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Preoperative Chemoradiotherapy for Locoregional Esophageal Cancer : Preliminary Report

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Conventional treatment of esophageal cancer with surgery or radiation alone has afforded few long-term survivors. In order to improve outcome and determine the efficacy of a combined modality approach, this prospective study was performed.

Between May 1993 and August 1994, 27 patients with loco-regional squamous cell carcinoma of the esophagus were treated with 2 courses of combined fluorouracil(1000mg per square meter of body-surface area daily for 5 days) and cisplatin(60mg per square meter on the first day)(D1 and D29) plus 48Gy of radiation therapy(RT) over 4 weeks. A transhiatal esophagectomy was planned 3-4 weeks after chemoradiotherapy. Twenty-seven patients completed a full course of therapy.

Clinical response was evaluable in 26 patients : 22 patients showed improvement and relief from dysphagia, 2 patients stable disease,and 2 patients progression.

One patient died of sepsis 1 week after completion of chemoradiotherapy and was excluded from the analysis. Ten patients underwent operation after chemoradiation. Of them, 5 showed complete histologic response. One of the complete responders died of recurred disease 8.5months after operation, the other 2 patients died of sudden death,and sepsis from wound deheiscence 7 days after operation, respectively. Nine patients refused operation because of excellent relief of their dysphagia and 6 patients were denied because of disease progression(2), fear of operations(2), old age and family member's disapprovement(1), and underlying liver cirrhosis(1). The last one patient was awaiting for operation.

Of 13 patients who refused or denied operation, 6 patients finished further chemotherapy and radiatherapy(external radiation 1200 cGy+intracavitary radiation 900 cGy, 2 cycles of 5FU+cisplatin).

This intensive preoperative chemoradiotherapy is feasible,and allows for a high rate of resectability and a high rate of complete pathlogic response in a locoregional esophageal cancer.

Toxicity is considerable but manageable. This study warrants further investigation.

Key Words : *Preoperative chemoradiotherapy, Esophagectomy, Esophageal cancer*

INTRODUCTION

Esophageal cancer is the 5th leading primary cancer among men in Korea(Ministry of Health and Social Affairs,1992). In esophageal cancer, the outcome with single modality therapy is very poor, with a 5-year survival rate of about 5-10%, median survival being less than 10 months(Earlam and Cunha-Melo,1980). Combined therapy including preoperative treatment with chemotherapy and/or radiation therapy has been used in an attempt to downstage the tumor and improve long term results(Bains et al., 1982 ; Liu et al., 1986 ; Ajani et al., 1990). Although some reports have suggested that these treatment strategies are beneficial in terms of palliation and survival rates, further prospective studies are warranted to confirm the survival advantage of preoperative chemoradiotherapy.

We therefore began a prospective phase II trial to determine the efficacy of concurrent preoperative chemotherapy and radiotherapy using the end point of histologic CR (complete response) rate, and overall survival. The toxicity of this combined modality regimen was also evaluated.

MATERIALS AND METHODS

Patient population

Between May 1993 and August 1994, 27 patients with biopsy-proven, newly diagnosed,squamous cell carcinoma of the esophagus, cardia, or gastroesophageal junction were entered into the study.

Disease had to be limited to the esophagus and regional lymph nodes, and all known sites of involvement had to be encompassable within a single (tolerable) radiation field. Celiac adenopathy was accepatable for mid-or distal third tumors because these nodes could be included in the radiation port.

There should be no evidence of distant metastases or involvement of the tracheobronchial tree or major structures that would preclude removal of the tumor. Patients had to be at acceptable operative risks without cardiac or other medical contraindications to surgery. Patients were required to have a Karnofsky performance status of at least 60%, adequate bone marrow reserve (WBC>3,500/ul, platelets 100,000/ul), and adequate renal function(creatinine cleareance >50mg/mL).

Informed consent was got from every patient.

