 9903

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Abstract

Purpose: Irinotecan and cisplatin (IP) significantly improved survival compared with etoposide and cisplatin (EP), in patients with extensive-stage small cell lung cancer (SCLC) in a previous Japan Clinical Oncology Group (JCOG) randomized trial. JCOG9903 was conducted to evaluate the safety of sequentially given IP following concurrent EP plus twice-daily thoracic irradiation (TRT) for the treatment of limited-stage SCLC (LSCLC).

Experimental Design: Between October 1999 and July 2000, 31 patients were accrued from 10 institutions. Thirty patients were assessable for toxicity, response, and survival. Treatment consisted of etoposide 100 mg/m^2 on days 1 to 3, cisplatin 80 mg/m^2 on day 1, and concurrent twice-dailyTRTof 45 Gy beginning on day 2. The IP regimen started on day 29 and consisted of irinotecan 60 mg/m^2 on days 1, 8, and 15 and cisplatin 60 mg/m^2 on day 1, with three 28-day cycles.

Results: There were no treatment-related deaths. The response rate was 97% (complete response, 37%; partial response, 60%). Median overall survival was 20.2 months; 1-, 2-, and 3-year survival rates were 76%, 41%, and 38%, respectively. Of the 24 patients who started the IP regimen, 22 received two or more cycles. Hematologic toxicities of grade 3 or 4 included neutropenia (67%), anemia (50%), and thrombocytopenia (4%). Nonhematologic toxicities of grade 3 or 4 included diarrhea (8%), vomiting (8%), and febrile neutropenia (8%). Of the 20 patients with recurrence, none had local recurrence alone and only two had both local and distant metastasis as the initial sites of disease progression.

Conclusions: IP following concurrent EP plus twice-dailyTRT is safe with acceptable toxicities. A randomized phase III trial comparing EP with IP following EP plus concurrentTRT for LSCLC is ongoing (JCOG0202).

Despite efforts to curb smoking, lung cancer remains the leading cause of cancer deaths in many industrialized countries. Small cell lung cancer (SCLC) accounts for about 15% of all lung cancer histology. Whereas combination chemotherapy is the cornerstone of SCLC treatment, meta-analyses showed that adding thoracic radiotherapy to combination chemotherapy significantly improves the survival of patients with limited-stage SCLC (LSCLC; i.e., disease confined to the hemithorax; refs. 1, 2). Several randomized trials have shown that early use of concurrent thoracic radiotherapy is superior to sequential or late use when etoposide and platinum are employed as combination chemotherapy (3–5). An intergroup phase III study showed accelerated hyperfractionated radiotherapy with etoposide and cisplatin (EP) to be superior to standard fractionation, with 5-year survival rates of 26% and 16%, respectively (6). Although substantial progress has been made during the past two decades, many LSCLC patients experience tumor recurrence and succumb to the disease, indicating the need for improved LSCLC therapy.

The Japan Clinical Oncology Group (JCOG) previously conducted a randomized phase III trial comparing irinotecan and cisplatin (IP) with EP in patients with extensive-stage SCLC. The response rate and overall median survival were significantly better for IP (i.e., 84.4% and 12.8 months with IP versus 67.5% and 9.4 months with EP, respectively). The 2-year

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Note: Portions of this study were presented at the 39th Annual Meeting of the American Society of Clinical Oncology, May 31 to June 3, 2003, Chicago, Illinois.

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survival rates were 19.5% for IP and 5.2% for EP (7). These encouraging results prompted us to explore the use of IP in LSCLC. We therefore undertook a pilot study to evaluate the safety of IP following concurrent EP plus twice-daily thoracic irradiation (TRT) for LSCLC.

