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Diseases of the Esophagus (2005) 18, 388–397
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DISEASES OF THE ESOPHAGUS

Original article

Neoadjuvant chemoradiotherapy followed by esophagectomy for initially resectable squamous cell carcinoma of the esophagus with multiple lymph node metastasis

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SUMMARY. **Neoadjuvant chemoradiotherapy (CRT) was expected to improve surgical curability and prognosis for advanced esophageal cancer. However, the clinical efficacy of neoadjuvant CRT followed by esophagectomy with three-field lymphadenectomy (3FL) for initially resectable esophageal squamous cell carcinoma (SCC) remains unclear. Since 1998, we have defined the status of metastases to five or more nodes, or nodal metastases present in all three fields as multiple lymph node metastasis, which was previously shown to be associated with poor prognosis. Between 1998 and 2002, 83 patients with initially resectable esophageal SCC were prospectively allocated into two groups, according to the clinical status of nodal metastasis. Nineteen patients clinically accompanied by multiple lymph node metastasis initially underwent neoadjuvant CRT followed by curative esophagectomy with 3FL (CRT group). The other 64 patients clinically without multiple lymph node metastasis immediately received curative esophagectomy with 3FL (control group). Although the overall morbidity rate was significantly higher in the CRT group, no in-hospital death occurred in either group. Patients without pathologic multiple lymph node metastasis in the CRT group showed a significantly better disease-free survival rate than either patients pathologically with multiple lymph node metastasis in the control group or those in the CRT group. However, the differences in the overall survival rate among the groups were not significant. Thus, the significant survival benefit by neoadjuvant CRT in addition to esophagectomy with 3FL was not confirmed, although it may have been advantageous, without increase in mortality, to at least some patients who responded well to neoadjuvant CRT. Therefore, neoadjuvant CRT can be an initial treatment of choice for resectable esophageal SCC clinically with multiple lymph node metastasis. The prediction of response to CRT and the development of alternative treatment for hematogenous recurrence could achieve a further survival benefit of this trimodality treatment.**

KEY WORDS: **esophageal squamous cell carcinoma, esophagectomy, lymph node metastasis, neoadjuvant chemoradiotherapy, three-field lymphadenectomy.**

INTRODUCTION

The prognosis for patients with advanced esophageal cancer remains dismal, even for those undergoing curative resection.[1–3] Adjuvant chemotherapy and radiotherapy, when administered in combination or individually, have failed to increase survival.[1,2,4] On the other hand, recent success with the marked direct effects of chemoradiotherapy (CRT), as an initial treatment for down-staging, has been evaluated as induction CRT or 'neoadjuvant CRT' for its potential to achieve better surgical curability and prognosis.[5–9] The non-randomized studies have suggested that this combined modality therapy may prolong the survival of esophageal cancer patients when compared with that of patients treated with surgery alone. In contrast, a few previous randomized studies examining the benefit of neoadjuvant CRT produced conflicting results,[10–13] and no report has shown a positive result favoring neoadjuvant CRT for esophageal squamous cell carcinoma (SCC).

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However, because of possible weaknesses in each previous study (such as doubtful staging accuracy and stratification, possibly unbalanced randomization, variable radiation doses and their delivery, variable regimens of chemoradiotherapy, variable operative procedures, and relatively poor outcome of the surgery-alone group), the true efficacy of neoadjuvant CRT for esophageal SCC is uncertain.

At present, CRT may be acceptable as an initial treatment for clinically unresectable (cT4 according to TNM/UICC classification[14]) esophageal cancers.[15] However, there are three major concerns for the application of the trimodality therapy, neoadjuvant CRT followed by surgery, for initially resectable esophageal cancers. First, neoadjuvant CRT may increase risks at the time of surgical operation, particularly in radical esophagectomy with three-field (bilateral cervical, mediastinal, and abdominal) lymphadenectomy (3FL). Although the surgical mortality for esophageal cancer surgery has been reduced to approximately 2–5% due to the considerable recent improvements in surgical techniques and perioperative management,[2,3,16–18] esophagectomy with 3FL following neoadjuvant CRT reportedly appears to be a high-risk operation, with a mortality rate that is approximately 10% or more.[5,7,19] Second, some patients may fail to receive surgery due to tumor progression after neoadjuvant CRT unless it is effective. Third, the survival advantage of additional esophagectomy after neoadjuvant CRT has yet to be confirmed when a complete response is clinically achieved.[7,20] In some of such cases, either additional CRT or no more treatment may be more beneficial than surgery, because the results of definitive CRT without surgery even for advanced esophageal SCC has been reported to be excellent and comparable to surgical treatment.[21,22] Therefore, we must evaluate the oncological benefit of neoadjuvant CRT as well as the surgical risk of the following esophagectomy with 3FL in patients with initially resectable esophageal SCC. In addition, the indication for neoadjuvant CRT should be strictly determined.

A previous study revealed that an increased number of metastatic lymph nodes was a poor prognostic indicator of esophageal SCC after surgery.[23] In addition, we revealed that patients pathologically accompanied with either five or more positive nodes in any field, or metastatic nodes present in all three (cervical, mediastinal, and abdominal) fields (defined as 'multiple lymph node metastasis' in this prospective study) showed poorer survival rates than those without pathologic multiple lymph node metastasis determined after surgery.[24] Based on these results of survival analyses, we decided to individualize the initial treatment for each esophageal SCC patient strictly according to not only cT, but also the clinical status of multiple lymph node metastasis determined at presentation. Thus, since 1998, at our Department, all patients with initially resectable (≤ cT3) esophageal SCC have been prospectively divided into two groups. Patients who were clinically diagnosed as have multiple lymph node metastasis initially underwent CRT, while the other patients clinically without multiple lymph node metastasis immediately received esophagectomy with 3FL. Afterwards, the patients who responded to the preceding CRT, defined as neoadjuvant CRT, were selected for planned esophagectomy with 3FL, based on the therapeutic effect, resectability, and general condition. In addition, during this period, several newly developed surgical procedures, including the perioperative use of methylprednisolone, were introduced in all patients undergoing esophageal cancer surgery.[25,26] We have already reported that our newly devised procedures were effective in minimizing surgical invasiveness and improved the postoperative survival rate of esophageal SCC patients undergoing esophagectomy with 3FL without neoadjuvant CRT.[26] However, such improvement of prognosis may also be attributable to our strict selection of patients for esophagectomy with 3FL as an initial treatment.

The aim of this study was to evaluate whether the neoadjuvant CRT in addition to surgery could potentially influence the clinical outcome in patients with esophageal SCC which was clinically resectable but accompanied with multiple lymph node metastasis, since such patients were known to show poor prognosis after immediate surgery. The preliminary results of our prospective study suggest that the trimodality therapy must provide a survival benefit for, at least, some of the esophageal SCC patients who responded well to neoadjuvant CRT for multiple lymph node metastasis.

PATIENTS AND METHODS

Patient population

From January 1998 to December 2002, at the Department of Frontier Surgery, Chiba University Hospital, Japan, 71 consecutive Japanese patients with histologically proven primary SCC of the thoracic esophagus received CRT as an initial treatment, because they were diagnosed at presentation as have either of the following factors and gave informed consent: (i) clinically unresectable tumor invading an adjacent organ (cT4 according to TNM/UICC classification[14]) regardless of the status of lymph node metastasis ($n = 46$); or (ii) initially resectable (≤ cT3) tumor but clinically accompanied with multiple lymph node metastasis, defined as the status of either five or more positive nodes in any field, or metastatic nodes present in all three fields ($n = 25$). This selection criteria for the initial CRT as an individualized treatment was decided according to the previously reported data showing that patients pathologically

with such multiple lymph node metastasis provided poor prognosis after immediate surgery.[23,24] Thus, the initial treatment for clinically resectable esophageal SCC was prospectively allocated to CRT as well as immediate surgery, according to the clinical status of lymph node metastasis. After CRT, the therapeutic effect was evaluated by objective reassessment. Out of the 25 patients with initially resectable SCC and clinical multiple lymph node metastasis, two patients (8.0%) failed to undergo a surgical exploration, because carcinomatous pleuritis in one patient and multiple liver metastases in the other patient were found after CRT. Of the other 23 patients, two other patients eventually received non-curative operations because of unexpected dissemination in one patient and skin metastasis at operation in the other patient. Finally, the remaining 21 patients with initially resectable esophageal SCC and clinical multiple lymph node metastasis successfully received curative esophagectomy with 3FL following the CRT, defined as neoadjuvant CRT, as a planned procedure. However, two patients who were concomitantly found to have another primary cancer were excluded, and the remaining 19 patients were adopted as the CRT group in this study. While all 19 patients were initially diagnosed as possessing five or more metastatic nodes, six (31.6%) out of the 19 patients were also diagnosed as having nodal metastases in all three fields.

In contrast, during the same period at our Department, 72 consecutive Japanese patients with primary SCC of the thoracic esophagus diagnosed as resectable and without clinical multiple lymph node metastasis, underwent curative esophagectomy with 3FL without any preoperative treatment. However, eight patients synchronously had another primary cancer, and the other 64 patients were adopted as the control group in this study.

Although thoracic esophageal cancer with metastasis in either cervical or celiac lymph nodes was staged as IV according to the TNM/NICC classification,[14] the metastatic nodes could be curatively removed (as an R0 resection) by 3FL. Therefore, if surgically resectable, patients with such stage IV esophageal cancers were also included in this study. However, all 83 patients fulfillled the criteria of no hematogenous organ metastasis at presentation, no previous treatment for esophageal SCC before presentation, and a World Health Organization status below 2. Informed consent according to the Declaration of Helsinki was obtained from all patients, and this study was performed according to the guidelines of protocols approved by the institutional review boards.

