Table 3. Factors Related to Overall Survival

Factor	No. of Patients	Overall Survival at 2 Years (%)	Univariate *P*	Multivariate *P*	Hazard Ratio	95% CI
Age, years			.263	.665	1.54	0.22 to 10.75
< 70	15	59				
≥ 70	15	71				
Sex			.829	.732	1.44	0.18 to 11.65
Male	20	67				
Female	10	60				
Tumor size, mm			.045	.159	0.34	0.08 to 1.52
20 to 50	19	71				
> 50	11	44				
Pretreatment ICG R15			.006	.026	0.19	0.05 to 0.82
≤ 40%	21	80				
> 40%	9	30				
Clinical stage			< .001			
I	9	73				
II	19	68				
III	2	0				
Child-Pugh classification			.006			
A	20	78				
B	10	38				
Vascular invasion			.930	.650	1.44	0.30 to 7.03
Yes	12	67				
No	18	66				
Serum AFP level, ng/mL			.313	.061	0.20	0.04 to 1.07
< 300	21	67				
≥ 300	9	60				
V_{30}%			.213	.141	0.25	0.04 to 1.58
≤ 25%	24	65				
> 25%	6	40				
Prior treatment			.455	.091	3.63	0.82 to 16.18
No	13	69				
Recurrence	17	60				

Abbreviations: ICG R15, percentage of indocyanine green clearance at 15 minutes; AFP, alpha-fetoprotein; V_{30}%, percentage of hepatic noncancerous portion receiving ≥ 30 cobalt gray equivalent.

advanced HCC and underlying cirrhosis showed that overall survival rate at 3 years ranged from 13% to 38%, and rarely exceeded 50% even for those with most favorable prognostic factors.[1] In this study, actuarial overall survival rate at 3 years for all 30 patients including those who had HCC with vascular invasion and/or severe cirrhosis was 62%. Furthermore, 21 patients with initial ICG R15 of ≤ 50% and V_{30}% of ≤ 25% achieved 79% of overall survival rate at 3 years. All of the eight patients with favorable liver functional reserve (ICG R15, 15% to 20%) were alive at 20 to 54 months as shown in Figure 3. This suggests that adequate local control with PRT provides survival benefit for selected patients with HCC and moderate cirrhosis. On the other hand, prognoses of aggressive PRT were disappointing for patients, with poor functional liver reserve showing an ICG R15 of 50% or worse, and, therefore, indication of PRT for such patients was thought to be extremely limited.

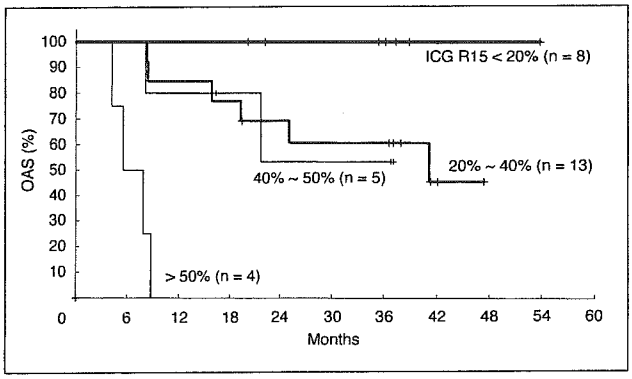

Fig 3. Overall survival (OAS) rates according to pretreatment indocyanine green clearance at 15 minutes (ICG R15).

A part of noncancerous liver suffering from PRT-inducing hepatitis gradually developed dense fibrosis and resulted in almost complete atrophy,[20] whereas the absorbed dose in a large proportion of the remaining liver was 0 Gy_E, as shown in Figures 1 and 4. This change is similar to

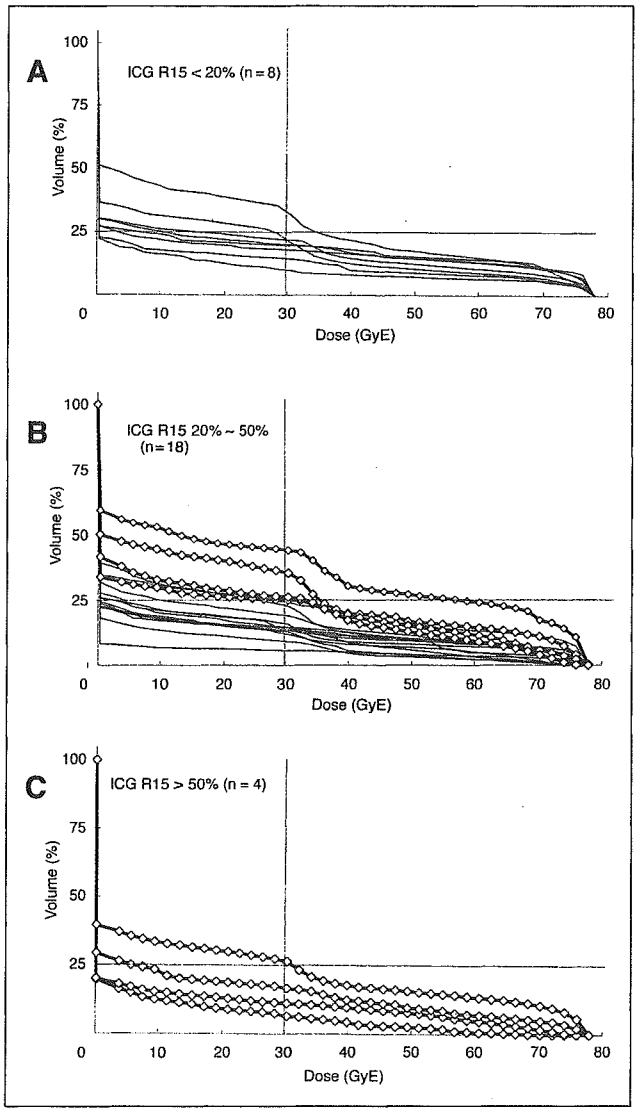

Fig 4. Dose-volume histogram (DVH) for all patients according to their pretreatment ICG R15 values, as noted in panels A, B, and C. Thick line with rhombi represents DVH for patients suffering from hepatic insufficiency within 6 months after completion of proton beam radiotherapy.