Experimental design

Eligibility criteria. Patients with histologically or cytologically documented LSCLC, defined as disease confined to one hemithorax including bilateral supraclavicular nodes, were enrolled in this study. Additional eligibility criteria consisted of measurable or assessable disease, age <75 years, Eastern Cooperative Oncology Group performance status of 0 to 2, no previous treatment, leukocyte count $\geq 4{,}000/mm^3$, platelet count $\geq 10^5/mm^3$, hemoglobin ≥ 9.5 g/d, serum creatinine ≤ 1.5 mg/d, creatinine clearance ≥ 60 mL/min, serum bilirubin ≤ 1.5 mg/d, serum transaminase $\leq 2 \times$ ULN, and $PaO_2 \geq 70$ mm Hg. Exclusion criteria included active infection, uncontrolled heart disease or a history of myocardial infarction within the previous 3 months, interstitial pneumonia/active lung fibrosis on chest X-ray, peripheral neuropathy, malignant pleural or pericardial effusion, diarrhea, intestinal obstruction or paralysis, and active concomitant malignancy. The TRT portal should be no more than half of the hemithorax. No prior chemotherapy or radiotherapy was permitted. Pregnant or lactating women were excluded. Before enrollment in the study, each patient provided a complete medical history and underwent physical examination, blood cell count determinations, arterial blood gas, biochemical laboratory examinations, chest X-ray, electrocardiogram, chest computed tomographic scan, and whole-brain computed tomographic or magnetic resonance imaging, abdominal ultrasound and/or computed tomographic, and isotope bone scans. Blood cell counts, differential white counts, and other laboratory data were obtained weekly during each course of chemotherapy. All patients were reassessed at the end of treatment in the same manner as at the time of enrollment.

Treatment plan. Induction chemotherapy consisted of cisplatin 80 mg/m^2 on day 1 and etoposide 100 mg/m^2 on days 1 to 3. TRT was begun on day 2 of the induction chemotherapy and given twice daily (1.5 Gy per fraction, with ≥ 6 hours between fractions) and directed to the primary tumor for a total dose of 45 Gy in 3 weeks. The initial field included the primary disease site with a 1.5-cm margin around the mass, the ipsilateral hilum, the entire width of the mediastinum, and the supraclavicular lymph nodes (only if there was nodal tumor involvement). TRT was done with linear accelerators and the energy was 6 to 10 MV photons. After the administration of 30 to 36 Gy, the radiation field was reduced around the primary tumor and involved lymph nodes using parallel opposed oblique fields to limit the dose to the spinal cord and protect the uninvolved lung field. Following chemoradiotherapy, patients were treated with three cycles of IP. The IP regimen started on day 29 and consisted of irinotecan 60 mg/m^2 on days 1, 8, and 15 and cisplatin 60 mg/m^2 on day 1, with three 28-day cycles. If the leukocyte count decreased to $<3{,}000/mm^3$ or the platelet count fell below $100{,}000/mm^3$ on the first day of IP, chemotherapy was withhold until the counts recovered to $\geq 3{,}000/mm^3$ and $\geq 100{,}000/mm^3$, respectively. Administration of irinotecan was skipped on day 8 and/or 15 if the leukocyte count was $\leq 2{,}000/mm^3$, the platelet count was $\leq 50{,}000/mm^3$, or there was any diarrhea regardless of grade, or a fever of $\geq 37.5°C$. The dose of irinotecan in subsequent cycles was reduced by 10 mg/m^2 from the planned dose if grade 4 hematologic toxic effects or grade 2 or 3 diarrhea developed. Administration of granulocyte colony-stimulating factor was prohibited on the days of chemotherapy or radiotherapy. Primary prophylactic granulocyte colony-stimulating factor was not given. For patients who had developed grade 4 neutropenia during the previous cycles of chemotherapy, secondary prophylactic granulocyte colony-stimulating factor administration was allowed. Prophylactic antibiotics were not given.

Treatment was discontinued in patients with grade 4 nonhematologic toxicity. Prophylactic cranial irradiation (25 Gy in 10 fractions) was conducted for patients showing a complete response or near complete response defined as a reduction of >90% in the sum of the products of the greatest perpendicular dimensions of bidimensional lesions. Tumor responses were assessed radiographically. Standard WHO response criteria (8) were used, and all responses were confirmed ≥ 28 days after initial documentation of the response. JCOG criteria were used to assess toxicity (9). JCOG criteria are similar to those of the National Cancer Institute Common Toxicity Criteria (10). Esophageal toxicity was graded as follows: grade 3, moderate to severe ulceration and edema, cannot eat, requires narcotic drugs; grade 4, serious ulceration and edema, resulting in complete obstruction or perforation.

Statistical consideration. The primary objective of this study was to evaluate the safety and feasibility of sequential administration of IP following EP plus concurrent twice-daily TRT. Simon's optimal two-stage design was used to determine the sample size and decision criteria (11). The regimen would be considered feasible if two cycles or more of IP were completed without grade 4 nonhematologic toxicity or treatment related death in at least 90% of patients and not feasible if the completion rate was ≤70%. The required number of patients was estimated to be 27, with $\alpha = 0.05$ and $\beta = 0.80$. We determined the planned sample size for the study to be 30 patients accrued over 12 months, with 36 months of additional follow-up.