Chemoradiotherapy

CRT consisted of a regimen of systemic combination chemotherapy with 5-fluorouracil and cisplatin plus external irradiation. Chemotherapy was given concurrently with radiation therapy. 5-fluorouracil was administered as a continuous infusion for 120 h at a rate of 500 mg/m^2 over 24 h, on days 0 (the day just before the beginning of radiation therapy) through 4, resulting in approximately 3.75 g of total dosage administered to most patients. Cisplatin was administered as an intravenous bolus (15 mg/m^2) over 2 h on days 1–5, resulting in approximately 100 mg of total dosage administered in most patients. Radiation therapy was also given with 10 MV photons through anterior and posterior opposed fields. The treatment field usually covered a prophylactic large port including three lymph node areas, which were the bilateral cervical, mediastinal, perigastric, and celiac compartments (T-shape field). A daily fractional dose of 1.8–2.0 Gy (gray) at the midplane, up to a total dose of 46 Gy, was delivered.

Surgery and perioperative care

The anesthesia, operative procedure of esophagectomy with 3FL, and postoperative care of esophageal cancer surgical patients were standardized in our department, as previously described.[16,25,26] All 83 patients in this study had been considered acceptable candidates for esophagectomy with 3FL with routine functional assessment of the vital organs and underwent complete (R0 according to TNM/UICC classification[14]) resection by esophagectomy with 3FL. The esophagectomy with 3FL consisted of the removal of the thoracic esophagus and lymph nodes in the neck, mediastinum and abdomen, by our newly devised surgical procedures.[26] Esophageal reconstruction was achieved in all patients by means of a gastric or colon tube. A colon tube was required in patients who had undergone gastrectomy, and the esophagocolonic anastomosis was completed in the left neck. Perioperatively, all 83 patients were similarly managed, as previously described,[25,26] and received 250 mg of intravenous methylprednisolone during surgery followed by 125 mg on postoperative days.[25,26] The patients were postoperatively admitted to the intensive care unit of Chiba University Hospital, and initial postoperative care was provided.

Definition of postoperative complications

The postoperative course of patients was monitored daily, and complications were defined as follows. According to the definition previously reported,[27,28] pulmonary complications in this study were objectively determined as the patient's status that required: tracheostomy; mechanical respiratory support for more than 1 week; or the administration of oxygen for more than 2 weeks because of an arterial oxygen pressure < 70 mmHg without inspiration of oxygen,

due to massive atelectasis, pneumonia, or pulmonary edema. Anastomotic leakage was diagnosed by gastrography or apparent clinical features. Recurrent nerve palsy was diagnosed by clinical features. Postoperative hyperbilirubinemia was defined as a peak bilirubin level > 4 mg/dL.[25] Liver dysfunction was defined by elevated liver enzymes of aspartate aminotransferase or alanine aminotransferase greater > 200 IU (normal: < 40 IU/L, at our institute).[25] Mortality was defined as in-hospital death in consideration of possible adverse effect of CRT after surgery.

Clinical and pathological diagnosis and staging

The depth of primary tumor infiltration, the presence of lymph node metastasis or the presence of distant organ metastasis was clinically determined by a detailed examination by esophagography, endoscopy including a lugol staining, endoscopic ultrasonography (EUS), ultrasonography (US) and postcontrast computed tomography (CT). An EUS-, US-, or CT-enlarged, round-shaped lymph node of more than 1 cm was regarded as clinically positive, and the mapping of clinically metastatic nodes was performed by each diagnostic modality of EUS, US, and CT, respectively. Taken together, the total number of clinically positive nodes was finally determined in each patient. After surgery, all parts of the esophagectomy specimens were examined pathologically with full-step sections. All of the dissected lymph nodes were also examined pathologically to assess the absence or presence of metastatic disease in the equatorial section of the nodes. Patients were staged clinically (as cTNM stage) or pathologically (as pTNM stage), according to the TNM/UICC classification.[14]

Statistical analysis

Fisher's exact probability test and Chi-square analysis were used for qualitative analysis between two or more groups. Mann–Whitney *U*-test was performed to compare two unpaired groups. Survival was calculated from the date of definitive diagnosis to the day of death, the last follow-up, or when recurrence was evident. The Kaplan-Meier method was used for survival analyses and statistical significance was analysed by log rank test. Analyses of data were carried out using a software package for Macintosh (Statview 5.0, SAS Institute Inc., Cary, NC), and a *P*-value of < 0.05 was considered significant.

RESULTS

Patient characteristics

Patients' characteristics are shown in Table 1. Although all 19 patients in the CRT group were male and diagnosed as cTNM stage IIB–IVB at presentation, which were significantly different from the distributions in the control group, no significant differences were found between the groups for the other clinical characteristics, including the initial tumor length and the pTNM stage defined after surgery. In the CRT group, the tumor length after neoadjuvant CRT (before surgery) was significantly less than that at presentation (average, 3.7 and 6.0 cm, respectively: $P = 0.003$). For esophageal reconstruction, a prepared gastric tube was used primarily and a postmediastinal route was most frequently selected in either group.

Compliance with neoadjuvant CRT

In the 19 patients who completed neoadjuvant CRT followed by esophagectomy with 3FL, chemotherapy with an average of 39.6 Gy (range, 23.4–46.0) of irradiation was administered before esophagectomy with 3FL. One patient received only 23.4 Gy because of grade 3 leukopenia (< 2000/mm^3) during radiation therapy. However, granulocyte colony-stimulating factor was given, and the patient successfully underwent esophagectomy with 3FL. The mean interval between the end of neoadjuvant CRT and the time

Table 1 Characteristics of patients according to treatment group

Characteristic	CRT group (n = 19)	Control group (n = 64)	P-value
Mean age at operation (range) (years)	63.2 (52–71)	61.8 (40–77)	0.614
Gender (male/female)	19/0	50/14	0.032*
Tumor site (upper/middle/lower)	1/9/9	8/37/19	0.308
Histopathological grading† (G1/G2/G3)	5/10/4	13/34/17	0.811
Mean tumor length at presentation (range) (cm)	6.0 (2.5–11.0)**	5.0 (1.5–10.0)	0.178
Mean tumor length after neoadjuvant CRT (range) (cm)	3.7 (0–7.0)**	–	
cTNM stage† at presentation (I, IIA/IIB–IVB)	0/19	17/47	0.009*
pTNM stage† defined after surgery (0–IIA/IIB–IVB)	6/13	25/39	0.601
Esophageal replacement (stomach/colon)	18/1	62/2	0.870
Reconstruction route (postmediastinal/retrosternal/subcutaneous)	16/2/1	57/4/3	0.811

†Defined according to TNM/UICC classification; *Significant; **$P = 0.003$ (significant); tumor length at presentation versus after neoadjuvant CRT; CRT, chemoradiotherapy.

Table 2 Postoperative morbidity and mortality according to treatment group

Type of complication	CRT group (n = 19)	Control group (n = 64)	P-value
Pulmonary	7 (36.8)	6 (9.4)	0.008*
Anastomotic leakage	4 (21.1)	5 (7.8)	0.199
Palsy of recurrent nerve	4 (21.1)	3 (4.7)	0.045*
Hyperbilirubinemia	2 (10.5)	8 (12.5)	0.589
Liver dysfunction	3 (15.8)	7 (10.9)	0.411
Chymothorax	2 (10.5)	1 (1.6)	0.130
Miscellaneous	3 (15.8)	5 (7.8)	0.264
Morbidity	14 (73.7)†	25 (39.1)†	0.010*
Mortality	0 (0)	0 (0)	–

Values in parentheses are percentages in each group; †Some of these patients had plural complications; *Significant; CRT, chemoradiotherapy.

of surgery was 31.5 days (range, 14–54). During the period of this study, no patient who had received CRT failed to undergo esophagectomy with 3FL due to an adverse effect related to the preceding CRT, and no treatment-related death occurred.

Postoperative morbidity and mortality

Postoperative morbidity and mortality rates were compared between the two groups (Table 2). In the CRT group, seven (36.8%) out of the 19 patients developed pulmonary complications, which was significantly more frequent than in the control group (P = 0.008). The incidence of recurrent nerve palsy was also significantly higher in the CRT group than in the control group. However, no significant differences were observed in the incidences of other postoperative complications between the two groups, while anastomotic leakage tended to occur more often in the CRT group. As a result, the CRT group was found to have a significantly higher rate of overall morbidity (73.7%) than the control group (P = 0.010), and the postoperative hospital stay in the CRT group (median, 36 days; range, 11–143) was significantly longer than that in the control group (median, 19 days; range, 12–79) (P = 0.043). However, it should be noted that there were no in-hospital deaths after esophagectomy with 3FL in the CRT group as well as in the control group (Table 2).

Relationship between the clinical and pathological status of lymph node metastasis with reference to the history of neoadjuvant CRT

The relationship between the clinical and pathological status of multiple lymph node metastasis is shown in Table 3. Although 14 (73.7%) out of the 19 patients in the CRT group, initially diagnosed as ≤ cT3 with multiple lymph node metastasis, were not accompanied with pathologic multiple lymph node metastasis, the remaining five patients (26.3%) pathologically possessed multiple lymph node metastasis regardless of neoadjuvant CRT completed (Table 3). Out of the five patients in the CRT group, three had five or more metastatic nodes over one or two fields, one had three positive nodes over all three fields (only one in each field), and the other patient had metastases of more than five nodes over all three fields. In the control group, pathologic multiple lymph node metastasis was eventually found in 13 (20.3%) out of the 64 patients. While all of the 13 patients had five or more metastatic nodes, four patients also had nodal metastasis present in all three fields, regardless of the preoperative negative diagnosis of multiple lymph node metastasis.