that seen in partial liver resection, rather than after 3-dimensional conformal or intensity-modulated radiotherapy delivering a low-dose of x-ray to a large proportion of noncancerous liver. Therefore, estimation of the risk of PRT-inducing hepatic insufficiency should be done with similar guidelines to evaluate liver tolerance to surgery, rather than that with normal tissue complication probability model using a mean dose administered to the entire liver.[21] Remnant liver volume and ICG R15 have been preferred indicators for that estimation, especially in Japan.[15] DVH analyses (Figs 4A to C) suggested that V_{30}% in combination with ICG R15 may be a useful indicator for estimation of liver tolerance to PRT, but no definite quantitative criteria emerged with the limited data obtained at present because of the small number of patients evaluated. The current staging system for HCC is based on survival data obtained in surgical series.[22] There is no reliable system to stratify the prognosis of patients with solitary but unresectable HCC on the assumption that they achieve good local control after PRT. Because of the limited availability of PRT at present, the establishment of particular criteria for patient selection using quantitative parameters of hepatic function such as ICG R15, and volume parameter like V_{30}%, is needed to maximize the cost-effectiveness of PRT.

Applicability of PRT instead of surgery for patients with early-stage disease should be considered with caution. Intraoperative ultrasonography (IOUS) has an important role in detecting small metastatic lesions, which could not be demonstrated in preoperative examinations. The high incidence of intrahepatic recurrences seen outside the PTV might be partly ascribable to the limit of pretreatment imaging studies. Infiltration of HCC to the portal vein and spread via portal blood flow is one of the mechanisms for the development of intrahepatic recurrence.[15] Actually, five recurrences occurred within the same segment of the primary tumor in this study. Although anatomic resection according to the architecture of the portal vein using IOUS offered a better chance of cure only for patients with noncirrhotic livers,[23] systematic segmental PRT based on multimodal imagings such as CT during arterial portography or MRI as well as image fusion technique[24] has a theoretical advantage compared with nonanatomic PRT confined to GTV only. Because there were few potentially curative approaches other than surgery for patients with HCC showing vascular invasion, further study is warranted to scrutinize an efficacy of PRT for patients with HCC of $\geq$ 5 cm in diameter, of which a large majority will demonstrate vascular invasion around the periphery of the tumor,[25] while giving attention to their V_{30}% values.

The risk of this aggressive dose-fractionation for sites such as the gastrointestinal loop, hepatic hilum, skin, or subcutanous tissues must be carefully considered, and more conventional fractionation must be adopted when these structures are critically involved in the PTV.

In conclusion, PRT for localized HCC using an aggressive dose-fractionation scheme (76 Gy_E for 5 weeks) achieved excellent local control rate regardless of vascular invasion or tumor size, if $\leq$10 cm, without devastating acute toxicity. Further study is warranted to scrutinize adequate patient selection according to quantitative parameter of hepatic function, such as ICG R15, and irradiated noncancerous liver volume in order to maximize survival benefit of this promising modality.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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Clinical Impact of Criteria for Complete Response (CR) of Primary Site to Treatment of Esophageal Cancer

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Background: With the development of chemoradiotherapy for esophageal cancer, the complete response (CR) rate would become an important surrogate end-point. However, the Response Evaluation Criteria in Solid Tumors (RECIST) do not provide criteria for a response at the primary site of esophageal cancer. The objective of this study was to assess the validity of the endoscopic CR criteria for the primary site of esophageal cancer treated with chemoradiotherapy.
Methods: We reviewed 139 patients with T1–T4, N0–1, M0–1a esophageal cancer treated with definitive chemoradiotherapy from August 1992 to April 1999. CR was tentatively defined upon endoscopic observation of the entire esophagus as: (i) disappearance of the tumor lesion; (ii) disappearance of ulceration (slough); and (iii) absence of cancer cells in biopsy specimens.
Results: CR at the primary site (primary-CR) was achieved in 80 patients (58%). Of these, 71 (89%) were evaluated as having primary-CR within 6 months from the start of therapy. With a median follow-up of 53 months, a remarkable difference in the 5-year survival rate was observed between patients evaluated as having primary-CR and having non-CR (46 and 6%, $P < 0.0001$). Local failure was observed in 15 patients and the local control rate in patients with primary-CR was 78% at 5 years.
Conclusions: These criteria appear to represent an appropriate surrogate end-point because they are convenient to apply, require only a short time before a primary-CR can be declared and their fulfillment can predict long-term survival. It is recommended that RECIST include precise endoscopic findings for primary lesions in esophageal cancer in the CR criteria.

Key words: Response Evaluation Criteria in Solid Tumors (RECIST) – esophageal cancer – chemoradiotherapy – complete response (CR) – endoscopy

INTRODUCTION

Definitive chemoradiotherapy for patients with locally advanced esophageal cancer has resulted in high complete response (CR) rates and has greatly impacted on survival (1–4). Recent results obtained with chemoradiotherapy in clinical trials have supported a new standard of care in non-surgical treatment of potentially curable esophageal cancer. With the development of chemoradiotherapy, the CR rate would become an important surrogate end-point in the treatment of esophageal cancer. However, we are not aware of any published clinical studies on chemoradiotherapy for locally advanced esophageal cancer that have precisely outlined CR criteria for the primary site. Slabber et al. (5) used standard Eastern Cooperative Oncology Group (ECOG) response criteria, which considered gastrointestinal malignancies as 'non-measurable, non-evaluable' lesions and defined CR as: (i) complete disappearance of all clinically detectable malignant disease for at least 4 weeks; and (ii) pathological proof of a clinically CR after rebiopsying areas of known malignant disease. The Radiation Therapy Oncology Group (RTOG) phase III intergroup trial (RTOG 85-01) described evaluation after treatment as including esophagoscopy and barium esophagography, with biopsy if the patient was symptomatic (2). However, these methods of evaluation have not been fully validated.