Time-to-progression was calculated from the date of entry into study until the date of documented progression or death (in the absence of progression). Survival was calculated from the protocol treatment start date until the date of death. Both intervals were determined by the Kaplan-Meier method.

The protocol was approved by the Clinical Trial Review Committee of JCOG and the Institutional Review Board of the participating institutions. All patients provided written informed consent.

Results

Patient characteristics. Between October 1999 and July 2000, 31 patients were accrued from 10 institutions. Patient characteristics are detailed in Table 1. Although eligible, no patients with a performance status of 2 were actually enrolled in this trial. Thirty-one patients ultimately participated. One patient did not receive the protocol treatment because of a problem with the radiation equipment in the institution providing treatment. Thus, this patient was not evaluable.

Adherence to treatment plan. All patients completed concurrent chemoradiotherapy. Six patients did not receive the IP regimen, because of disease progression, septic shock

Table 1. Patient characteristics

Patient registered	31
Assessable	30
Not assessable (not treated)	1
Median age (range)	64 (43-74)
Gender	
Male	27
Female	4
Performance status 0/1	8/23

during chemoradiotherapy, renal dysfunction, or leukocytopenia, and two refused IP. Of the 24 patients given the IP regimen, 22 received two cycles or more of IP. The reasons for terminating IP before the second treatment cycle were grade 4 diarrhea in one patient and refusal, not significant toxicity, in one patient. Of the 22 patients who received two cycles or more of IP, nine received the original planned dose. In five patients, dose reductions in the second cycle of IP were necessary, 11 patients skipped day 8 and/or 15 irinotecan, and one patient had a minor protocol violation. Fifteen patients required that the second cycle of IP be delayed for 1 to 14 days. Of 17 patients (58%) who received the entire treatment, the median time delay from the planned protocol was 4 days (range, 0-21 days). Six patients were able to start the third cycle of IP without delay, relative to the first cycle of IP.

Toxicity. Toxicities associated with concurrent chemoradiotherapy are summarized in Table 2. The major toxicity was neutropenia. One patient had febrile neutropenia and septic shock. The same patient experienced grade 3 fatigue and anterior chest pain. IP was well tolerated (Table 3), despite diarrhea, vomiting, and hematologic toxicities. One patient, who had grade 2 nausea/vomiting, refused further treatment after the first cycle of IP. Another patient, who refused days 8 and 15 irinotecan during the second cycle, had grade 2 diarrhea and nausea/vomiting. No grade 3 or 4 pulmonary toxicity was observed. There were no treatment-related deaths.

Table 2. Major toxicities concurrent EP/TRT ($n = 30$)

Toxicity	Grade 3, no. patients (%)	Grade 4, no. patients (%)
Hematologic		
Anemia	0	0
Leucopenia	13 (43)	15 (50)
Neutropenia	9 (30)	19 (63)
Thrombocytopenia	2 (7)	1 (3)
Nonhematologic		
Esophagitis	2 (7)	0
Infection	1 (3)	0
Hypotension*	0	1 (3)
Fatigue*	1 (3)	0
Anterior chest pain*	1 (3)	0
Febrile neutropenia	2 (7)	

*These events occurred in the same patient.

Table 3. Major toxicities irinotecan and cisplatin (IP), ($n = 24$)

Toxicity	Grade 2, no. patients (%)	Grade 3, no. patients (%)	Grade 4, no. patients (%)
Hematologic			
Anemia	6 (25)	12 (50)	0
Leucopenia	6 (25)	12 (50)	5 (21)
Neutropenia	5 (21)	12 (50)	5 (21)
Thrombocytopenia	5 (21)	1 (4)	0
Nonhematologic			
Diarrhea	4 (17)	1 (4)	1 (4)
Vomiting	3 (13)	2 (8)	0
Febrile neutropenia	—	2 (8)	0
Fever	2 (8)	0	0
Infection	4 (17)	0	0

Neither grade 2, or more severe, late radiation toxicities nor radiation recall reactions were reported.

Response and survival. The overall response rate was 97% (complete response, 37%; partial response, 60%). Overall and progression-free survivals are depicted in Figs. 1 and 2 The median follow-up time of all patients was 20 months and that for surviving patients 40 months. The median progression-free survival was 9 months, and the median overall survival was 20 months. The 24- and 36-month overall survivals were 41% and 38%, the 24- and 36- month progression-free survivals 30% and 26%, respectively.