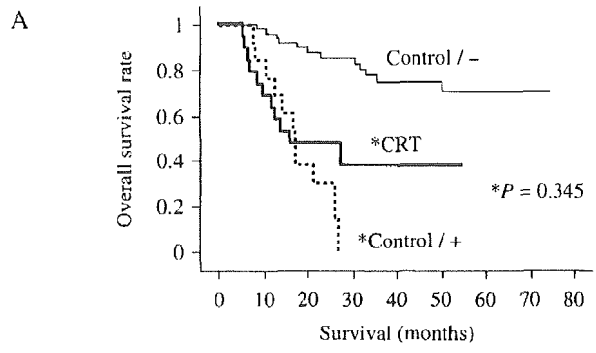
Postoperative survival according to the status of preoperative treatment and pathologic multiple lymph node metastasis

We evaluated the postoperative prognosis of all 19 patients in the CRT group, compared with that of patients in the control group with reference to the pathological status of multiple lymph node metastasis. In the control group, seven (53.8%) of the 13 patients pathologically with multiple lymph node metastasis received postoperative adjuvant chemotherapy with 5-fluorouracil and cisplatin after giving informed consent, while all of the 51 patients without multiple lymph node metastasis did not. After evident recurrence, most patients in the CRT group received chemotherapy with 5-fluorouracil and cisplatin or nedaplatin. In the control group, most of the recurrent patients underwent radiotherapy and chemotherapy with 5-fluorouracil and cisplatin.

Table 3 Relationship between the clinical and pathological status of multiple lymph node metastasis

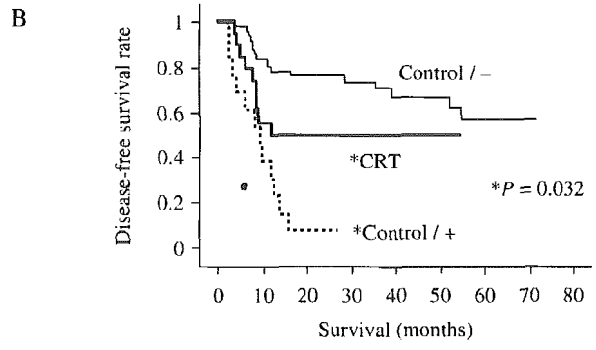
Group	Clinical status of multiple lymph node metastasis	Neoadjuvant CRT	No. of patients	Pathological status of multiple lymph node metastasis (+)	(–)
CRT	(+)	(+)	19	5 (26.3)	14 (73.7)
Control	(–)	(–)	64	13 (20.3)	51 (79.7)
Total no. of patients			83	18 (21.7)	65 (78.3)

Values in parentheses are percentages in each group; Multiple lymph node metastasis, defined as the status requiring five or more metastatic nodes in any field, or metastatic nodes present in all three (cervical, mediastinal, abdominal) fields; CRT, chemoradiotherapy.



No. at risk

Control / –	51	50	43	35	23	19	12	4
CRT	19	14	7	4	4	2	0	0
Control / +	13	11	5	0	0	0	0	0



No. at risk

Control / –	51	42	35	28	19	14	9	2
CRT	19	9	6	4	4	2	0	0
Control / +	13	5	1	0	0	0	0	0

Fig. 1 Kaplan-Meier analyses of overall survival (A); and disease-free survival (time to evident recurrence) (B) for 83 patients undergoing esophagectomy with 3FL for initially resectable (≤ cT3) esophageal squamous cell carcinoma. The analysis was based on the history of neoadjuvant CRT and the status of pathologic multiple lymph node metastasis, defined as metastases to five or more nodes in any field, or nodal metastastases present in all three (cervical, mediastinal, abdominal) fields. CRT (*bold line*), 19 patients in the CRT group; Control/– (*fine line*), 51 patients without pathologic multiple lymph node metastasis in the control group; Control/+ (*dotted line*), 13 patients pathologically with multiple lymph node metastasis in the control group. Patients without pathologic multiple lymph node metastasis in the control group had a significantly better prognosis than patients in the other groups (A, B). No significant difference in the overall survival rate was observed between the patients in the CRT group and those with pathologic multiple lymph node metastasis in the control group (A). Patients in the CRT group showed a significantly better disease-free survival rate than those with pathologic multiple lymph node metastasis in the control group (B).

As shown in Fig. 1A, analysis of the actual overall survival rate demonstrated that 51 patients pathologically without multiple lymph node metastasis in the control group had a significantly better prognosis with a 2-year survival rate of 85.9% (95% confidence interval [CI], 76.1–95.6%) than either the 19 patients in the CRT group with a 2-year survival rate of 47.4% (95% CI, 24.9–69.8%; $P < 0.001$), or the 13 patients pathologically with multiple lymph node metastasis in the control group with a 2-year survival rate of 30.8% (95% CI, 5.7–55.9%; $P < 0.001$). No significant difference in the overall survival rate was observed between the patients in the CRT group and those with pathologic multiple lymph node metastasis in the control group ($P = 0.345$). While the median overall survival time of patients without pathologic multiple lymph node metastasis in the control group could not be defined, that of the patients in the CRT group was 16.2 months, and that of the patients with pathologic multiple lymph node metastasis in the control group was 17.0 months (Fig. 1A).

As shown in Fig. 1B, patients pathologically without multiple lymph node metastasis in the control group also had a significantly better disease-free survival with a 2-year rate of 76.2% (95% CI, 64.5–88.0%), defined as the time to evident recurrence after surgery, than either patients in the CRT group with a 2-year disease-free survival rate of 48.9% (95% CI, 25.2–72.6%; $P = 0.036$), or patients pathologically with multiple lymph node metastasis in the control group with a 2-year disease-free survival rate of 7.7% (95% CI, –6.8–22.2%; $P < 0.001$). The 13 patients pathologically with multiple lymph node metastasis in the control group showed a significantly worse disease-free survival rate than the patients in the CRT group ($P = 0.032$) (Fig. 1B). The median disease-free survival time was 9.44 months for patients pathologically with multiple lymph node metastasis in the control group, and 12.3 months for patients in the CRT group; once again, that of patients pathologically without multiple lymph node metastasis in the control group could not be defined (Fig. 1B).

According to the TNM/UICC classification,[14] patients diagnosed as pTNM stage IIB–IVB (pN1 or pM1 LYM) had a significantly worse prognosis than those staged as 0–IIA (pN0 and pM0) in the CRT group as well as in the control group (data not shown). However, there were no significant differences in the patient disease-free survival with respect to the pTNM stage between IIB and IVB in the CRT group ($P = 0.170$) as well as in the control group ($P = 0.509$).

Postoperative survival in patients who received neoadjuvant CRT according to the pathological status of multiple lymph node metastasis

We evaluated the postsurgical prognosis of patients in the CRT group, according to the pathological status of multiple lymph node metastasis, compared with that of patients pathologically with multiple lymph node metastasis in the control group. As shown in Fig. 2A, 14 patients pathologically without multiple lymph node metastasis in the CRT group apparently showed a better overall survival with a 2-year survival

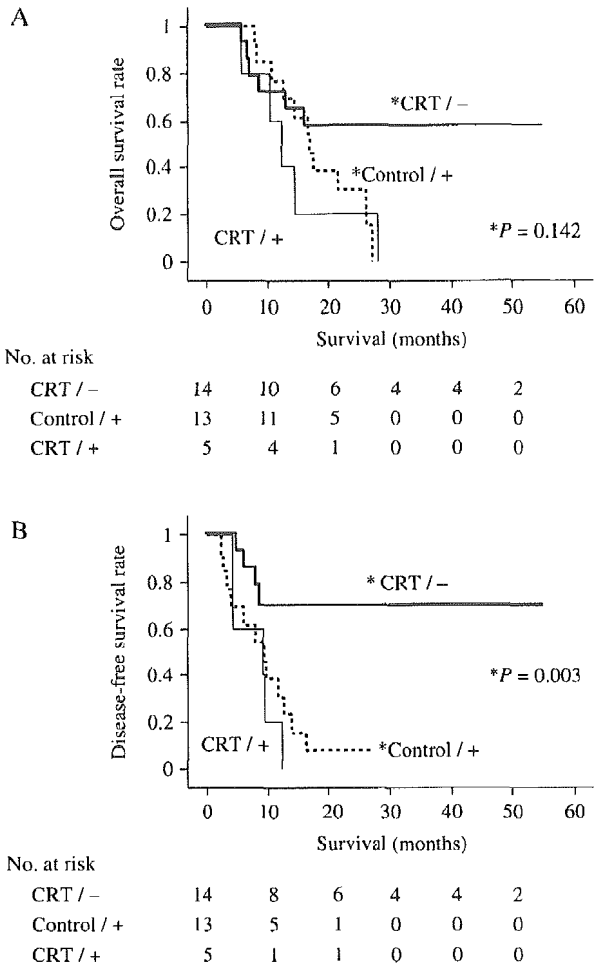


Fig. 2 Kaplan-Meier analyses of overall survival (A); and disease-free survival (B) for patients in the CRT group and those with pathologic multiple lymph node metastasis in the control group. CRT/– (*bold line*), 14 patients pathologically without multiple lymph node metastasis in the CRT group: CRT/+ (*fine line*), five patients pathologically with multiple lymph node metastasis in the CRT group; Control/+ (*dotted line*), 13 patients with pathologic multiple lymph node metastasis in the control group. No statistically significant differences were observed among the overall survival rates of the three groups (A). However, patients pathologically without multiple lymph node metastasis in the CRT group had a significantly better disease-free survival rate than that of either patients with pathologic multiple lymph node metastasis in the control group or those in the CRT group (B).

rate of 57.1% (95% CI, 31.2~83.1%), than 13 patients pathologically with multiple lymph node metastasis in the control group with a 2-year survival rate of 30.8% (95% CI, 5.7~55.9%), as well as five patients pathologically with multiple lymph node metastasis in the CRT group with a 2-year survival rate of 20.0% (95% CI, −15.1~55.1%). However, the differences were not significant at $P = 0.142$ and 0.056, respectively. Although the median overall survival time could not be defined for patients without pathologic multiple lymph node metastasis in the CRT group, it was 17.0 months for patients with pathologic multiple lymph node metastasis in the control group, and 12.3 months for those in the CRT group, respectively (Fig. 2A).