New guidelines, 'Response Evaluation Criteria in Solid Tumors (RECIST)', were published in 1999 (6) and have become the most commonly used criteria worldwide. RECIST

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gives specific size requirements for measurable lesions at baseline to distinguish target from non-target lesions. It is difficult to measure accurately the primary site of esophageal cancer as distinct from the normal esophageal wall in one dimension, because a computed tomography (CT) scan detects a primary lesion of esophageal cancer according to wall thickness of the esophagus. Therefore, the primary site of esophageal cancer is often identified as a 'non-target lesion'.

Although non-target lesions are taken into account in the evaluation of the best overall response, CR for non-target lesions is defined as the disappearance of all non-target lesions and normalization of tumor marker levels. However, it is impossible to confirm the disappearance of primary site lesions in esophageal cancer by CT scan. Furthermore, development of cicatrical stenosis of the esophagus after chemoradiotherapy often prevents accurate evaluation of tumor response by esophagography, which is usually performed to provide useful information on the degree of luminal narrowing and the location and length of the lesion in the diagnosis of esophageal cancer.

RECIST does not refer to CR criteria for primary lesions by endoscopy in detail, and endoscopic methods of evaluation have not yet been fully validated. Additionally, RECIST has recommended that utilization of endoscopy for an objective tumor response should be restricted to purposes related to validation in specialized centers.

In the treatment of esophageal cancer, we have utilized endoscopy to evaluate tumor response accurately, and propose new endoscopic CR criteria for the primary site of esophageal cancer. Therefore, the objective of this study is to assess the validity of endoscopic criteria for CR of the primary site of esophageal cancer treated with chemoradiotherapy.

PATIENTS AND METHODS

PATIENTS

A total of 217 esophageal cancer patients were treated with definitive chemoradiotherapy between April 1992 and April 1999 at the National Cancer Center Hospital East (NCCHE). For this study, we selected 139 patients from the database who fulfilled the following criteria: (i) esophageal cancer patients treated with definitive chemoradiotherapy at the NCCHE between April 1992 and April 1999; (ii) histologically proven squamous cell carcinoma; (iii) clinical stage T1–T4, N0/1, M0/M1a by the International Union Against Cancer tumor node metastasis (TNM) classification; (iv) age $\leq$75 years with an ECOG performance status of $\leq$2; (v) adequate bone marrow, renal and hepatic function; (vi) no prior chemotherapy; (vii) no severe medical complications; and (viii) no other active malignancies (except early cancer). Patients with non-cervical primary tumors with positive supraclavicular lymph nodes were defined as M1a.

Details of the treatment including the schedule and radiation field were described previously (4,7). Briefly, chemoradiotherapy consisted of two cycles of protracted infusion of 5-fluorouracil (5-FU) 400 mg/m^2/day on days 1–5 and 8–12, and cisplatin (CDDP) 40 mg/m^2 on days 1 and 8, every 5 weeks with concurrent radiotherapy consisting of 60 Gy in 30 fractions over 8 weeks. For patients who showed an objective response to treatment, additional chemotherapy was administered and consisted of protracted infusion of 5-FU 800 mg/m^2/day on days 1–5 combined with CDDP 80 mg/m^2 on day 1.

PROPOSED ENDOSCOPIC CR CRITERIA

Response at the primary site was evaluated as CR (primary-CR) by endoscopic examination when all of the following criteria were satisfied under observation of the entire esophagus: (i) disappearance of the tumor lesion; (ii) disappearance of ulceration (slough); and (iii) absence of cancer cells in biopsy specimens. When these criteria were not satisfied, a non-CR was designated. Existence of an erosion, a granular protruded lesion, ulcer scar and lugol voiding lesion did not prevent a CR evaluation. The first evaluation was performed $\sim$1 month after the completion of chemoradiotherapy to determine whether or not disease progression was observed. Although repeat assessments were not essential to confirm primary-CR after the criteria for response were first met, endoscopic examinations were performed every 2 or 3 months. All 139 patients were reviewed according to the above criteria. Responses of metastatic lymph nodes were assessed according to the World Health Organization (WHO) criteria for measurable disease.

STATISTICAL ANALYSIS

Overall survival time was determined from the date of the first administration of chemoradiotherapy to the date of death or the last confirmation of survival. Time to locoregional failure was calculated from the date of the first administration of chemoradiotherapy to the date of documented locoregional disease, which was designated as the first failure. Time to determination of a primary-CR was considered to be the period between the date of the first administration of chemoradiotherapy and the date of the first confirmation of primary-CR. Survival analysis was performed using the Kaplan–Meier method (8).

RESULTS

PATIENT CHARACTERISTICS

Out of 217 patients who received definitive or palliative chemoradiotherapy during the period studied, 78 patients were excluded from analysis. The reasons for exclusion have been described in a previous report of this study population (7). For the present study, 139 patients were selected as subjects. Patient characteristics are shown in Table 1. The median age was 62 years (range 38–75). Most of the patients had good performance status. All had histologically proven squamous cell carcinoma. Fifteen patients had T1, 11 had T2, 60 had T3, 53 had T4 and 38 had M1a disease. Clinically involved sites in the 53 cases of T4 disease were as follows: tracheobronchial

Table 1. Patient characteristics

Characteristic	No. of patients (n = 139)
Age, years	
Median	62
Range	38–75
Sex	
Male	121
Female	18
Performance status	
0	96
1	42
2	1
Histology	
Squamous W/D	5
Squamous M/D	88
Squamous P/D	45
Adenosquamous	2
Tumor length, cm	
Median	5
Range	1–20
Site	
Ut	23
Mt	81
Lt	35
T stage	
T1	15
T2	11
T3	60
T4	53
N stage	
N0	55
N1	84
M stage	
M0	101
M1a	38
Stage	
I	13
IIA	22
IIB	8
III	58
IVA	38
Involved sites of T4	
Bronchial tree only	21
Aorta only	22
Bronchial tree and aorta	8
Other	2

W/D, well differentiated; M/D, moderately differentiated; P/D, poorly differentiated; Ut, upper thoracic portion; Mt, mid-thoracic portion; Lt, lower thoracic portion.

tree (n = 21), thoracic aorta (n = 22), both sites (n = 8) and other (n = 2). One hundred and thirty-three patients (96%) completed at least the chemoradiotherapy segment that included a total radiation dose of 60 Gy. Sixty-six patients (47%) received two or more additional cycles of chemotherapy.