Pattern of relapse. First sites of disease progression are presented in Table 4. Of the 18 patients who have died to date, all died of progressive disease. Surprisingly, no patient showed relapse solely at the local-regional site (within TRT field). Only two patients had both local and distant involvement. There were 11 patients whose initial site of relapse was the brain. Of these, six had relapses solely in the brain. Whereas two patients had complete response and received prophylactic cranial irradiation, four had partial remission and did not receive prophylactic cranial irradiation.

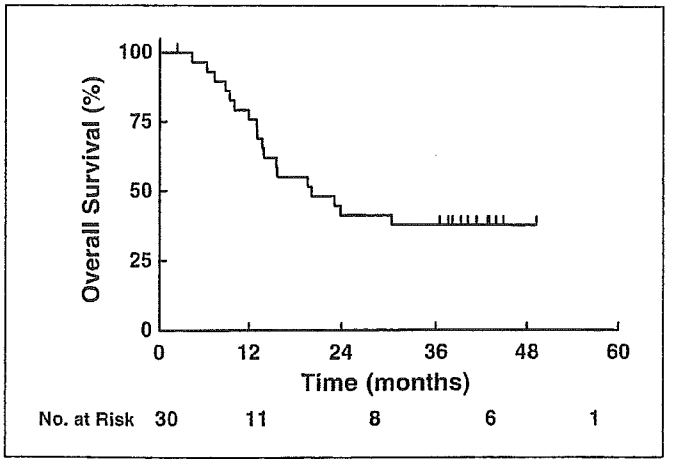

Fig. 1. Overall survival.

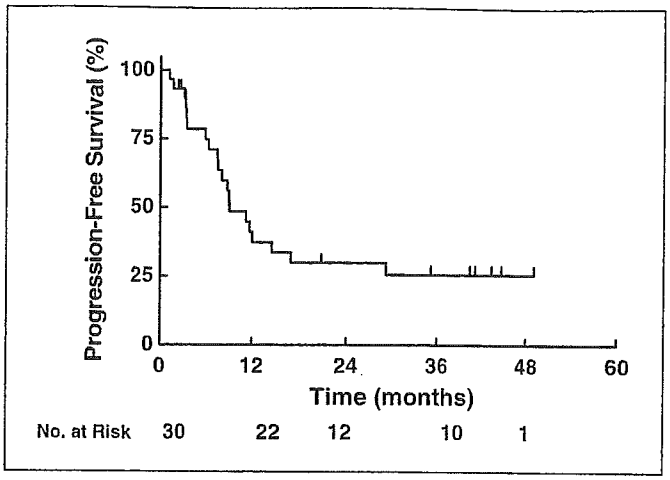

Fig. 2. Progression-free survival.

Other relapse sites included the liver in four patients, bone in three, pleural effusion in three, and supraclavicular lymph nodes in two.

Discussion

Irinotecan is one of the most active agents against SCLC (12). A phase II study of irinotecan and cisplatin yielded a response rate of 86% and median survival of 13.2 months in patients with extensive SCLC (13). A phase III study confirmed excellent results and showed IP to be more effective than etoposide and cisplatin in extensive SCLC (7). Three confirmatory trials, comparing IP with EP for extensive SCLC are ongoing in Europe and the United States. Although dose-finding studies to explore integrating irinotecan into the early concurrent phase of chemoradiation for LSCLC are also currently being conducted by the Radiation Therapy Oncology Group and other U.S. groups. The dose-finding JCOG study of concurrent use of IP with TRT in stage III non-small cell lung cancer showed that the full dose of irinotecan could not be given due to neutropenia, diarrhea, and pulmonary toxicity (14). Thus, we employed IP as a sequential treatment following EP plus concurrent TRT.

The present trial showed IP following concurrent EP plus twice-daily TRT to be safe, with acceptable toxicities. Hematologic toxicities and diarrhea, while on the IP regimen following concurrent chemoradiotherapy, are similar to those of a previous phase III trial conducted by JCOG (JCOG9503; ref. 7). Neither grade 3 or 4 pulmonary toxicity nor treatment related deaths were observed. The West Japan Thoracic Oncology Group conducted a similar phase II study of EP plus twice-daily TRT followed by IP for LSCLC (15). Promising response (88%) and 2-year survival (51%) rates were reported, with acceptable toxicities.

Table 4. Sites of first failure ($n = 20$)

Site	No. patient (%)
Isolated local-regional failure	0 (0)
Local-regional and distant	2 (10)
Distant	18 (90)
Brain only	6 (30)
Other sites of failure*	12 (60)

*Recurrence at sites other than the primary tumor or brain only.