In contrast, as shown in Fig. 2B, the disease-free survival rate of patients pathologically without multiple lymph node metastasis in the CRT group proved to be significantly better than that of either patients pathologically with multiple lymph node metastasis in the control group or those in the CRT group ($P = 0.003$ and $P = 0.011$, respectively). Within 2 years after definitive diagnosis, recurrences were found in all (100%) of the five patients with pathologic multiple lymph node metastasis in the CRT group (95% CI of 2-year disease-free survival rate, 0%), and in 12 (92.3%) of the 13 patients with pathologic multiple lymph node metastasis in the control group (95% CI of 2-year disease-free survival rate, −6.8~22.2%). However, only four (28.6%) of the 14 patients without pathologic multiple lymph node metastasis in the CRT group developed evident recurrences (95% CI of 2-year disease-free survival rate, 43.9~94.6%). The median disease-free survival time was 9.18 months for patients with pathologic multiple lymph node metastasis in the CRT group, and 9.44 months for those in the control group. In contrast, the median disease-free survival time could not be defined for patients without pathologic multiple lymph node metastasis in the CRT group.

Among the 32 patients shown in Fig. 2A and 2B, all four survivors without recurrence for more than three years were in the CRT group without pathologic multiple lymph node metastasis. Among the four survivors without recurrence, two patients had no residual SCC in all surgical specimens (pathologically complete response to neoadjuvant CRT), one had no metastasis (pT2pN0pM0), and one had no residual tumor in the esophagus with one metastatic node (pT0pN1pM0). As an initial recurrence in the CRT group, hematogenous organ metastasis was found in two (40.0%) out of the five recurrent cases with pathologic multiple lymph node metastasis and two (50.0%) out of the four recurrent cases without pathologic multiple lymph node metastasis. In contrast, out of the 12 recurrent cases with pathologic multiple lymph node metastasis in the control group, 10 patients (83.3%) developed lymph node metastasis as an initial recurrence, and no hematogenous metastasis was initially found. The median survival time after recurrence in a total of nine patients in the CRT group (2.03 months; range, 0.56–23.5) was significantly shorter than that of 12 patients with pathologic multiple lymph node metastasis in the control group (7.90 months; range, 1.71–15.0) ($P = 0.028$).

DISCUSSION

The optimal therapy for advanced esophageal cancer has yet to be determined. Recently, some clinicians

suggested that a primarily non-surgical approach with definitive CRT alone should be the treatment of choice for esophageal cancer, and they questioned the need for surgical intervention.[21,22,29,30] The objection against surgical resection for esophageal cancer can be attributed to its high morbidity, despite the recent decrease in mortality rates.[1,2,8,16–18] Also, the objection can be attributed to the difficulty in selecting patients who are oncologically fit for surgery,[1] particularly following CRT.

In the current series, it is notable that we achieved no in-hospital deaths in all the patients who underwent esophagectomy with 3FL, even those following neoadjuvant CRT. This favorable result in comparison with previous reports[5–10,19] can be attributed to the careful surgical technique used by surgeons trained in esophageal surgery, our newly developed surgical procedures, and our experienced perioperative management.[25,26] However, the overall morbidity rate in our series was similar to that reported in the recent literature.[1,5,8,10,18,19] The difficulty in surgeries for advanced-staged tumors treated by neoadjuvant CRT may have accounted for the high incidences of pulmonary complications and recurrent nerve palsy. The recurrent nerve palsy may have led to some of the postoperative pulmonary complications. Otherwise, the high incidence of pulmonary complications may be associated with possible physical damage that was prolonged until surgery. The apparently higher incidence of anastomotic leakage in the CRT group than in the control group may be attributed to inclusion of the anastomotic site within the radiation field. These clinical observations suggest that, even if all patients underwent curative esophagectomy with 3FL under the same 'less invasive' operative procedures and perioperative management,[25,26] much more surgical stress may have been inflicted on the patients previously treated by neoadjuvant CRT. This supposition can be supported by the fact that the postsurgical hospital stay in the CRT group was significantly longer compared with that in the control group. Although the control group in this study was not a perfect comparison because of demographic differences in the tumor and patient factors, it provided a baseline for our surgical team to assess the feasibility of esophagectomy with 3FL after neoadjuvant CRT. The exploration of the oncological significance of such a multimodal treatment, as well as the proper risk estimation prior to surgery has yet to be established to justify the relatively 'high-risk' esophagectomy with 3FL for the patients treated by neoadjuvant CRT.

Previous prognostic analyses, including ours of esophageal SCC patients who underwent esophagectomy, revealed that the status of either pT4 or pathological multiple lymph node metastasis was an important prognostic factor.[23,24] These lines of evidence suggest that the prognosis of esophageal SCC patients who were initially diagnosed as cT4 or as having multiple lymph node metastasis would not be promising if they received esophagectomy with 3FL as an initial treatment. Thus, since 1998, we have strictly maintained that patients with either cT4 or clinical multiple lymph node metastasis should have CRT as an initial treatment. We recognize that no reported randomized trials that compared CRT followed by surgery with surgery alone in esophageal SCC patients demonstrated a significant improvement in the overall survival rate in favor of the trimodality treatment.[10–13,22] One randomized trial in patients with resectable SCC of the esophagus revealed a significant improvement in disease-free survival.[12] However, the significantly higher postoperative mortality in the trimodality group compared with the surgery-alone group[12] negated any overall survival benefit that may have been achieved by neoadjuvant CRT. In contrast, some individual trials showed a survival benefit for the neoadjuvant CRT and surgery compared with surgery alone in esophageal cancer patients.[5–9,22] Although the evidence is very encouraging, these non-randomized studies included patients with different histological types or those who received different types of therapeutic procedure, and the criteria for treatment selection were not necessarily strictly defined. In contrast, in our prospective study, the postoperative mortality was 'zero', all patients had SCC of the esophagus, and the criteria for CRT was strictly determined. Therefore, the survival rate observed reflects the oncological outcome of each treatment group for esophageal SCC, even if our study was not a randomized one without selection bias.

The promising result of our study is that all 19 patients clinically with multiple lymph node metastasis in the CRT group showed a significantly better disease-free survival rate than the 13 patients pathologically with multiple lymph node metastasis in the control group. In the 13 patients, the number of metastatic nodes was underestimated before surgery. With the limitation of diagnostic accuracy, the negative predictive value of multiple lymph node metastasis was 79.7% (51/64) in the control group, while the positive predictive value could not be determined in the CRT group. Furthermore, 14 patients finally without pathologic multiple lymph node metastasis in the CRT group provided a significantly better disease-free survival rate than either the 13 patients with pathologic multiple lymph node metastasis in the control group or the five patients who eventually had pathologic multiple lymph node metastasis in the CRT group. Therefore, this preliminary survival data suggest a potential benefit from neoadjuvant CRT in some patients. However, we could not demonstrate a significant difference in the overall survival rate among the three groups. An additional number of patients and a longer follow-up

may be required to determine modest differences in the outcomes. Another explanation for the lack of a significant difference in overall survival rate may be provided by the difference in distribution of initial recurrence types. The high incidence of hematogenous organ metastasis may be associated with a significantly shorter survival time after recurrence in the CRT group compared to that in the control group, in which lymph node metastasis accounted for the majority of recurrences. In the future, some effective treatment, such as second-line chemotherapy, for hematogenous metastasis should be established to improve the survival of esophageal SCC patients who underwent neoadjuvant CRT. At present, all of the five patients pathologically with multiple lymph node metastasis in the CRT group recurred and died: their prognosis was as poor as that of the 13 patients pathologically with multiple lymph node metastasis in the control group. In contrast, all four long-term survivors without recurrence in the CRT group responded well to neoadjuvant CRT, and were not accompanied by pathologic multiple lymph node metastasis. Whereas we have reported that the expression of angiogenic factors predicted the response to CRT and the outcome of esophageal SCC patients,[31] the development of more convenient biomarkers that help determine which patients are most likely to respond to CRT would allow therapeutic strategies to be targeted to patients who would most likely benefit from them according to the disease status.

The application of neoadjuvant CRT for initially resectable esophageal cancers is controversial.[1,5–13] Other than the direct effect of radiotherapy for locoregional control, occult distant metastases receive earlier systemic chemotherapy and are more responsive to it. In addition, the histopathological examination of the resected specimens makes it possible to assess the effectiveness of the treatment regimen delivered. Nevertheless, this approach must be balanced against the risk of disease progression if the treatment delivered is ineffective. In our series, of the 25 patients initially diagnosed as ≤ cT3 with multiple lymph node metastasis, four patients (16.0%) failed to receive curative resection after the preceding CRT. However, our study revealed that the prognosis of esophageal SCC patients with pathologic multiple lymph node metastasis, irrespective of whether neoadjuvant CRT was administered or not, was very dismal even after curative esophagectomy with 3FL. Like the patients pathologically with multiple lymph node metastasis in the CRT group, the four patients clinically with multiple lymph node metastasis who missed curative surgery, while their pathological status of multiple lymph node metastasis was not determined, were also considered as non-responders to the preceding CRT. Otherwise, even if the four patients clinically with multiple lymph node metastasis had undergone surgical exploration as an initial treatment, they would have possessed pathologic multiple lymph node metastasis. Thus, most of the patients clinically with multiple lymph node metastasis in whom neoadjuvant CRT was ineffective would be potentially not curable at present. Accordingly, even if resectable, esophageal SCC patients accompanied with clinical multiple lymph node metastasis would not be at an oncological disadvantage after neoadjuvant CRT. The initial CRT may act as a selection tool for patients who would not receive survival benefit from esophagectomy with 3FL. Thus, neoadjuvant CRT can be an initial treatment of choice for patients with clinically resectable esophageal SCC and multiple lymph node metastasis. On the other hand, the cTNM stage was not considered as an appropriate indicator of neoadjuvant CRT for initially resectable esophageal SCC.