Response and Survival

Primary-CR was achieved in 80 of the 139 patients [58%; 95% confidence interval (CI), 45–70]. Primary-CR rates in patients with T1, T2, T3 and T4 were 93% (14 out of 15), 82% (nine out of 11), 62% (38 out of 61) and 37% (19 out of 52), respectively. Persistence of local disease was observed in 59 patients (42%; 95% CI 31–53). Among the 87 patients with T1–T3, persistence of local disease was observed in 24 patients (28%; 95% CI 16–39). Among the 80 patients with primary-CR, persistence of regional lymph nodes was observed in seven (5%) patients. With a median follow-up of 53 months, the overall survival rate at 3 and 5 years among all patients was 37% (95% CI 31–43) and 29% (95% CI 24–34), respectively. The overall survival at 3 and 5 years was 55% (95% CI 43–67) and 46% (95% CI 36–56), respectively, among the primary-CR group, while overall survival was 11% (95% CI 8–13) and 6% (95% CI 4–8), respectively, among the primary-non-CR group ($P < 0.0001$, Fig. 1).

Time to Determination of a Primary-CR

Time until determination of a primary-CR is provided in Table 2. Of the 80 patients, 71 (89%) were evaluated as having a primary-CR within 6 months from the start of therapy. However, in nine patients (11%), primary-CR was only determined after 6 months from the start of therapy because before that time biopsy specimens from the primary site were not obtained in two patients, disappearance of ulceration (slough) was not observed in three patients due to radiation esophagitis, and cicatrical stenosis of the esophagus was observed in four patients.

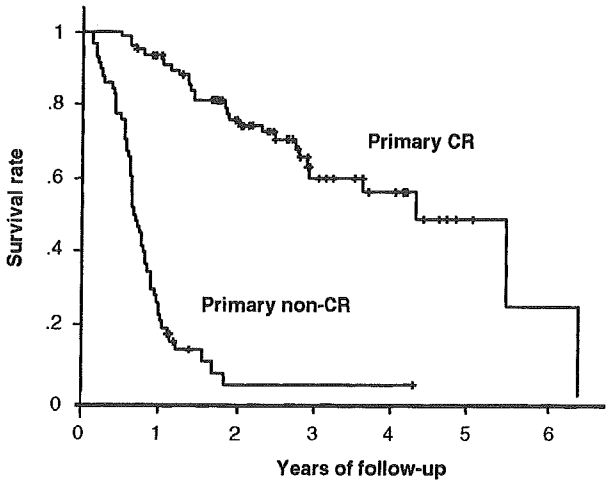

Figure 1. Overall survival in patients according to proposed endoscopic CR criteria.

Table 2. Time from the initial date of treatment to determine a CR at the primary site

	No. of patients (n = 80)	%
<3 months	25	31
3–6 months	46	58
>6 months	9	11

Table 3. First relapse site in patients with primary-CR

	No. of patients (n = 80)	%
Local failure	13	16
Regional failure	1	1
Local and distant failure	2	3
Distant failure	13	16
Treatment failure	29	36

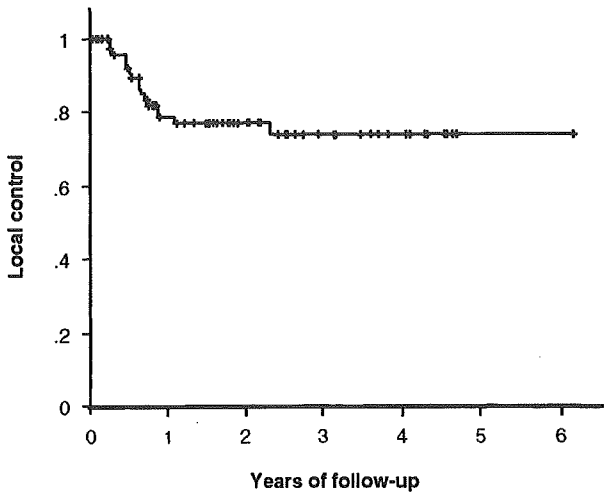

Figure 2. Local control in patients with primary CR. The local control rate is 74% at 3 years, and the curve seems to plateau after 2.2 years.

First Relapse Site

The first relapse sites in patients with primary-CR are shown in Table 3. Among the 80 patients with primary-CR, local failure occurred in 15 (19%) patients, including two with both local and distant failure. Local failure was detected within 1 year from the start of therapy in 10 of these 15 patients (67%). Regional failure alone was observed in one patient (1%). Distant failure alone as the first failure occurred in 13 (16%) patients. Twenty-nine patients (36%) experienced treatment failure. Local control in patients with primary-CR is shown in Fig. 2. The local control rate among patients with primary-CR was 78% at 5 years; this curve appeared to plateau after 2.2 years.

Death from Causes Other Than Treatment Failure

Acute and late toxicity from this treatment regimen have been described previously (7). Briefly, there were three treatment-related deaths (2%), one each due to renal failure, septic shock or pneumonia. Seven patients (5%) without cancer recurrence died due to late cardiopulmonary toxicity, which was manifested as acute myocardial infarction, radiation pneumonitis or chronic heart failure. Sudden death of unknown origin occurred in three patients without disease failure. Another eight patients died of intercurrent disease. In summary, 19 patients (14%) died from causes other than treatment failure.