Local failure is an important problem in the treatment of LSCLC. Turrisi et al. showed the rate of local failure to be reduced in the twice-daily TRT plus EP group as compared with the once-daily TRT plus EP group: the rate was 52% in the group receiving once-daily therapy and 36% in that receiving twice-daily therapy (6). Eighteen percent of patients who received EP plus concurrent twice-daily TRT had first progression within the thorax in the previous JCOG phase III trial (5). It is noteworthy that no patient relapsed solely at the local-regional site and only two patients had both local and distant involvement in the present trial. There may be an interaction between TRT and IP even given sequentially. Another possibility relates to recent improvements in radiotherapeutic techniques with better imaging of the target volume by chest computed tomographic. This possibility should be assessed in a future randomized trial.

It is important to integrate new active anticancer agents to the combined modality treatments for LSCLC. Irinotecan has been clearly shown to have clinical activity in a randomized trial, against extensive-stage SCLC. Several other new agents including targeted therapies have failed to show clinical activity against SCLC. Based on these considerations, we conducted a randomized phase III trial comparing EP with IP following EP plus concurrent TRT for the treatment of LSCLC (JCOG0202). In the JCOG0202, eligible patients were randomized after the completion of induction chemoradiotherapy. Although feasibility may be a limitation of the present study, improvements are anticipated with appropriate use of granulocyte colony-stimulating factor, antibiotics, and patient education.

In summary, irinotecan and cisplatin following EP plus concurrent twice-daily TRT is a safe and active regimen for LSCLC. The observed low rate of local recurrence is encouraging. A randomized phase III trial comparing EP with IP following EP plus concurrent TRT for the treatment of LSCLC is currently under way.

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Phase 1 Clinical Trials in Oncology

TO THE EDITOR: Horstmann et al. (March 3 issue)[1] assume that a tumor response is of benefit to subjects in phase 1 oncology trials. This assumption is not valid. A complete or partial tumor response in a phase 1 trial is a surrogate end point, which for most agents has not been linked to a clinically meaningful outcome, such as improved survival.[2]

Informing subjects that they have a 10.6 percent chance of a tumor response is potentially misleading unless accompanied by an explicit discussion of clinical end points and whether any connection exists between a tumor response and clinical end points.[3] This discussion should include an explanation that a tumor response is not a cure or a life extender.

Kurzrock and Benjamin's editorial[4] serves only to increase the misrepresentation of phase 1 research.[5] It is important to know that phase 1 research is essential for the development of future treatments. But it is simply misleading to treat an improvement in the rate of tumor response as an increase in the likelihood of direct clinical benefit to subjects.

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TO THE EDITOR: The article by Horstmann et al. and the accompanying editorial indicate rates of clinical benefit higher than those reported in previous meta-analyses. Horng et al.,[1] in a critique of informed consent in phase 1 oncology trials, decried the frequent lack of an explicit statement that efficacy was not to be expected. However, in addition to evidence presented by Horstmann et al., recent phase 1 trials with established drugs have often resulted in high response rates. Among nine trials involving patients with refractory non–small-cell lung cancer that were presented at the meeting of the American Society of Clinical Oncology in May 2002, the reported response rate was 41 percent (range, 0 to 57 percent) in 150 patients, with one drug-related death recorded. Prior estimates of the risks and benefits of phase 1 oncology trials need updating, and insistence on not conveying therapeutic intent in the informed-consent process in all instances is misplaced.

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1. Horng S, Emanuel EJ, Wilfond B, Rackoff J, Martz K, Grady C. Descriptions of benefits and risks in consent forms for phase 1 oncology trials. N Engl J Med 2002;347:2134-40.

TO THE EDITOR: In their review of 460 phase 1 oncology trials sponsored by the Cancer Therapy Evaluation Program between 1991 and 2002, Horstmann et al. report that the overall toxicity-related death rate was 0.49 percent, which suggests that these trials are relatively safe, considering that virtually all participants have a deadly disease and have exhausted the conventional treatments.[1]

We analyzed the data from 363 trials of investigational new drugs, involving 12,395 adults with solid tumors, that were published between 1976 and

1993.[2] A total of 117 toxicity-related deaths (0.94 percent) and 33 early deaths from unknown causes (0.27 percent) were noted. In addition, 36 trials were excluded from the analysis because further clinical development of the drug was not recommended. We found that toxicity-related death occurred in 26 of 1039 patients in these trials (2.5 percent). Thus, the rate of death due to toxic events varies among phase 1 oncology trials and may be higher than suspected.