Patients Characteristics

The most frequent initial presenting symptoms were dysphagia(66%), chest pain(19%), epigastric pain(15%), hematemesis(7%). The median performance status was 80%(range, 60% to 100%). Clinical tumor stage was : 9 T1, 16 T2, 2 T3. Twelve of 27 patients had nodal disease on CT scan of more than 1cm and suspicious for metastasis. Thus, although no attempt was made to biopsy suspicious lymphadenopathy determined by CT scan, 48% of patients had findings that suggested regional involvement(Table 1).

Table 1. Characteristics of Patients with Esophageal ca

No of patients 27	
Age	
<60	9(33%)
60-69	12(44%)
>70	6(23%)
Median ages 61(42-75)	
Sex	
M	26(96%)
F	1(4%)
Tumor location	
Cervical	0
Thoracic	
upper	0
middle	19(70%)
lower	8(30%)
Wt. loss, last6Mo	
≥10%	7(26%)
<10%	14(52%)
no change	6(22%)
KPS score	
90-100	15(56%)
70-80	11(41%)
50-60	1(3%)
Median KPS	80%
Degree of dysphagia	
All	2(7%)
Most	10(37%)
Soft	13(48%)
Liquid	2(8%)
none	0
Tumor length	
<5cm	8(30%)
≥5cm	19(70%)

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Tumor staging	
T1	9(33%)
T2	16(59%)
T3	2(8%)
Clinical node status	
N0	14(52%)
N1	13(48%)
Clinical staging	
I	6(22%)
II	19(70%)
III	2(8%)

On the Karnofsky scale, a score of 90 to 100 indicates that the patient is at least able to carry on normal activity or has minor effects of disease : a score of 70 to 80 indicates that the patient at least cares for himself or herself : and a score of 50 to 60 indicates that the patient requires assistance and may require medical care but is not disabled and does not require special care. Tumors stages are defined as follows : T1, tumor involues ≤5cm of esophageal length, with no esophageal obstruction, incomplete circumferential involvement and no evidence of spread beyond the esophagus ; T2, tumor is >5cm long or complete circumferential involvement is evident, and there is no evidence of extension outside the esophagus ; and T3, any of the above with evidence of extension outside the esophagus. Node stages are defined as follows : N0, no regional involvement is evident of CT scanning ; and N1, mediastinal involvement is evident.

Treatment plan

The treatment plan called for initiating preoperative radiationtherapy, cisplatin, and 5-FU on day 1 (Fig. 1).

Fluoroucil(1000mg per square meter of body surface area per day) was administered as a continuous intravenous infusion for the first five days of weeks 1 and 5.Cisplatin(60mg per square meter of body surface area per day)was administered for 5 hours on days 1 and 29.

Radiotherapy was delivered for five days per week for 4 weeks at 120cGy bid for a total dose of 4800cGy. Treatment portals encompassed the tumor volume with 5cm longitudinal margins and 2cm lateral margins and included the mediastinum, celiac, and/or supraclavicular nodes as the pretreament evaluation dictated. Three or four weeks after completion of chemoradiotherapy, each patient was reevaluated for response or the presence of distant metastatic disease by physical examination, esophagogram, esophagoscopy, chest and upper abdomen CT, and bone scan. To rule out the trachebronchial invasion ,bronchoscope was done in upper third and mid esophageal cancer patients. Endoscopic sonography was performed with an Olympus EU M3 endoscope (Olympus Optical Co.,Tokyo) of 13-mm diameter with a 7.5-MHz probe in cases that gastrofiberoscope could be passed beyond the tumor.

5-FU 1,000 mg / m^2 / D continuous infusion×5,	D2-6, D30-34
Cis-platin 60mg / m^2,	D1, D29
XRT4800cGy	D1-28
THE, esophagogastrosomy	3-4 week after chemotherapy

Fig. 1. Treatment Plan

When no disease progression was observed, the patient was scheduled for surgery approximately 4 weeks after the last day of chemotherapy. Surgery was an tranhiatal esophageal resection without thoracotomy. Alimentary continuity was established with the stomach mobilized into the posterior mediastinum in the original esophageal bed and anastomosed to cervical esophagus.