DISCUSSION

We have proposed new endoscopic CR criteria for the primary site in the treatment of esophageal cancer. The development of cicatrical stenosis of the esophagus with this treatment often prevents observation of the entire esophagus. Therefore, 'observation of the entire esophagus' is considered to be necessary for endoscopic evaluation of the response to treatment. In common with the RECIST criteria, 'disappearance of tumor lesion' and 'absence of cancer cells in biopsy specimens' are indispensable to confirm CR after chemoradiotherapy. When we first began to evaluate CR by endoscopy, it was problematic how to deal with granular protruded lesions, erosions, ulceration and lugol voiding lesions. Granular protruded lesions were often observed with this treatment (Fig. 3). In the course of careful observation and obtaining repeat biopsy specimens from these lesions, local relapse was not observed. Therefore, this granular protruded lesion was considered as a hypertrophic cicatrix and would not prevent determination of a CR. After chemoradiotherapy, local relapses were often detected by endoscopy as ulceration (slough) of the esophagus. Therefore, 'disappearance of ulceration (slough)' is indispensable to confirm not only CR but also no recurrence. Chromoendoscopy using iodine solution is the most effective method of detecting squamous cell mucosal cancer (T1a) in the esophagus, which is an appropriate candidate for endoscopic mucosal resection (9,10). Iodine staining is based on a chemical reaction between iodine and glycogen. Glycogen-rich granules are mainly included in the prickle-cell layer of the normal stratified squamous epithelium. Therefore, esophagitis, cicatrix due to an ulcer scar and cancerous lesions that are immature and lose glycogen-rich granules at the prickle-cell layer can be recognized as an uncolored layer which is said to be a 'lugol voiding lesion' (Fig. 4). Because biopsy of the lugol voiding lesion makes it possible to distinguish between cancer, erosion due to esophagitis and cicatrix due to ulcer scar, the existence of a 'lugol voiding lesion' would not prevent application of the primary-CR criteria.

The main goal of objective confirmation of the response in clinical trials is to avoid overestimating the observed response rate. However, RECIST described that repeat studies to confirm changes in tumor size may not always be feasible or may

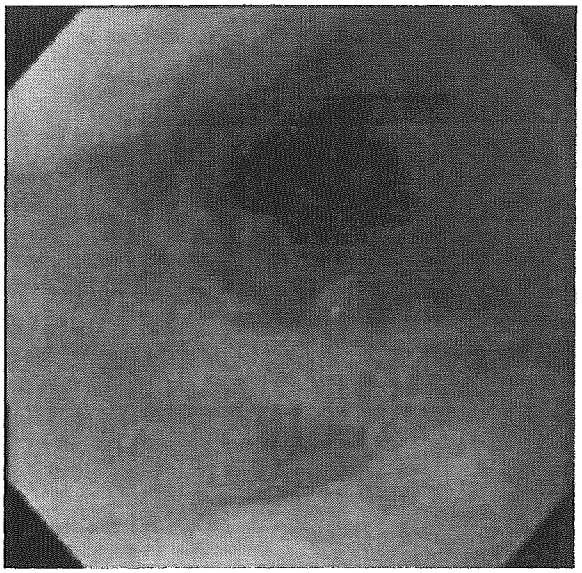

Figure 3. Granular protruded lesion.

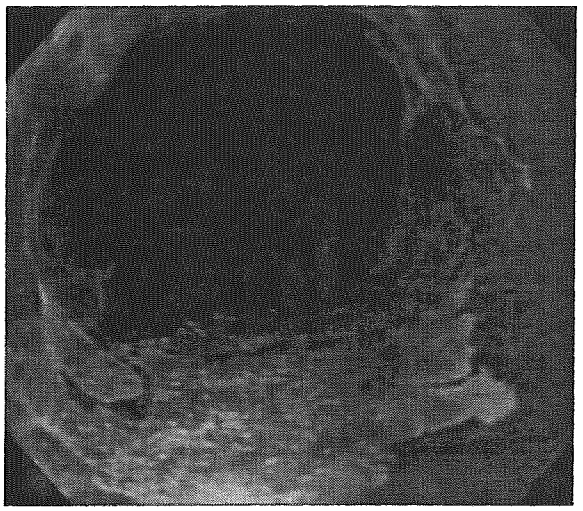

Figure 4. Lugol voiding lesion.

not be part of standard practice in protocols where progression-free survival and overall survival are the key end-points (6). In chemoradiotherapy for locally advanced esophageal cancer, a key end-point is survival. Therefore, repeat assessments were not essential in applying this criterion to confirm primary-CR after the criteria for response are first met.

For a surrogate end-point to be an effective substitute for the clinical end-point, the effects of the intervention on the surrogate must reliably predict clinical benefit or harm based on epidemiological, therapeutic, pathophysiological or other scientific evidence (11,12). Furthermore, these surrogate end-points have been used to reduce the cost and duration of clinical trials. Surrogate end-points are rarely, if ever, adequate substitutes for definitive clinical outcomes in phase III trials. Among several explanations for this failure is the possibility that the disease process could affect the clinical outcome through several causal pathways that are not mediated through the surrogate, with the intervention's effect on these pathways differing from its effect on the surrogate. Even more likely, the intervention might also affect clinical outcome by unintended, unanticipated and unrecognized mechanisms of action that operate independently of the disease process (11).

Tumor response frequently has been used as a surrogate end-point in therapeutic trials of advanced cancer. Unfortunately, tumor response is not a reliable replacement outcome for survival (13). Many of the trials that have established treatment effects on this surrogate end-point have not shown any change in mortality rates. Some of the factors contributing to the failure of a surrogate end-point are a low proportion of CRs rather than just partial responses, a low proportion of responses that are truly durable long-term effects and a high likelihood that unintended mechanisms of action from these aggressive and toxic cancer therapies adversely affect survival. When administering chemoradiotherapy for locally advanced esophageal cancer, any cause of death other than from treatment failure was recognized as an unintended mechanism of action that adversely affects survival (11). Therefore, it is reasonable to propose that an adequate surrogate end-point for CR criteria in esophageal tumors should include the following: (i) simple procedure; (ii) short duration to determine a CR; (iii) possibility to predict long-term survival; (iv) low incidence of disease failure; and (v) acceptable incidence of death from causes other than treatment failure.

RECIST has recommended that utilization of endoscopy for objective determination of tumor response should be restricted to purposes of validation in specialized centers (6). No special endoscopic technique is required for meeting the following criteria by endoscopic examination of the entire esophagus: (i) disappearance of the tumor lesion; (ii) disappearance of ulceration (slough); and (iii) absence of cancer cells in biopsy specimens. Therefore, these criteria should be recognized as involving only a simple procedure and should gain wide acceptance.