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TO THE EDITOR: Kurzrock and Benjamin argue that clinical benefit is an objective of phase 1 cancer trials, citing my article as an instance of an opposing "misconception."[1] The misconception is theirs, as is evident in authoritative definitions.[2,3] Moreover, in failing to distinguish between what phase 1 trials are specifically designed to measure (dose–toxicity profiles) and what is incidental to the design (e.g., the possibility of benefit), Kurzrock and Benjamin ignore the way in which the strictures of protocol constrain the goals of medicine. This misunderstanding, known as the "therapeutic misconception,"[4] reinforces the fiction that clinical research is an extension of clinical care, rather than a fundamentally distinct and sometimes contrary enterprise. Patients in early cohorts in these trials who receive, by design, what Kurzrock and Benjamin call "subtherapeutic" doses are not involved in a trial that aims to maximize their clinical benefit. Failure to see this as a conflict between the objectives of science and those of personal care is the reason the therapeutic misconception has been called "the most important threat to the validity of informed consent to research."[5]

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1. Miller M. Phase 1 cancer trials: a crucible of competing priorities. Int Anesthesiol Clin 2001;139:13-33.
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THE AUTHORS REPLY: The letters from Drs. Rothschild and King and from Dr. Muggia demonstrate the complexity of understanding "benefits" in the context of phase 1 oncology trials. As Drs. Rothschild and King suggest, tumor response, the most common measure of the effect of agents used for the treatment of cancer, is indeed a surrogate marker. Although tumor response does not necessarily correlate with clinical benefit, it is predictive of potential benefit, and there is evidence that tumor response is associated with symptom relief, improved quality of life, and increased survival.[1-4]

We agree that information provided to potential participants in phase 1 trials should be comprehensive, contextual, and clear about the uncertain or inconsistent relationship of possible tumor responses to clinically meaningful benefit.

Furthermore, it should be made clear that although some participants in phase 1 trials may benefit clinically, these trials are designed to evaluate safety, not therapeutic effect. There is a difference between the possibility of benefit from an intervention in a trial and the intent of the researchers when designing the trial. In this regard, we disagree with Dr. Muggia and maintain that consent forms should not describe the purpose or intent of phase 1 trials as therapeutic. Nonetheless, we recognize that although institutional review boards, bioethicists, and others might emphasize the intention of a trial, prospective patients may be more interested in possible benefits than in whether or not the trial is intended to be therapeutic. Our data demonstrate that sometimes there is therapeutic benefit, regardless of the intention of the research.

The statement by Drs. Sekine and Tamura that "the rate of death due to toxic events varies among phase 1 oncology trials" is consistent with the findings of our study. The data they cite emphasize two important realities that should be considered with

regard to response or toxicity rates in phase 1 trials: first, different subsets of data have strikingly different benefit and toxicity rates, and second, response and toxicity rates based on published data may be biased. Their data support the view that the details of a trial matter in interpreting the data on response and toxicity. Simply labeling a trial phase 1 is not sufficiently informative about risks and benefits; more specific details about the trial and the intervention are necessary.

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THE EDITORIALISTS REPLY: Rothschild and King's allegation that it is "misleading to treat an improvement in the rate of tumor response as an increase in the likelihood of direct clinical benefit to subjects" is at variance with our clinical experience and the oncology literature. Decades ago, Freireich et al.[1] established that improvement in survival in leukemia could be attributed directly to the duration of a response. A response to chemotherapy in randomized trials improved the quality of life despite significant side effects.[2] Differences in benefit between patients with and those without a response may be obscured, however, by an inadequate definition of a response. For example, patients with gastrointestinal stromal tumors who were treated with imatinib mesylate and who had stable disease according to the criteria of the Response Evaluation Criteria in Solid Tumors group derived a benefit that was indistinguishable from the benefit in those with a partial response.[3] Logic dictates that patients with good performance status and intact organ function — the eligibility criteria for most phase 1 studies — will not die of their cancer unless it progresses.

The perception that, in phase 1 studies, drugs are administered to patients solely to reveal drug toxicity is incorrect, since the objectives of phase 1 trials specifically include describing the response. Oncologists refer patients for phase 1 studies because they determine that participation in those studies offers their patients, whose disease has progressed after recognized therapies, their best chance of benefit. Thus, the primary concern of treating physicians and patients is efficacy. Miller's contention that the scientific restrictions of the protocols interfere with patient care is partially valid. For instance, some patients who might benefit are excluded from phase 1 trials by the eligibility criteria. Low initial doses and small dose increases, resulting from excessive caution about patient safety, can detract from benefit to patients. Nonetheless, as Horstmann et al. have demonstrated, phase 1 studies resulted in stable disease or better in up to 44.7 percent of patients, including those treated at the lower doses.