Definitive CRT may be recommended in some patients with advanced esophageal cancer, as previously described.[22] The results of definitive CRT without surgery for advanced esophageal cancers have been reported to be excellent and comparable to surgical treatment.[21,22] In fact, no obvious benefit was reportedly given for the small number of patients treated surgically after a complete response to the preceding CRT.[7] However, as we experienced in our study, as well as the previously reported study,[20] the absence of residual tumor in the esophagus does not rule out the presence of lymph node metastasis. In addition, it is very hard to distinguish residual tumor from postneoadjuvant fibrosis. Therefore, the clinical diagnosis of complete response after neoadjuvant CRT is not considered necessarily as reliable in the management of esophageal SCC, and we consider esophagectomy with 3FL to be an integral and important part of the multimodal treatment option for advanced esophageal SCC. Improvement in post-chemoradiotherapy restaging would help predict which patients are most likely to benefit from surgical intervention of esophagectomy with 3FL following neoadjuvant CRT.

In conclusion, with the limitations of this retrospective, non-randomized study, esophagectomy with 3FL can be performed without mortality, even if neoadjuvant CRT is administered, but the current data are insufficient to reveal a significant survival benefit of neoadjuvant CRT for initially resectable esophageal SCC patients with clinical multiple lymph node metastasis. At present, the benefit of neoadjuvant CRT can indeed be achieved in a selected group of patients, who have responded well to the CRT, and neoadjuvant CRT may be a treatment of choice for clinically resectable esophageal SCC with multiple lymph node metastasis. For the future, the staging of patients needs to be improved, and some predictive markers for response to CRT needs to be explored to select the patients for whom CRT before surgery would be indicated as beneficial from a view

of oncological benefit, as well as surgical risk. In addition, another alternative treatment modality for hematogenous recurrence has yet to be developed to achieve a further survival advantage of this trimodality treatment.

Acknowledgments

This work was supported in part by a Grant-in-Aid from the Ministry of Education, Science, and Culture of Japan (21st century COE project).

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Int J Clin Oncol (2005) 10:418–424
DOI 10.1007/s10147-005-0525-6

ORIGINAL ARTICLE

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Phase I study of cisplatin and irinotecan combined with concurrent hyperfractionated accelerated thoracic radiotherapy for locally advanced non-small cell lung carcinoma

Received: April 25, 2005 / Accepted: August 1, 2005

Abstract

Background. Irinotecan, when combined with cisplatin, is an effective treatment for advanced non-small cell lung cancer (NSCLC). This constitutes a rationale for conducting a phase I study of chemoradiotherapy including this combination for locally advanced NSCLC.

Patients and methods. Patients with locally advanced NSCLC and a performance status of 0 or 1 were eligible. The protocol consisted of escalating doses of irinotecan on days 1 and 15, and daily low-dose cisplatin (6 mg/m^2 daily for a total dose of 120 mg/m^2) combined with concurrent hyperfractionated accelerated thoracic irradiation (1.5 Gy twice daily for a total dose of 60 Gy).

Results. The maximum tolerable dose was 50 mg/m^2 of irinotecan, and the dose-limiting toxicity was esophagitis. Tumor response was observed in 50% of cases, and the median survival time of the 12 patients enrolled was 10.1 months, including two patients with 5-year disease-free survival. A pharmacokinetics study demonstrated an accumulation of total platinum, but not of free platinum, during the 26-day treatment period.

Conclusion. The recommended dose for phase II studies was determined.

Key words Locally advanced non-small cell lung cancer · Cisplatin · Irinotecan · Radiotherapy · Phase I study

Introduction

The current standard treatment for locally advanced non-small cell lung carcinoma (LA-NSCLC) consists of platinum-based chemotherapy combined with thoracic radiotherapy.[1] Several randomized controlled trials have shown superiority of the combined modality over radiotherapy alone.[2–7] Some of these studies[2,3,6] eventually reported the clinical relevance of concurrent chemoradiotherapy, and a recent randomized controlled study demonstrated the advantage of concurrent over sequential chemoradiotherapy.[8] A standard protocol defining the most suitable chemotherapeutic agents and radiotherapy schedule, however, has not been established. To improve the efficacy of the combined modality, some researchers have investigated the relevance of multidrug chemotherapy with new agents[9] or hyperfractionated accelerated radiotherapy (HART).[6,10]

HART, in theory, might result in more efficient killing of cancer cells and less damage to normal cells by taking advantage of the differences in repair capacity between them.[11] The advantage of HART over conventional thoracic irradiation has been demonstrated in treating patients with limited-disease small cell lung cancer.[12] Although a recently published study demonstrated a positive statistical trend suggesting a survival advantage with the HART regimen over standard thoracic irradiation, when delivered after two cycles of induction chemotherapy,[13] a clear advantage has never been established in the treatment of patients with LA-NSCLC.

On the other hand, irinotecan (CPT-11) is one of the promising cytotoxic agents for advanced NSCLC. The agent is most active when it is metabolized and converted to the potent topoisomerase I poison SN-38. Its clinical relevance for advanced NSCLC has been suggested by phase II studies.[14–20] A recent phase III study comparing combinations of CPT-11 plus cisplatin and vindesin plus cisplatin, the latter a standard chemotherapy for advanced NSCLC in Japan, has established the clinical relevance of CPT-11.[21] In addition, preclinical studies have demonstrated the synergistic effects of either CPT-11[22,23] or cisplatin[24–27] on irradiation in NSCLC. Interestingly, these synergisms do not necessarily depend on the drug sensitivity of the cancer cells.[22,28] Furthermore, CPT-11 and cisplatin have also been shown to be synergistic.[29,30]

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Therefore, a combination protocol consisting of cisplatin, CPT-11, and concurrent thoracic irradiation could in theory, be expected to be an efficient treatment for LA-NSCLC. Among the combination protocols for LA-NSCLC, Schaake-Koning et al.[2] employed a unique therapeutic regimen consisting of daily cisplatin combined with daily conventional thoracic irradiation that might maximize the potential radiosensitizing effect of cisplatin. They demonstrated a survival advantage in patients treated by low-dose daily cisplatin (6 mg/m^2 per day) over patients treated by weekly cisplatin (30 mg/m^2 per week) when combined with standard thoracic irradiation. The pharmacokinetics of this chronic administration of cisplatin, however, have not been fully investigated. Therefore, we conducted a phase I study based on this protocol, along with a pharmacokinetics analysis, to elucidate the feasibility of a new regimen consisting of daily cisplatin and biweekly CPT-11 combined with HART for patients with LA-NSCLC. As to the dose for HART, Choi et al.[31] determined a maximum tolerated dose (MTD) of 45 Gy in 30 fractions for small cell lung cancer, when combined with the standard dose of chemotherapy consisting of one cycle of cisplatin (33 mg/m^2, days 1–3), cyclophosphamide (500 mg/m^2, day 1), and etoposide (80 mg/m^2, days 1–3), followed by two cycles of cisplatin and etoposide. They also noted, however, that the total dose seemed as important as the dose-intensity in radiotherapy, and that a total dose of 60 to 66 Gy would be needed for a high probability of local tumor control. In fact, HART with a higher dose, 67.6 Gy in 52 fractions in combination with low-dose daily chemotherapy consisting of carboplatin and paclitaxel, is reportedly safe and effective for LA-NSCLC.[32] Therefore, the present study employed a fixed dose (60 Gy, twice daily, in 40 fractions) for HART and a fixed dose of cisplatin (6 mg/m^2, daily), based on the Schaake-Koning's protocol, with an escalating dose of irinotecan.

Patients and methods

Patient eligibility

Patients meeting the following inclusion criteria were enrolled in the study: (1) histologically or cytologically proven NSCLC; (2) unresectable stage III disease; (3) age 15 to 75 years; (4) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; (5) no prior chemotherapy or thoracic radiotherapy; (6) measurable lesions; (7) adequate bone marrow function (leukocyte count ≤12,000/μl and ≥4000/μl; hemoglobin ≥10.0 g/dl, platelet count ≥100,000/μl), renal function (creatinine ≤1.5 mg/dl; creatinine clearance ≥50 ml/min), hepatic function (bilirubin ≤1.5 mg/dl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ twice the upper limit of normal), and pulmonary function (PaO_2 ≥70 torr; no interstitial pneumonia demonstrated on chest roentgenogram); and (8) written informed consent. Exclusion criteria were patients with (1) extended lesions not containable in an irradiation field as determined below; (2) malignant pleuritis, pericarditis, or ascites; (3) previous or concomitant malignancy; (4) any serious complication (such as infectious disease, pseudomembranous colitis, diarrhea, ileus, uncontrolled angina pectoris, acute myocardial infarction less than 3 months previously, cardiac insufficiency, or uncontrolled diabetes mellitus); (5) past history of severe allergic reaction to any medication; (7) pregnancy or breast feeding; or (8) any other disqualifying conditions. The study fully complied with local regulations.