With this chemoradiotherapy as scheduled, 4 months are needed for completion, and the first evaluation of the primary site for complete response is performed approximately 5 months from the start of therapy. In this study, most of the patients (89%) were evaluated as having primary-CR within 6 months from the start of therapy. This finding suggests that these criteria can be met in a short period of time not only from the start of therapy (mostly within 2 months) but also after completion of therapy (mostly within 2 months) to declare primary-CR.

A remarkable difference in the 5-year survival rate between patients evaluated as having primary-CR and non-CR was observed in this study. Furthermore, persistence of disease was the greatest cause of treatment failure. Therefore, we could predict long-term survival for patients with locally

advanced esophageal cancer treated with definitive chemoradiotherapy according to these criteria.

In trials of cisplatin-based concurrent chemoradiotherapy for esophageal cancer, data on clinical outcomes for comparison with the present study were available from only two trials, which were the RTOG 85-01 and INT 0123 trials. The incidence of locoregional failure, distant failure and death from causes other than treatment failure in this study were similar to those in the above trials (3,14), suggesting that the clinical outcomes in this study were acceptable.

The accuracy of endoscopic ultrasound (EUS) for initial staging of esophageal cancer is widely accepted. After chemoradiotherapy, however, EUS examination is not helpful in patient management because it cannot accurately identify patients with pathological CR (15–17). This is largely because EUS cannot distinguish between residual tumor and the post-inflammatory changes that characterize effective chemoradiotherapy. EUS is of limited utility in guiding clinical decision making after chemoradiotherapy.

Recently, a retrospective study showed that EUS and EUS-guided fine needle aspiration biopsy (FNA) have the potential of identifying residual lymphadenopathy after pre-operative chemoradiotherapy (18). However, this result was very controversial because EUS-guided FNA was performed in only eight patients.

[^{18}F]Fluorodeoxyglucose ([^{18}F]FDG) positron emission tomography (PET), an emerging imaging technology based on differences in glucose uptake between neoplastic and surrounding normal tissue, has improved the accuracy of clinical staging of untreated esophageal cancer by detecting otherwise occult metastases (19–23). Many studies have reported that [^{18}F]FDG PET is a valuable tool for non-invasive assessment of histopathological tumor response after the completion of neoadjuvant therapy for locally advanced esophageal cancer (24–26). Furthermore, some studies indicated that changes in [^{18}F]FDG uptake or changes in standard uptake value (SUV) were predictive of disease-free survival and overall survival (25–27).

Furthermore, PET/CT is a new imaging modality that provides simultaneous functional and anatomic information. PET/CT has been reported to increase diagnostic confidence compared with either PET or CT imaging alone (28–30). PET/CT also helps in target volume delineation during planning for radiotherapy treatment of esophageal cancer (31,32). Better characterization of the target may improve local control as well as spare normal tissues from radiotherapy sequelae. After therapy, subtle metabolic findings on [^{18}F]FDG PET may result in detection of residual disease after correlation with simultaneously acquired morphologic data. Alternatively, equivocal CT findings, which could represent either recurrent tumor or post-therapy fibrosclerosis, now can be distinguished with the additional information provided by [^{18}F]FDG PET data. In the post-therapy setting, PET/CT might improve the accuracy of PET imaging in distinguishing recurrent disease from benign post-therapy changes. Radiation-induced esophagitis, however, results in false-positive [^{18}F]FDG uptake. Furthermore, because of the limited spatial resolution of PET, lesions <0.5 cm may be undetectable. For these reasons, [^{18}F]FDG PET cannot differentiate partial response from complete response and is of limited utility in guiding clinical decision making after chemoradiotherapy. As PET/CT systems are not yet in widespread use, further studies including comparison with the proposed endoscopic CR criteria or differential evaluation are necessary to establish its role in the evaluation of the response to therapy.

In order to improve local control, many attempts including intensification of radiation dose and accelerated or hyperfractionation radiation methods were made, but all of these methods failed to improve local control or survival (14,33–35). The addition of new agents, other than 5-FU plus cisplatin, may be promising. The addition of paclitaxel to the standard chemoradiotherapy regimen increased the response rate of locally advanced esophageal cancer, with a pathological complete response rate of 38% and an actuarial 3-year survival of 41%, which warrant further investigation (36). The addition of cetuximab, a monoclonal antibody to epidermal growth factor receptor, to high-dose radiation in locoregionally advanced squamous cell head and neck carcinoma resulted in a statistically significant and clinically meaningful improvement in locoregional control and overall survival (37). The use of molecular targeting agents in combination with chemoradiotherapy will be a major focus in future studies, because their toxicity profiles are clearly different from those of cytotoxic agents.

The survival of patients who have residual or recurrent tumor after chemoradiotherapy is dismal, and salvage treatment for such patients is indicated to improve the overall survival. Although some small studies have shown the feasibility and efficacy of salvage surgery, the high mortality associated with salvage surgery after chemoradiotherapy is another important issue. Although the optimal timing and modes of salvage treatment should be investigated in the future, early detection of residual or recurrent tumor that was limited to within the submucosal layer enabled endoscopic mucosal resection (EMR) as a substitute for salvage surgery (38). Photodynamic therapy (PDT) is an experimental cancer treatment modality that selectively destroys cancer cells by the interaction between absorbed light and a retained photosensitizing agent (39). In our experience, PDT was a safe and effective salvage treatment with a CR rate of 62% (40). A phase II trial of PDT for residual or recurrent esophageal cancer after definitive chemoradiotherapy is ongoing at our hospital.

In conclusion, the proposed endoscopic CR criteria appear to represent an appropriate surrogate end-point because they are convenient, require a short period of time (mostly within 6 months) to declare primary-CR, predict favorable survival and are associated with an acceptable frequency of disease failure and death from causes other than treatment failure. The proposed criteria would be of major importance in the process of evaluation of new treatment strategies. Since persistence of disease was the greatest cause of treatment failure

for locally advanced esophageal cancer after chemoradiotherapy, it is important to evaluate accurately the tumor response. In the treatment of locally advanced esophageal cancer, moreover, the fact that RECIST does not refer to CR criteria for primary lesions in detail prevents not only appropriate clinical evaluation of response but also the fulfillment of requirements of a clinical trial. We feel that the RECIST criteria do not provide information to evaluate the primary sites of esophageal cancer. It is recommended that the precise endoscopic findings of primary lesions in esophageal cancer be added to the CR criteria in RECIST.