Accessible subcarinal, paraesophageal and celliac axis lymph nodes were sampled routinely for staging purposes.

Patients who refused or were denied esophagectomy were scheduled to undergo further chemotherapy and radiotherapy(external radiation 1200cGy+intracavitary radiation 900cGy, 2 cycles of 5FU+cisplatin).

Treatment modifications for toxicity were as follows : for hematologic toxicity, if granulocytes were less than 1,000/uL or platelets less than 50,000/uL, then 5-FU, cisplatin and radiation were held back until counts recovered to greater than these critical values. Chemotherapy was then resumed at full doses.

For Grade 3 or greater stomatitis and diarrhea, 5-FU was held back until toxicity resolved. If renal function did not return to normal by the time of the next scheduled dose of cisplatin, the cisplatin administration was withheld.

Criteria for Response and Toxicity

Clinical response to preoperative chemothepapy and radiotherapy was categorized as improvement, stable disease, or progression, and was based on a comparison of the baseline and preoperative imaging staging.

After resection, patients were categorized as either pathological complete responders(path negative) or as having residual tumor in the resected spe-

cimen(path positive).

Statistical Methods

Survival time was calculated from the date of registration.

The Kaplan-Meier method was used to estimate event-time distributions and log-rank statistics were used for comparisons.

RESULT

Tumor Response

Of 26 patients, 22 demonstrated clinical improvement, 2 had stable disease, and 2 had progression(Table 2, Fig. 2,3). Endoscopic passing was possible in 9/26 at first and 16/26 after concurrent chemoradiotherapy.

Table 2. Clinical response to preoperative chemoradiation

Response	No. of patients
Improvement	22
Stable disease	2
Progression	2
Incomplete assessment	1
Total	27

Two patients turned out to have progression at 6 weeks,and 9 weeks after chemoradiation respectively. The reevaluation examinations were delayed because they hesitated to have the operation and because of financial problems.

Surgical Results

The surgical results were as follows(Table 3).

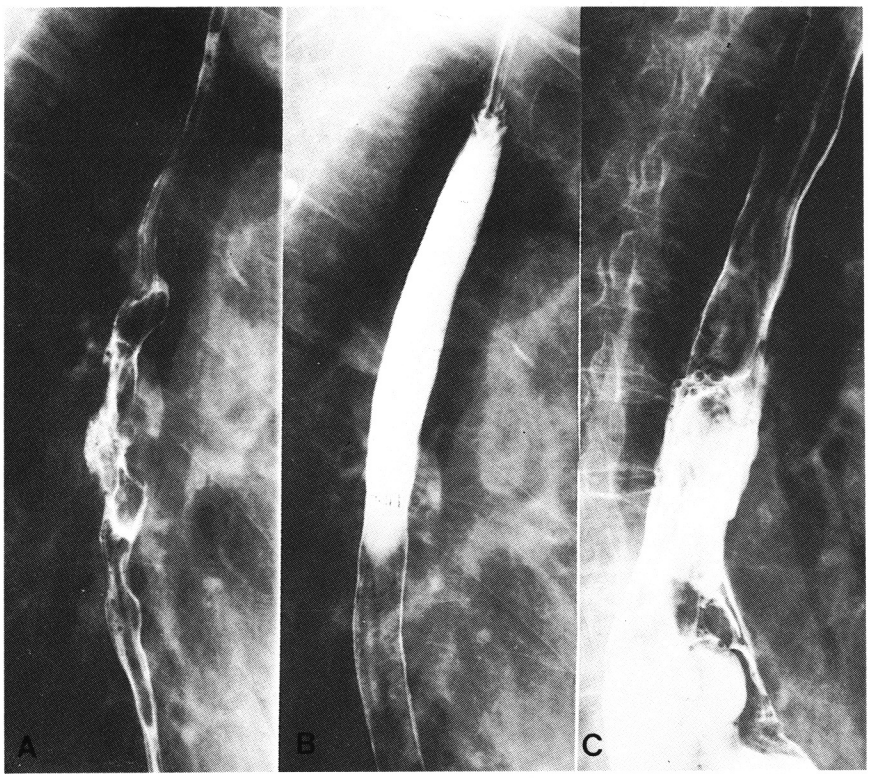

Fig. 2. A : At diagnosis, esophagogram showed irregular mucosa with ulceration in midesophaus, B : 4 week after chemoradiotherapy, previous irregular mucosal changes were improved, C : 1 year after esophagectomy, stomach conduit maintained with good patency.