Chemotherapy and evaluation of toxicity and tumor response

Chemotherapy consisted of cisplatin (fixed dose of 6 mg/m^2 per day) × (5 days/week) × 4 weeks to reach 120 mg/m^2 in total, and CPT-11 (escalating dose) on days 1 and 15. CPT-11 was dissolved in 500 ml of saline and delivered intravenously in 90 min. Cisplatin was diluted in 100 ml of saline and delivered intravenously in 30 min. Cisplatin administration was started 60 min after the start of irinotecan administration to complete both agents simultaneously on days 1 and 15. Oral ondansetron at 4 mg or granisetron at 2 mg was given as prophylaxis for nausea/vomiting with every cisplatin administration. Daily chemotherapy was completed approximately 30 min before thoracic irradiation. The first three patients were entered into the first level, from which CPT-11 administration was excluded. In the second level, the CPT-11 dose was set at 40 mg/m^2, with escalations set at increments of 10 mg/m^2. Dosage was escalated in successive cohorts of three new patients as long as the dose-limiting toxicity (DLT) was not encountered in the three patients enrolled in the same level. If DLT was observed in two or more patients in the cohort, this dose level was defined as the MTD. If DLT was found in one patient out of the three, three additional new patients would be treated at the same dose level, and the dose level would be escalated to the next level if none of these three patients experienced DLT; otherwise the dose level would be defined as MTD. DLT was defined as grade 3 or 4 nonhematological toxicity excluding nausea/vomiting and alopecia, or grade 4 hematological toxicity according to the National Cancer Institute Common Toxicity Criteria version 2.0. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors of the National Cancer Institute.

Radiotherapy

For all patients, radiotherapy was delivered using a linear accelerator with a 10-MV photon beam. For the first two patients, an X-ray simulator was used for the treatment planning. For the rest of the patients, after the introduction of the computed tomography (CT)-simulation system, CT-based three-dimensional treatment planning was performed. No tissue heterogeneity correction, however, was used to calculate a prescribed dose, uniformly throughout the study. Radiotherapy consisted of twice daily thoracic irradiation (1.5 Gy at the midplane, two times/day) × (5 days/

week) × 4 weeks to reach 60 Gy in total). Although the original protocol required a minimum interfraction interval of 4 h each day, an interval of at least 6 h was obtained for all, eventually, because of our institutional standard operating procedures for radiotherapy. The original irradiation volume included all of the involved lesions, the ipsilateral hilum, the superior mediastinum, and the subcarinal region, with a margin of 2 cm in a single field. If supraclavicular lymph nodes were involved, only the involved side was included. The irradiation field was reduced to spare the spinal cord when the accumulated radiation dose reached 39 Gy.

Pharmacokinetics study of CPT-11 and cisplatin

In patients who gave additional informed consent for the pharmacokinetics studies of cisplatin and CPT-11, venous blood samples were collected in heparinized tubes at the following time points of days 1 and 15: before the start of administration of the drugs and at 0.5, 1.5, 2.0, 2.5, 3.5, 5.5, 9.5, 13.5, and 24 h after the completion of their administration. For cisplatin, additional sets of plasma samplings, before and 30 min after the start of cisplatin administration, twice a week, were performed. All samples were immediately centrifuged at 3000 rpm for 20 min to isolate the plasma. For cisplatin, a 2-ml portion of each plasma gradient was then placed on a Centrifree MPS-3 conical filter (Amicon, Lexington, MA, USA) and centrifuged again at 3000 rpm for 20 min to eliminate existing protein and protein-bound platinum. Filtered and unfiltered samples were stored at −70°C until measurement. These samples were measured for platinum concentrations by flameless atomic absorption spectroscopy using the same instrumentation and method as reported earlier.[33] By this analysis, the lowest detectable total and free platinum concentration was 50 and 25 ng/ml, respectively. For CPT-11 and its derivatives, the plasma samples were measured for CPT-11, SN-38, and SN-38-glucuronide (SN-38G) by means of high-performance liquid chromatography, and the lowest detection limits were 54, 2 and 2 ng/ml, respectively. The measured concentrations of the derivatives were fitted to a noncompartmental model. All pharmacokinetics parameters calculated on days 1 and 15 were compared by Student's paired t test, and the differences were judged as statistically significant when the P value was 0.05 or less.

Results

Patients enrolled and determination of MTD

Initially, a total of 12 patients were enrolled in this study between April 1995 and July 1999. Among the 12, one patient, of level 2, with the primary tumor adjacent to thoracic vertebrae was judged, in the course of the treatment, to be ineligible because the irradiation field could not be set so as to spare the spinal cord upon reaching a total dose of 39 Gy. Another patient, of level 3, at day 18, refused to continue the study because of grade 2 esophagitis. Therefore, only the remaining ten patients were analyzed for dose escalation, whereas all 12 patients were analyzed for toxicity, tumor response, and intent-to-treat survival. Level 1 was accomplished without DLT by three patients, and level 2 was completed without DLT by four patients, including the one ineligible patient. As the second patient in level 3, however, presented grade 3 esophagitis, one additional patient was treated at this dose level. However, because this fourth patient refused to continue the treatment, as mentioned above, one additional patient was treated at this dose level. As a consequence, two out of the four patients who completed level 3 experienced grade 3 esophagitis, that is, DLT. Therefore this dose level was defined as MTD, and the preceding level (40 mg/m^2 CPT-11 on days 1 and 15, combined with daily cisplatin and twice daily radiotherapy) was accepted as the recommended dose level. The characteristics of the 12 patients according to dose level are summarized in Table 1.

Dose intensity

Among the ten patients analyzed for dose escalation, all patients of levels 1 and 2 were completely treated without any delay. The second patient of level 3, however, discontinued the treatment on day 23 (100% CPT-11, 80% cisplatin, and 80% radiotherapy of the scheduled doses) because of grade 3 esophagitis (DLT). The third patient of level 3 had a 14-day treatment delay because of grade 2 thrombocytopenia, but then completed the entire protocol. The fifth patient of level 3 experienced grade 3 esophagitis, that is, DLT, just at the end of the full-dose protocol.

Pharmacokinetics study of CPT-11 and cisplatin

Six patients, one in level 2 and five in level 3, gave additional informed consent for their entry into the pharmacokinetics study for cisplatin and CPT-11. One other patient in level 2 also consented, but only for CPT-11. The pharmacokinetics parameters of CPT-11 and its derivatives at days 1 and 15 are summarized in Table 2. There was no statistically significant difference between the parameters on days 1 and 15. As to cisplatin, some important pharmacokinetics parameters, including the area under the curve, were not calculated because it was repeatedly administered with the previous trough value still significantly high. Therefore, time–concentration curves of total and free platinum were drawn (Fig. 1). Total platinum concentration significantly increased, finally reaching a maximum concentration of more than 1 μg/ml. In contrast, free platinum decreased in concentration to less than the minimum detection level (25 ng/ml) at 24 h after every repeated administration, and no concentration-related accumulation trend was found (Fig. 1).

Tumor response and survival

A tumor response was observed in five of the ten patients analyzed for dose escalation, and in six out of the total of 12

Table 1. Patient characteristics and summary of treatment results

Case no.	Dose level	Sex	Age	PS	Histology	Clinical stage	Response	Toxicities[b]						First site of relapse
								Neut	Hb	Plt	Eso	Diarr	N/V	
1	1	M	63	1	Ad	IIIB	SD	1	1	0	1	0	1	Bone
2	1	M	70	0	Ad	IIIA	PR	3	1	1	1	0	0	Primary
3	1	M	61	1	Ad	IIIB	PR	2	2	1	1	0	0	Primary
4	2	M	60	0	Ad	IIIB	PD	2	1	2	1	0	0	Lung
5	2	M	72	0	Sq	IIIA	SD	2	2	1	1	0	2	No relapse
6[a]	2	M	63	1	Sq	IIIB	SD	1	1	0	0	0	1	Bone
7	2	M	47	1	Ad	IIIA	PR	0	1	0	1	1	3	Salivary gland
8	3	M	66	1	Sq	IIIB	PR	2	2	1	2	0	0	Primary
9	3	F	59	0	Ad	IIIB	PR	2	2	0	3[c]	0	1	Brain
10	3	F	63	0	Ad	IIIB	SD	2	2	3	2	0	0	No relapse
11[a]	3	M	63	0	Ad	IIIB	PR	1	1	0	2	0	1	Lung and brain
12	3	M	66	0	Ad	IIIB	SD	2	1	0	3[c]	0	0	Primary

Neut, neutropenia; Hb, hypohemoglobinemia; Plt, thrombocytopenia; Eso, esophagitis; Diarr, diarrhea; N/V, nausea/vomiting; PS, performance status; SD, stable disease; PR, partial response; PD, progressive disease; Ad, adenocarcinoma; Sq, squamous cell carcinoma

[a] Ineligible because of unfit irradiation field (case 6) or patient's refusal to continue the protocol (case 11)

[b] Graded by NCI-CTC, version 2.0

[c] Dose-limiting toxicity

Table 2. Comparison of pharmacokinetics parameters of irinotecan derivatives between days 1 and 15