Increased time before the progression of cancer benefits patients unless the therapy has serious toxic effects. The worse "toxicity" is most often that due to progressive disease. We agree with Muggia, who demonstrates that recent phase 1 trials have higher response rates than previously reported and have extraordinarily low death rates. Although participants in any study should be informed that patients who have a response to therapy may not always benefit, it is misleading to tell patients that there is no clinical benefit from a response and that phase 1 trials have no therapeutic aim.

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Standard Thoracic Radiotherapy With or Without Concurrent Daily Low-dose Carboplatin in Elderly Patients with Locally Advanced Non-small Cell Lung Cancer: a Phase III Trial of the Japan Clinical Oncology Group (JCOG9812)

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Background: The purpose of this study was to evaluate whether radiotherapy with carboplatin would result in longer survival than radiotherapy alone in elderly patients with unresectable stage III non-small cell lung cancer (NSCLC).
Methods: Eligible patients were 71 years of age or older with unresectable stage III NSCLC. Patients were randomly assigned to the radiotherapy alone (RT) arm, irradiation with 60 Gy; or the chemoradiotherapy (CRT) arm, the same radiotherapy and additional concurrent use of carboplatin 30 mg/m^2 per fraction up to the first 20 fractions.
Results: This study was terminated early when 46 patients were registered from November 1999 to February 2001. Four patients (one in the RT arm, three in the CRT arm) were considered to have died due to treatment-related causes. The JCOG Radiotherapy Committee assessed these treatment-related deaths (TRDs) and the compliance with radiotherapy in this trial. They found that 60% of the cases corresponded to protocol deviation and 7% were protocol violation in dose constraint to the normal lung, two of whom died due to radiation pneumonitis. As to the effectiveness for the 46 patients enrolled, the median survival time was 428 days [95% confidence interval (CI) = 212–680 days] in the RT arm versus 554 days (95% CI = 331 to not estimable) in the CRT arm.
Conclusions: Due to the early termination of this study, the effectiveness of concurrent use of carboplatin remains unclear. We re-planned and started a study with an active quality control program which was developed by the JCOG Radiotherapy Committee.

Key words: non-small cell lung cancer – elderly patients – carboplatin – chemoradiotherapy

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in the USA, Europe and Japan. In Japan, the number of elderly is increasing dramatically. In 2001, the proportion of Japanese population older than 65 years was 18%; in other words, the number of people older than 65 years exceeded 22 million (1). Lung cancer death rates for men and women aged 75 or more have increased to ~531 and 138 per 100 000 population, respectively (1). To establish the effective treatment for the elderly with lung cancer has thus become of greater importance.

Until recently, the standard treatment for locally advanced non-small cell lung cancer (NSCLC) was radiotherapy alone. However, the 5-year survival rate of patients with stage III remained under 10% (2–4). To improve the survival rates, many clinical trials comparing radiotherapy with chemoradiotherapy have been conducted (5–11). A recent meta-analysis suggested that the combination of chemotherapy containing cisplatin (CDDP) and radiation could improve the survival rate compared with radiotherapy alone (12,13). However, it is still unclear whether the combined chemoradiotherapy is also suitable for elderly patients. This is partly because the elderly had been considered inappropriate as study patients.

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Almost all evidence available has thus been derived from subset analysis of trials for locally advanced NSCLC. A secondary analysis of RTOG 94-10 revealed a greater survival benefit for concurrent chemotherapy (14). Schild et al. reported no significant difference in tumor regression between younger and older patients in an NCCTG trial (15). Meanwhile, some reports on inoperable NSCLC patients indicate that chemoradiotherapy has survival benefit compared with radiotherapy, but this may not be applicable for those >70 years of age, for whom radiation alone could be most beneficial (16,17).

Therefore, we cannot treat the elderly in the same way as we can younger patients: first, as elderly patients have poorer prognosis than younger patients, they may think that their quality of life is more important than risking radical treatment. Secondly, the elderly tend to be vulnerable to intensive care and toxicities of treatment drugs (18–21). Less toxic therapy may be more effective for the elderly with NSCLC.