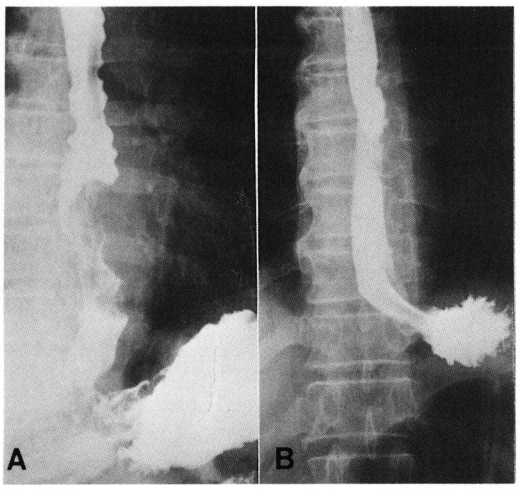

Fig. 3. Esophagogram of 46 year old man with esophageal cancer obtained before(A)and after (B)concurrent chemoradiotherapy. Irregular filling defect in distal esophagus was improved after chemoradiotherapy.

Table 3. Outcome

Total registered	27
preoperative deaths	1
preoperative Tx finished	27
surgical candidates	10
THE performed	8
Ivor-Lewis	2
Disease free postoperatively	9
Histlogic finding	
T0, N0	5
T0, N+	1

Tx : treatment, THE : transhital esophagectomy

Nine of 10 patients had a potentially curative operation, which was defined as total gross removal of tumor and negative margins of resection. Of these, 5 patients were classified as pathology negative(Fig. 4,5). One of them died of recurred disease 8.5 Mo after operation. High resectability(9/10) was achieved by this neoadjuvant chemoradiotherapy.

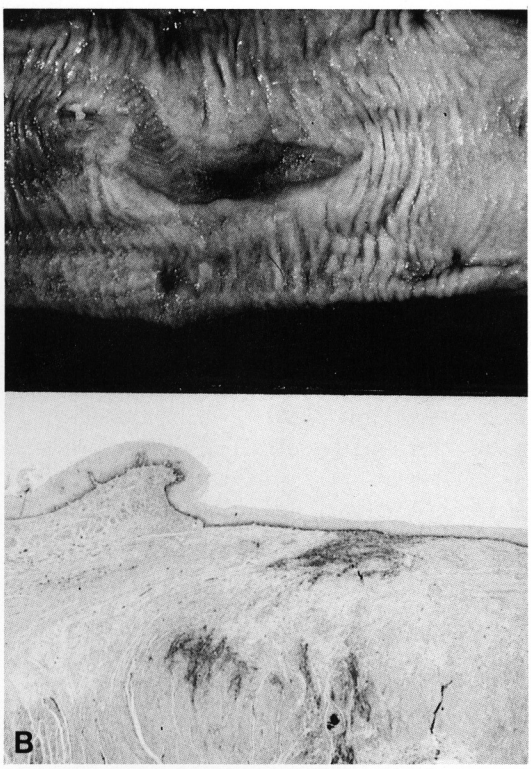

Fig. 4. A : Note a shallow depressed healed ulcer measuring 2.5×0.5cm with reepithelialization(Gross) and B : Note a dystrophic calcification in the muscle layer(Micro×200).