		T1/2 (h)	Cmax (ng/ml)	AUC (ngh/ml)	CL (l/h per meter^2)	Vdss (l/m^2)
Level 2	(n = 2)					
CPT-11	Day 1	8.0 ± 4.3	324.0 ± 42.4	1221.3 ± 180.3	18.9 ± 10.2	184.3 ± 12.2
	Day 15	4.8 ± 0.3	694.0 ± 377.6	1892.5 ± 18.7	17.2 ± 0.1	101.4 ± 27.9
SN-38	Day 1	13.2 ± 0.7	10.1 ± 2.9	99.7 ± 33.3	NA	NA
	Day 15	52.6 ± 60.1	11.1 ± 3.5	85.5 ± 23.1	NA	NA
SN-38G	Day 1	12.9 ± 4.2	37.1 ± 7.3	374.6 ± 190.6	NA	NA
	Day 15	16.8 ± 9.9	42.4 ± 13.1	367.0 ± 146.6	NA	NA
Level 3	(n = 5)					
CPT-11	Day 1	5.5 ± 0.8	383.2 ± 41.0	1736.7 ± 368.1	22.9 ± 4.3	145.8 ± 15.4
	Day 15	5.7 ± 2.8	427.2 ± 69.4	2067.0 ± 803.5	21.5 ± 6.9	143.6 ± 20.4
SN-38	Day 1	14.2 ± 3.6	16.9 ± 5.7	125.8 ± 28.9	NA	NA
	Day 15	9.0 ± 4.9	16.1 ± 3.4	147.9 ± 28.8	NA	NA
SN-38G	Day 1	16.0 ± 11.5	27.1 ± 8.9	222.3 ± 59.8	NA	NA
	Day 15	10.1 ± 7.3	26.0 ± 4.0	257.4 ± 62.0	NA	NA

Mean and standard deviation of the pharmacokinetics parameters are presented in each column. There is no statistically significant difference between days 1 and 15 in any of the parameters (Student's paired t test)

T1/2, half-time; Cmax, maximum concentration; AUC, area under the curve from 0 to 25.5 h of administration; CL, total clearance; Vdss, volume of distribution

patients (Table 1). The first site of relapse in the 12 patients was the primary site in four patients and distant site in six patients. In the other two patients, no relapse occurred (Table 1). As to intent-to-treat survival, median survival time (MST) was 10.1 months, with 1-year and 2-year survival rates of 50% and 25%, respectively. Two patients, cases 5 and 10, survived for more than 5 years without any evident disease progression (Fig. 2).

Late toxicity

Nine patients encountered late toxicities. Briefly, evident pulmonary fibrosis accompanied by partial atelectasis was observed in 8 out of 11 and in 3 out of 4 still living patients at 6 and 12 months from the start of treatment, respectively. Benign pleural effusion was observed in 3 out of 11 and in 1 out of 4 patients at 6 and 12 months from the start of treatment, respectively. No symptomatic esophageal stenosis, benign pericarditis, or cardiac failure was observed.

Discussion

The MTD of CPT-11 administered on days 1 and 15, in combination with daily cisplatin of 6 mg/m^2 for 4 weeks (5 days/week, 20 administrations resulting in 120 mg/m^2 in total) and HART of 60 Gy (in 40 fractions, twice/day) during the same period as cisplatin, was determined in this study. Schaake-Koning et al.[2] reported that daily cisplatin with concurrent conventional thoracic radiotherapy for patients with LA-NSCLC gave a survival advantage over thoracic radiotherapy alone. The present protocol was based on theirs, with the addition of CPT-11. However, in contrast

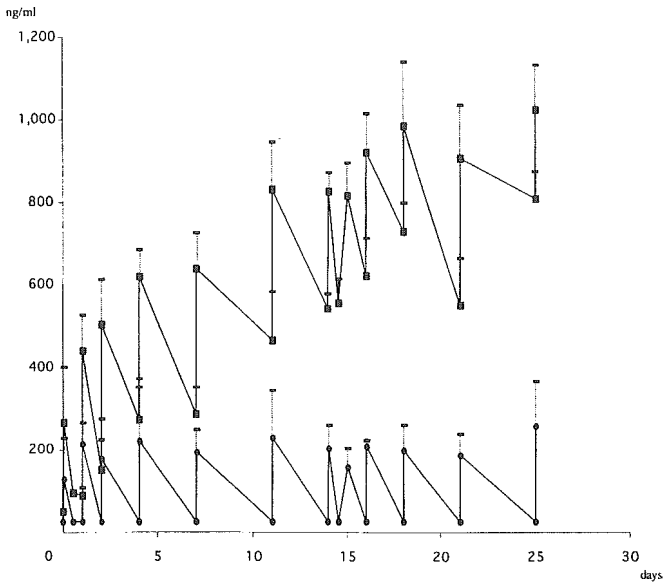

Fig. 1. Mean concentrations of free and total platinum with daily (5 days a week) administration of 6 mg/m^2 of cisplatin for 4 weeks ($n = 6$). The *dotted vertical lines* beyond the means represent standard deviations. Free platinum (*circles*) reached its maximum concentration with every administration and then dropped to a level under the minimum detection limit each time. In contrast, the concentration of total platinum (*squares*) accumulated with repeated administrations, resulting in as much as 1020 ± 109 ng/ml at day 26 and an unusually high rate of protein-bound platinum

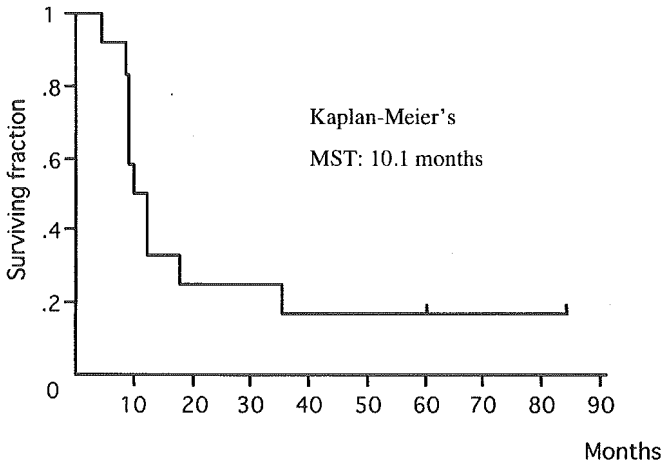

Fig. 2. The intent-to-treat survival curve (Kaplan-Meier's method) revealed 10.1 months of median survival time (*MST*) with two patients being 5-year progression-free survivors out of the 12 patients enrolled

to their protocol, which included a 3-week-interval, the present one did not contain a split radiotherapy schedule during the treatment period. Thus, we conducted a dose escalation test of the protocol, initially by omitting CPT-11 administration (level 1). As this level proved to be feasible, 40 mg/m^2 of CPT-11 was administered on days 1 and 15 (level 2). This dosage was a reduction of the conventional dose,[14,16] 60 mg/m^2 on days 1, 8, and 15, when combined with full-dose cisplatin on day 1 without concurrent thoracic radiotherapy. Thereafter, the CPT-11 dose was planned to be elevated at 10 mg/m^2 increments. As a consequence, level 3 was defined as MTD, because DLT was observed in two of the four eligible patients. The DLT consisted of grade 3 esophagitis in both of these patients. Bone marrow suppression and other toxicities, however, were not severe in any of the patients.

The recommended dose level, level 2, consisted of 40 mg/m^2 of CPT-11 on days 1 and 15, daily 6 mg/m^2 of cisplatin for 20 administrations, and 60 Gy of HART during a 4-week treatment period. This ensured a much higher dose intensity than the protocol by Schaake-Koning et al.,[2] as theirs did not contain CPT-11 and incorporated a 3-week radiotherapy split during the treatment course.

The response rate was 50% (six patients with a partial response among 12 total patients); survival was moderate with a MST of 10.1 months, a 1-year survival rate of 50%, and a 5-year progression-free survival rate of 17% (2 of 12). Although the response rate seemed disappointing, evaluation of the tumor response after radiotherapy or chemoradiotherapy is sometimes difficult because of fibrotic pulmonary lesions caused by irradiation. In fact, two patients, cases 5 and 10, for example, enjoyed 5-year progression-free survival, in spite of their tumor response of stable disease (SD), suggesting that their lesions after therapy might not have contained viable cells although the tumor size was unaltered. The present protocol, as well as that of Schaake-Koning et al,[2] is characterized by the daily administration of low-dose cisplatin with concurrent radiotherapy. The radiosensitizing activity of cisplatin might have played some role in this result. That is, when Schaake-Koning et al.[2] demonstrated the superiority of the concurrent multimodality consisting of cisplatin and radiotherapy, the daily administration of cisplatin was more advantageous than its weekly administration although the total dose was the same. These findings seem to suggest a supra-additive effect of cisplatin when combined with radiotherapy. In fact, similar protocols utilizing daily low-dose cisplatin (ranging from 5 to 10 mg/m^2) combined with radiotherapy have been reported to be effective in NSCLC[34–37] and other types of cancer.[38–40]

Although the supra-additive effect of cisplatin combined with irradiation has been shown in many in vitro studies,[24–27] the cisplatin doses in those studies were usually high. Therefore, interpretations of such preclinical studies may not be relevant to specific situations in which daily low-dose regimens of cisplatin are used. From the pharmacokinetics analysis of cisplatin and CPT-11 included in the present study, the pharmacokinetics of CPT-11 did not seem to have significantly interfered with cisplatin, as the values obtained on days 1 and 15 were comparable. As for the cisplatin pharmacokinetics, free platinum had a similar maximum concentration (Cmax) and dropped below the lowest detection level by 24 h after every administration. A cumulative effect was not observed with free platinum. In contrast, Cmax of total platinum accumulated from 266 ± 135 ng/ml at day 1 to 1020 ± 109 ng/ml at day 26 (Fig. 1). Other pharmacokinetics studies of daily low-dose or continuously infused cisplatin also revealed an accumulation of

total platinum but not of free platinum.[41,42] In addition, the final concentration of free platinum amounted to approximately 25% of all platinum compounds, by the daily low-dose administration in this protocol, in contrast to conventional single-dose cisplatin administration, which usually yields approximately 50% free platinum in plasma, at a level near Cmax. Most of the discussion on the pharmacokinetics and -dynamics of this agent, however, have focused on this conventional method. These ostensibly different regimens may lead to different consequences in terms of activity of the agent. The way in which these factors, that is, the significantly higher ratio of the protein-bound platinum and the significantly long-lasting cumulative total platinum, might influence the antitumor activity, radiosensitizing ability, and toxicity of the agent needs to be further investigated in preclinical studies.