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[資料]

がん診療の経済的な負担に関するアンケート調査

目次

がん診療の経済的な負担に関するアンケート調査

平成 17 年度　厚生労働科学研究費補助金
第 3 次対がん総合戦略研究事業

「がん医療経済と患者負担最小化に関する研究」
主任研究者：濃沼　信夫（東北大学教授）

＜調査の趣旨＞

このアンケートは、がん診療を受けておられる患者さんの経済的な負担を把握するためのものです。

質が高く安全で、患者さんの経済的な負担ができるだけ少ない、優れたがん医療の実践に向けた基礎資料を得ることを目的としています。

＜お願い＞

このアンケートは、がん診療で外来を受診されている全国の患者さんを対象にしております。

日数や金額などをおたずねする項目では、過去の領収書などを参考にしながらお答え下さい。正確にわからない場合は、おおよそで結構です。

お名前を書いていただく必要はありません。ご回答は統計的に処理されますので、個人が特定されることはありません。

まことに恐れ入りますが、ご回答いただいた調査票は1週間程度で、ご返送下さい。返信用の封筒に切手はいりません。何とぞ、よろしくお願い申し上げます。

＜お問い合わせ先＞

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記入日	月 日

1 通院・入院について

1-1 自宅から病院までの交通手段について、あてはまるものを○で囲んで下さい。

徒歩	電車	自家用車	飛行機
バス	新幹線	タクシー	その他（ ）

1-2 通院時間は片道どのくらいですか。

時間 分くらい

1-3 通院にかかる交通費（宿泊費を含む）は、往復でいくらですか。

ご自身	円くらい	つきそいの方	円くらい

1-4 通院回数はどのくらいですか。

1ヶ月間に	回くらい	1年間に	回くらい

1-5 いまの病気（がん）で、これまで何ヶ所の病院・診療所（現在受診中も含む）を受診しましたか。

ヶ所

1-6 いまの病気（がん）で、これまで何回入院しましたか。

回

1-7 昨年1年間（1月1日～12月31日）の入院期間は、合計しておよそ何日でしたか。

日

2 いまの病気（がん）によって、ご自身の仕事にどのような影響がありましたか。あてはまるものに○をつけて下さい。

1 お勤めの方
2 自営業の方
3 お勤め・自営業以外の方

1 専業主婦
2 学生
3 無職
4 その他（ ）

1 お勤めの方	2 自営業の方
1 特に影響はない	1 特に影響はない
2 これまでのように仕事をこなすことができない	2 これまでのように仕事をこなすことができない
3 仕事を休むことが多くなった	3 仕事を休むことが多くなった
4 仕事をやめた・解雇された	4 休業・廃業した
5 勤務時間が減った	5 営業時間が短くなった
6 給料が減った	6 収入が減った
7 異動・配置換えとなった	7 転業した
8 その他（ ）	8 その他（ ）

3 いまの病気（がん）によって、経済的にどのような影響を受けましたか。

1 変らない
2 ご自身の支出が増えた → 約（ ）割の増加
3 ご家族の支出が増えた → 約（ ）割の増加
4 ご自身の収入が減った → 約（ ）割の減少
5 ご家族の収入が減った → 約（ ）割の減少
6 その他（ ）

4 いまの病気(がん)に関する支出について

4-1 病院や薬局の窓口で支払った金額はいくらですか。

	入院分	外来分
先月1ヶ月間	円	円
昨年1年間	円	円

4-2 健康食品や民間療法などの支出額はいくらですか。

先月1ヶ月間	円	昨年1年間	円

4-3 その他の支出額(贈答費・かつら代など)はいくらですか。

先月1ヶ月間	円	昨年1年間	円

4-4 民間保険・簡易保険・県民共済などの保険料はいくらですか。

先月1ヶ月間	円	昨年1年間	円

5 いまの病気(がん)の給付について

5-1 高額療養費として、戻ってきた金額はいくらですか。

昨年1年間	円

5-2 医療費還付として、戻ってきた税金はいくらですか。

昨年1年間	円

5-3 民間保険・簡易保険・県民共済などから受け取った金額(入院給付金など)はいくらですか。

先月1ヶ月間	円	昨年1年間	円

6 いまの病気(がん)の経済的負担について、病院から説明がありましたか。○をつけて下さい。

1 十分な説明を受けた
2 説明を受けたがわからなかった
3 説明はなかった
4 覚えていない

→ 説明した人を○で囲んで下さい。

医師　看護師　その他の職員(　　)

7 いまの病気(がん)の経済的負担について、病院以外の情報源は何ですか。

1 雑誌・本
2 新聞
3 テレビ・ラジオ
4 インターネット
5 講演会
6 相談窓口
7 患者団体
8 保険外交員
9 家族・親戚
10 友人・知人
11 その他
(　　)

8 いまの病気(がん)の経済的負担について、外部の人に相談しましたか。

1 相談した → 相談先
2 相談していない → その理由

相談先
1 病院の相談窓口
2 役所の相談窓口
3 地域の世話人(民生委員など)
4 民間団体(NPOなど)
5 同じ病気の人
6 その他(　　)

その理由
1 相談しなくてもよい
2 相談したくない
3 相談したいができなかった

続く

9 いまの病気(がん)の経済的負担について、特に希望するものを3つまで(その他を含む)選び○をつけて下さい。

1 もっと情報がほしい
2 気軽に相談できるところがほしい
3 自宅の近くに、がん専門病院があってほしい
4 自己負担が多くなっても(保険適用外でも)、がん診療を続けたい
5 もし選べるなら、経済的負担の少ない治療(お薬)にしてもらいたい
6 がん診療の自己負担は、他の病気より軽くしてほしい
7 がん診療での特定療養費制度(室料差額など)の対象をひろげてもらいたい。
8 高額療養費の限度額を引き下げてもらいたい
9 がん診療は全額公費負担にしてもらいたい
10 外国でがん診療を受けた場合も、公的保険を適用してもらいたい
11 民間保険の内容・給付額を充実してもらいたい
12 その他