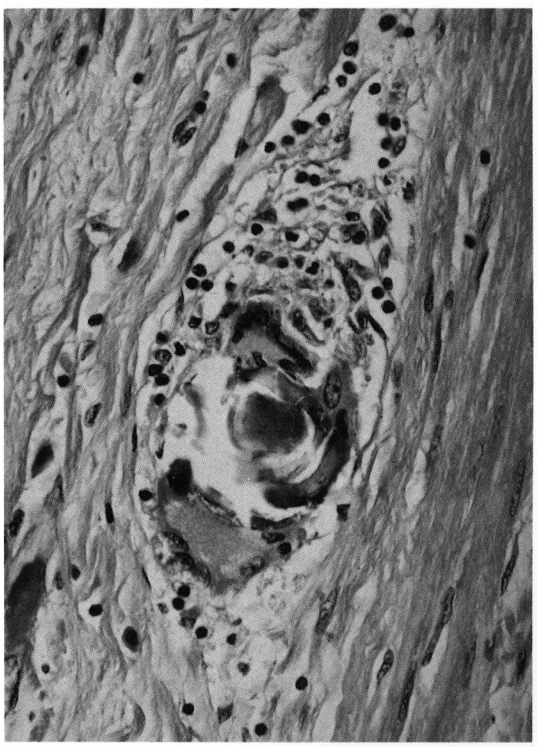

Fig. 5. Dystrophic calcification surrounded by multinucleated giant cells and lymphocytes, which is suggestive of necrosis of tumor cells. No viable tumor cell is present.

Table 4. Toxicity during concurrent chemoradiotherapy

Evaluable	27		
Hematologic	Gr2	Gr3(1000-1999)	Gr4(<1000)
Leukopenia	9/27(33%)	5/27(18%)	1/27(4%)
Thrombocytopenia	4/27(19%)	1/27(4%)	1/27(4%)
Nonhematologic			
Nausea/vomiting	13(48%)		
Esophagitis	12(44%)	2(7%)	
Wt. loss(>10% ofprev. wt)	5(18%)		
TPN	5(18%)		
Stent insertion	1(4%)		
Renal toxicity	0(0%)		
Skin desquamation	1(4%)		

Side effects of treatment

The combined treatment was more toxic than single therapy, as expected.

There was one treatment-related death preoperatively. The patient was a 45 year old man, and concurrent chemoradiation was started after stent insertion. He suffered from severe anorexia during concurrent chemoradiotherapy,aspiration pneumonia developed at home leading to septic death associated with myelosuppresion 1 week after the completion of chemoradiotherapy(Table 2).

But the majority of patients tolerated this regimen, if adequate nutritional supports were provided. Most of our patients received parenteral nutrition. 5 patients received total parenteral nutrition because of weight loss and dysphagia at entry onto the study.

Grade 3, 4 leukopenia and thrombocytopenia were observed in 22% and 8% respectively(Table 4). Two of them received a 3 week course of 5FU, cisplatin, vinblastine according to the Michigan University protocol(Forastiere AA et al., 1990). Their hematologic toxicity was severe, treatments were delayed for 7, 10 days. But there wereno episodes of bleeding and no transfusions were required.

Esophagitis was moderate to severe in 51% of the patients, 23 patients received the entire dose of chemoradiation without interruption.

There was no trend with regard to treatment-related changes in performance status. Two patients experienced stricture of anastomosis site, resolved by balloon dilatation. There were 2 postoperative mortalities : unexpected sudden death, and sepsis from wound deheiscence 7 days after operation respectively(Table 5).

Table 5. Postoperative complication

Complication	No. of patients
anastomosis site stricture	2
wound dehiecence	1
pleural effusion	7
sudden death	1
septic death	1
empyema	1

Compliance

After preoperative chemoradiotherapy and 3-4 weeks rest, 10 patientsunderwent operation. Another patient awaited for surgery. Low compliance to surgery ascribed to multifactorial reasons, but mostly due to symptomatic improvement.

Nine patients refused because of excellent relief of their dysphagia and 6 patients were denied because of disease progression(2), fear of operations(2), old age and family member's disapprovement(1), and underlying liver cirrhosis(1).