In conclusion, the recommended dose of CPT-11 on days 1 and 15 was defined as 40 mg/m^2 when combined with daily 6 mg/m^2 of cisplatin administered 5 days a week for 4 weeks and HART of 60 Gy in 40 fractions (twice daily) over the same period. This therapeutic regimen resulted in a 50% response rate and a MST of 10.1 months, with two patients being 5-year progression-free survivors, out of the 12 patients enrolled. Phase II studies might be warranted to clarify the activity of this regimen. In addition, further preclinical investigations will be required to clearly demonstrate the antitumor activity, including the radiosensitizing ability and toxicity of repeated administrations, of low-dose cisplatin. The present pharmacokinetics data should provide useful information for such studies.

Acknowledgments The technical assistance of Ms. Reiko Kunii and Ms. Yuki Mitsuda and the secretarial assistance of Ms. Chieko Miyagi-Handa are greatly appreciated. This work was financially supported by the Ministry of Education, Culture, Sports and Technology of Japan.

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診療
臨床放射線 50 969-976, 2005

ワルチン腫瘍のMRI所見
他の腫瘍との比較を含めて

金親克彦* 本折 健* 伊東久夫*

はじめに

耳下腺部腫瘤の診断には腫瘍性と非腫瘍性の鑑別，耳下腺内と耳下腺外腫瘍の鑑別を要する。また腫瘍であれば良性と悪性腫瘍の鑑別が必要となる。耳下腺腫瘍は，他の部位では比較的まれな様々な腫瘍が発生する。そのためか耳下腺腫瘍と周囲組織との関係を把握するためのMRIなどの画像診断の有用性は知られているが，鑑別診断に関してはあまり興味を持たれないことが多い。通常耳下腺腫瘍の術前診断は侵襲が少なく，経済的である点から針生検による診断が広く行われている。しかし針生検は検体採取が少量であることや深部に存在する小腫瘤の穿刺は手技的困難を伴うなど，診断が困難なことも多い。また，被膜を破ることによる再発の危険性が増大するといった欠点がある[1)2)]。これまで耳下腺腫瘍の良悪性の鑑別では通常のMRIの撮像法（T1強調像，T2強調像，造影MRI）の有用性は高くないと考えられていた[3)4)]。そこで我々はダイナミック造影MRIや拡散強調像を加えて耳下腺腫瘍の撮像を行い，ワルチン腫瘍およびその他の耳下腺腫瘍のMRI所見の特徴を明白にし，耳下腺腫瘍の鑑別におけるMRIの有用性について検討したので報告する。

1. 対　象

対象は過去3年間に臨床的に耳下腺腫瘤を疑いMRIを行った症例で，細胞診あるいは組織診にてワルチン腫瘍の診断が確定した27症例34腫瘍（男性22症例，女性5症例，年齢46～91歳，平均65.4歳）とワルチン腫瘍以外の耳下腺良性腫瘍56症例および悪性腫瘍33症例である。ワルチン腫瘍以外の耳下腺良性腫瘍の内訳は多形腺腫52症例，神経鞘腫2症例，脂肪腫および血管腫それぞれ1症例である。また，悪性腫瘍の内訳は腺房細胞癌6症例，粘表皮癌2症例，腺様嚢胞癌2症例，基底細胞癌1症例，腺癌3症例，唾液腺管癌9症例，扁平上皮癌2症例，悪性リンパ腫8症例である。

2. 方　法

全例GE社製Signa Horizon（1.5T）を用いて検査を行った。撮像コイルはneurovascular array coilを用いた。T1強調軸位断像（TR 400-50，TE 9-14），STIR軸位断像（TR 4000，TE 30，IR 150），拡散強調軸位断像，T2強調冠状断像（TR 4000，TE 104）をスライス厚6mm，スライス間隔1mm，matrix 256×256（拡散強調像は128×128），FOV 22×22cmにて撮像し，ダイナミック造影MRIは脂肪抑制3D-SPGR法（TR 6.3，TE 1.4）を用い，撮像条件は実効スライス厚4mm，FOV 22×22cm，matrix 256×224とした。ダイナミック

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〔索引用語：ワルチン腫瘍，MRI，拡散強調像〕

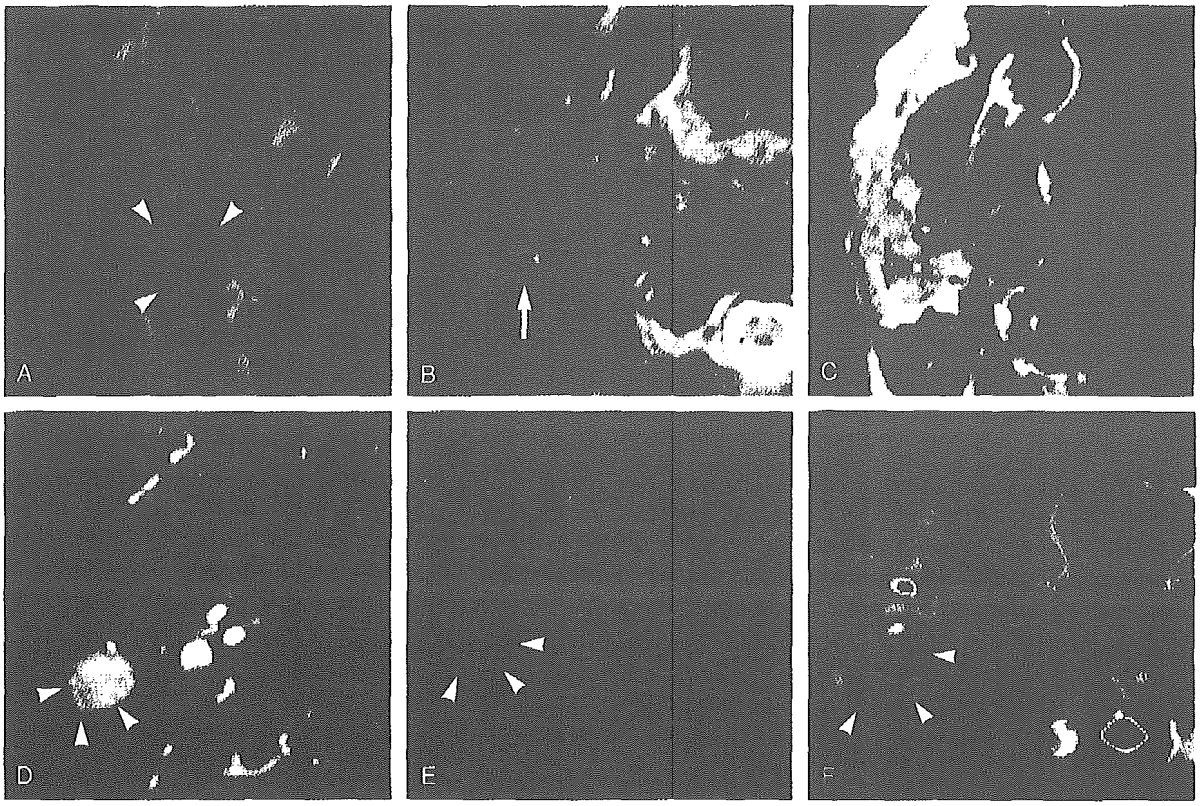

図1　54歳，男性　ワルチン腫瘍

T2強調冠状断像（A）において右耳下腺下極に横径2cmの境界明瞭な腫瘤が認められる（▲）。STIR軸位像（B）において腫瘤内部に低信号域（→）が認められ，同じレベルのT1強調軸位像（C）において同部位は周囲腫瘍組織よりも高信号（→）を呈している。ダイナミック造影（D）において造影剤注入後早期（30秒後）に強い増強効果が認められる（▲）。拡散強調像（E）において高信号（▲）を呈し，ADC map（F）におけるADC値は$1.04\times10^{-3}mm^2/sec$と低値を呈している（▲）。

MRIはガドリニウム造影剤を静注開始後より30秒間隔で7回撮像した。ダイナミックMRI撮像後に脂肪抑制T1強調軸位断像（TR 340～400，TE 20）を撮像した。

T1強調像，T2強調像，STIR像より病変の大きさ，位置，辺縁の性状，腫瘍内の信号強度について評価した。腫瘍内の信号強度の評価は，腫瘍内の信号強度の最大値をSImax，最小値をSIminとしてsignal intensity ratio（SIR）を脳脊髄液の信号強度をSIcsfとしてSIRmax＝SImax/SIcsf，SIRmin＝SImin/SIcsfとして算出した。また，T1強調像に関しては筋の信号強度をSImuscleとし，同様にしてSIRを算出した。

ダイナミックMRIにおいて腫瘍に関心領域（ROI）を設定し，信号強度の変化を時間—信号曲線（TIC）を作成した。腫瘍の増強効果が不均一な場合は複数のROIを設定した。Yabuuchiら[5]のTICの分類を参考に4種類のtypeに分類した。造影剤注入後より信号強度が最大になる時間をpeak timeとし，造影剤排泄率washout ratioとした。このときpeak time≦120秒かつwashout ratio≧30％をtype A，washout ratio≦30％をtype B，peak time＞120秒をtype C，造影されないパターンをtype Dとした。washout ratioは，造影後の信号強度の最大値をSImax，造影後3.5分後の信号強度をSI3.5min，造影前の信号強度をSIpreとしてWR＝[（SImax－SI3.5min）/（SImax－SIpre）]×100（％）として算出した。

拡散係数ADC値は腫瘍内の嚢胞成分を除き算出し，最高値と最低値についてワルチン腫瘍お