Some clinical trials, in which the elderly were not included, showed some efficacy of carboplatin (CBDCA), an analog of CDDP, having no nephrotoxicity, neurotoxicity or ototoxicity and being much less emesis-provoking than CDDP (22–24). Additionally, some investigators found the same radiosensitizing properties of CBDCA (25–28) as also found for CDDP. Therefore, we hypothesized CBDCA to be more acceptable in the treatment of elderly patients. A phase II study has reported the use of radiotherapy and concurrent low-dose daily CBDCA in elderly patients with locally advanced NSCLC (29). For stage III patients, the median survival time (MST) was 15.1 months. Given an MST of ~10 months by radiation alone (5,6,8,9,11,17), this combined chemoradiotherapy seemed promising. Here we performed a randomized study to determine whether this combined chemoradiotherapy has an impact on survival in elderly patients with unresectable locally advanced NSCLC compared with radiotherapy alone.

PATIENTS AND METHODS

PATIENTS

Eligibility criteria for this study were as follows: age ≥71 years; a histologically confirmed non-small cell carcinoma; unresectable disease; stage IIIA except T3N1M0 and IIIB which does not have disease extended to any contralateral hilar nodes or any supraclavicular nodes, atelectasis of the entire lung or malignant pleural effusions; measurable disease; a required radiation field of less than one half of one lung; no previous chemotherapy or radiotherapy; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; PaO_2 ≥70 torr, white blood cell count ≥4000/μl, hemoglobin level ≥9.5 g/dl, platelet count ≥100 000/μl, serum bilirubin level ≤1.5 mg/dl, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ twice the upper limit of normal, and serum creatinine level ≤ the upper limit of normal; a life expectancy of at least 3 months; and written informed consent. Exclusion criteria included patients with active infection, interstitial pneumonia or active lung fibrosis, chronic obstructive pulmonary disease (COPD) or uncontrolled heart disease, an active synchronous cancer, or a metachronous cancer within three disease-free years.

Staging was performed by chest radiograph in two directions, computed tomography (CT) scan or magnetic resonance imaging (MRI) of the head, CT scan of the chest, CT scan or ultrasound of the abdomen, and bone scintigraphy.

TREATMENT

Patients were randomly assigned to the radiotherapy (RT) arm or the chemoradiotherapy (CRT) arm, by the minimization method of balancing PS (0 or 1 versus 2), stage (IIIA versus IIIB) and institution. The RT consisted of 60 Gy in 30 fractions over 6 weeks. In the CRT arm, patients received the same radiotherapy as in the RT arm and concurrent intravenous administration of CBDCA 30 mg/m^2 (30 min infusion) 1 h before every radiation treatment up to the first 20 fractions (Fig. 1).

Radiotherapy was delivered with megavoltage (6–10 MeV photons) equipment using anterior/posterior opposed fields up to 40 Gy including the primary tumor, the metastatic lymph nodes and the regional node. A booster dose of 20 Gy was given to the primary tumor and the metastatic lymph nodes for a total dose of 60 Gy using bilateral oblique fields. The clinical target volume (CTV) for the primary tumor was defined as the gross tumor volume (GTV) plus 1 cm taking account of subclinical extension. CTV and GTV for the metastatic nodes (>1 cm in shortest dimension) were the same. Regional nodes excluding contra-lateral hilar and supraclavicular nodes were included in the CTV; however, lower mediastinal nodes were included only if the primary tumor was located in the lower lobe of the lung. The planning target volumes for the primary tumor, the metastatic lymph nodes and regional nodes were determined as CTVs plus 0.5–1.0 cm margins laterally and 1.0–2.0 cm margins cranio-caudally taking account of set up variations and internal organ motion. Lung heterogeneity corrections were not used.

The criteria for stopping the treatment are pulmonary toxicities, which include the National Cancer Institute-Common Toxicity Criteria (NCI-CTC; version 2.0) grade 2 respiratory distress and <60 torr PaO_2, other than hematopoietic toxicities (leukopenia, neutropenia and thrombocytopenia) or gastrointestinal toxicities (dysphagia).

EVALUATION

To assess the rate of tumor response and toxicity, all patients received a complete blood cell count; blood chemistry, including AST, ALT, lactate dehydrogenase, bilirubin, serum creatinine, blood urea nitrogen, total protein, serum albumin, serum electrolytes and calcium; and weekly chest X-rays during the treatment period. Best overall response was evaluated as tumor response by mono- or bi-dimensional measurement in accordance with the World Health Organization (WHO) criteria (30), and toxicity was evaluated in accordance with the NCI-CTC (version 2.0).