Of 13 patients who refused or denied operation, 6 patients finished further chemotherapy and radiatherapy(external radiation 1200 cGy+intracavitary radiation 900 cGy, 2 cycles of 5FU+cisplatin).

Survival

There were two operative mortalities,confined to the beginnning of this study. A patient with 60% Karnofsky performance score continued total parenteral nutrition from the onset of preoperative chemoradiation to the end, who tolerated poorly.The reevaluation examination showed no response(stable). Wound dehiescence followed after esophagectomy, and he

Table 6. Esophageal Cancer Failure Pattern : Autopsy Data

Site	Anderson*	Bosch	Mandard**
Patient number	79	82	111
Local only(%)	9	27	-
Distant only(%)	2	7	-
Local+distant(%)	82	50	75
"Tumor sites"(%)			
Local	91	77	61
Lung	52	20	31
Liver	47	28	23
Lymph nodes	73	61	74
Adrenal	20	12	9
Trachea-bronchus	17	33	16

Autopsy performed a median of 4* or 6.3** months from diagnosis.(Kelsen DP : Adjuvant therapy of upper gastrointestinal tract cancers. Seminars in Oncology 18(6) : 543-559, 1991)

died of sepsis postoperatively. The other patient,a 64 year-old man, who showed pathologic complete response to preoperative chemoradiotherapy died suddenly without any specific cause 7 days after operation. Survivals of 16 patients who did not undergo operation were compared with a those of 10 patients in whom esophagectomy was performed(Table 6). There were no significant differences with regard to clinical presentation and stage but there was a trend toward advanced age in the operative group.

Comparison of overall survival between esophagectomy and non-esophagectomy showed no significant difference. The median follow up was 7.2Mo(1.8-16.3)(Fig. 6).

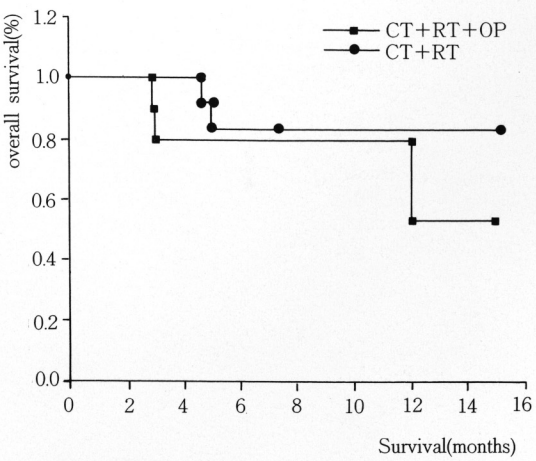

Fig. 6. comparision of overall survival between patients with esophagectomy and without esophagectomy.

The reasons that the survival rate of esophagectomy group(n=10) seemed to be lower than that of the nonesophagectomy group(n=16) were the small size and postoperative death at the beginning.

DISCUSSION

The prognosis for individuals diagnosed with cancer of the esophagus is exceedingly poor with less than 10% of 5-yr survival(Earlam and Cunha-Melo, 1980). Knowlege of the potential failure pattern (sites of recurrent disease) is crucial in order to plan the best therapy as in this like dismal cancer.

As shown in Table 6, although some patients had residual local disease only and some patients had only distant metastases, the vast majority of postmortem examinations revealed both local and systemic disseminated malignancy(Kelsen DP, 1991). So, the treatment of carcinoma of the esophagus with combination of radiation/surgery and chemotherapy was a logical approach, and began about 15 to 20 years ago.