(　　)

10 ご自身について

10-1

年齢	歳	性別	男　女	居住地	都道府県

10-2 いまの病気(がん)と診断されたのは

平成　　年　　月頃	あるいは	年前

10-3 がんと診断されたとき、それはどの部位でしたか(複数の場合は主たる部位)。○で囲んで下さい。

食道	胃	結腸	直腸	肝臓	胆管	すい臓		
肺	胸膜	乳房	子宮	卵巣	膀胱	腎臓	前立腺	精巣
血液	脳	いん頭	こう頭	舌	口腔	甲状腺		
骨	筋肉	リンパ腫	皮膚	その他 (　　)				

10-4 いまの病気(がん)の治療状況について、1つに○をつけて下さい。
1 がんに対する治療を継続中
2 がんに対する治療は終了し、検査などで通院中
3 その他(　　)

10-5 いままで受けた治療、すべてに○をつけて下さい。

1 外科手術(内視鏡手術を含む)	4 放射線療法	7 リハビリテーション
2 薬物療法(抗がん剤など)	5 緩和ケア	8 ストーマケア(人工肛門など)
3 内分泌療法(ホルモン剤など)	6 在宅ケア	9 その他(　　)

ご協力、どうもありがとうございました。

がん診療の経済的な負担に関するアンケート調査

平成 17 年度　厚生労働科学研究費補助金
第 3 次対がん総合戦略研究事業

「がん医療経済と患者負担最小化に関する研究」
主任研究者：濃沼 信夫（東北大学教授）
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＜調査の趣旨＞

このアンケートは、がん診療を受けておられる患者さんの経済的な負担を把握するためのものです。

質が高く安全で、患者さんの経済的な負担ができるだけ少ない、優れたがん医療の実践に向けた基礎資料を得ることを目的としています。

＜お願い＞

このアンケートは、がん診療で病院を受診されている全国の患者さんを対象にしております。

日数や金額などをおたずねする項目では、過去の領収書などを参考にしながらお答え下さい。正確にわからない場合は、おおよそで結構です。

お名前を書いていただく必要はありません。ご回答は統計的に処理されますので、個人が特定されることはありません。

まことに恐れ入りますが、ご回答いただいた調査票は1週間程度で、ご返送下さい。返信用の封筒に切手はいりません。何とぞ、よろしくお願い申し上げます。

＜お問い合わせ先＞

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1 通院・入院について

1-1 お住まいの都道府県はどちらですか

居住地	都道府県

1-2 自宅から病院までの交通手段について、あてはまるものを○で囲んで下さい。

徒歩	電車	自家用車	飛行機
バス	新幹線	タクシー	その他（　　）

1-3 通院時間は片道どのくらいですか。

時間	分くらい

1-4 通院にかかる交通費（宿泊費を含む）は、往復でいくらですか。

ご自身	円くらい	つきそいの方	円くらい

1-5 入院日数・通院回数はどのくらいですか。

	入院	通院
先月１ヶ月間	日くらい	回くらい
昨年１年間	日くらい	回くらい

2 いまの病気（がん）に関する支出について

2-1 病院や薬局の窓口で支払った保険診療分・自費分（差額ベッドなど）はいくらですか。

	入院分（円）		外来分（円）	
	保険診療	自費	保険診療	自費
先月				
2ヶ月前				
3ヶ月前				
4ヶ月前				
5ヶ月前				
6ヶ月前				

2-2 高度先進医療（陽子線治療など）の金額はいくらですか。

円

2-3 支払いの際に、どのように対応しましたか。当てはまるものすべてに○を付けて下さい。

1 貸付制度（高額療養費受領委任払制度・高額療養費貸付制度）を利用した
2 民間保険からの給付金で支払った
3 貯蓄から支払った
4 家族・友人から借りた
5 ローンを組んだ
6 分割払いにしてもらった
7 払えなかった
8 その他（　　）

2 いまの病気(がん)に関する支出について（続き）

2-4 健康食品や民間療法などの支出額はいくらですか。

先月1ヶ月間	円	昨年1年間	円

2-5 その他の支出額(贈答費・かつら代など)はいくらですか。

先月1ヶ月間	円	昨年1年間	円

2-6 民間保険・簡易保険・県民共済などの保険料はいくらですか。

先月1ヶ月間	円	昨年1年間	円

3 いまの病気(がん)に関する給付について

3-1 高額療養費として、戻ってきた金額はいくらですか。

昨年1年間	円

3-2 医療費還付として、戻ってきた税金はいくらですか。

昨年1年間	円

3-3 民間保険・簡易保険・県民共済などから受け取った金額(入院給付金など)はいくらですか。

先月1ヶ月間	円	昨年1年間	円

4 いまの病気(がん)の経済的負担について、病院から説明がありましたか。○をつけて下さい。

1 十分な説明を受けた
2 説明を受けたがわからなかった
3 説明はなかった
4 覚えていない

→ 説明した人を○で囲んで下さい。

医師　看護師　その他の職員(　　)

5 いまの病気(がん)の経済的負担について、外部の人に相談しましたか。

1 相談した → 相談先
2 相談していない → その理由

相談先
1 病院の相談窓口
2 役所の相談窓口
3 地域の世話人(民生委員など)
4 民間団体(NPOなど)
5 同じ病気の人
6 その他
(　　)

その理由
1 相談しなくてもよい
2 相談したくない
3 相談したいができなかった

6 いま受けている治療に◎、これまで受けた治療、すべてに○をつけて下さい。

1 放射線治療	5 外科手術	9 緩和ケア(在宅ケア)
2 ガンマナイフ	6 内視鏡的切除	10 その他
3 陽子線治療	7 化学療法(抗がん剤など)	(　　)
4 重粒子線治療	8 分子標的治療	

7 陽子線治療にかかる経済的負担が、陽子線治療以外のがん治療に影響しましたか。

1 影響した → 1 治療を変更した 2 治療を中止した 3 治療を延期した
4 治療を断念した 5 その他（自由にお書き下さい）

2 影響しない