Despite many reports suggesting encouraging survival rates for patients with esophageal cancer treated with preoperative chemotherapy and radiotherapy(Poplin E et al., 1987 ; Parker EF et al., 1989 ; Orringer MB et al., 1990), the debate continues as to whether combined modality therapy is better than either surgical therapy alone or cheomotherapy and radiotherapy. Proponents of surgical therapy alone have suggested that the major effect of preoperative chemotherapy plus radiotherapy is a longer hospitalization, causing both a greater financial burden and a delay in treatment.The role of surgery in the treatment of esophageal cancer and, in particular, as part of chemoradiation protocols has been questioned by advocates of nonsurgical treatment (Leichman L et al., 1987 ; Coia LR et al., 1991). Despite the encouraging results with combinations of chemotherapy plus radiation, local persistence and progression of disease still remains the problem. Coia et al, in their long term analysis of infusional 5-FU, mitomycin, and radiation, reported that 48%(14 of 29) of recurrences had local disease as a component of failure(Coia LR et al., 1991).

Leichman et al reported disease in the esophagus or mediastinum in 45% of all patients (nine of 20) or 64% of recurrences(nine of 14) after an aggressive program of cisplatin, 5-FU, mitomycin, and bleomycin

interdigitated with radiation(Leichman L et al., 1987).

Thus it can be hypothesized that the addition of a surgical esophagectomy after maximal tumor clearance by chemotherapy plus radiation therapy could contribute to the local control of disease, improve the quality of life, and possibly improve survival. A number of studies have been carried out to test this hypothesis(Leichman L et al., 1987 ; Poplin E et al., 1987 ; Forastier AA et al., 1990). Some of the earliest experiences with combined modality therapy in esophageal cancer came from Wayne State University, where treatment was based on the model of anal carcinoma, in which low doses of radiation (3000cGy) and concurrent 5-FU plus mitomycin C produced startling results(Leichman LP et al., 1985). The results from the first esophageal cancer study showed that 26% complete response could be obtained(Steiger Z et al., 1981). But results were not much different from those of effective surgical protocols or combination chemotherapy plus radiation therapy without surgery. Mostly this was due to high postoperative mortality.

In the SWOG/RTOG study cited above, operative mortality was 11% (Poplin E et al., 1987), and in the Leichman study, a full 30% of patients did not leave the hospital after their surgery(Leichman L et al., 1987). As surgical techniques improve, postoperative mortality will decrease, further enhancing the usefulness of the technique.

The comparision of survival in the operative and nonoperative groups is one of the interesting aspects of our study. Although the patients were not randomly assigned, there was no statistically significant difference between the groups with regard to age, weight loss,tumor size, or stage(Table 7). As the sample size was small and median survival was not reached, a larger sample size and long term follow up would be required to compare correctly.

Endoscopic sonography is useful for detecting esophageal tumors. Moreover, sonography can be used to determine the depth of invasion of a carcinoma and for the detection of metastases to lymph nodes.Endoscopic sonography was performed in 11 patients.

We could compare the results of endoscopic sonography and pathologic results in 6 patients who underwent surgery immediately after endoscopic sonography. Our results showed overall 50% accracy rate in the evauation of tumor depth,nodal involvement. The main pitfall of this study is the inability to insert the echoendoscope beyond the tumor and size criteria for malignant lymph node involvement is not helpful because of reactive lymph node hyperplasia after chemoradiotherapy.

Pathologic complete response(CR) rate is an important prognostic factor, because it has been documented that patients achieving CRs experienced prolonged survival. This was especially true for the University of Michigan experience (Forastiere AA et al., 1993), in which a 5-year survival rate of 60% (70-month median survival)for pathologic negative pa-

Table 7. Comparison of esophagectomy and nonoperative patients

	Esophagectomy	Nonoperative	P value
Age	69.9	59.1	NS
Wt. loss(>10%)	3/10	4/16	NS
Tumor length	6.4cm	4.8cm	NS
M/F	9 : 1	16 : 0	NS
Stage I	3	3	
II	7	11	NS
III	0	2	
Clinical Response			
Improvement	9	13	
Stable	1	1	NS
Progression	0	2	
Survival			
Alive, disease-free	7/10	14/16	
Alive with disease	0	0	
Dead of disease(or Tx toxicity)	3	2	NS
Dead of other disease	0	0	

NS : non significant

Table 8. Preoperative chemoradiotherapy

Reference	No. of Patients	Preperative Treatment	Pathologic CR Rate(%)	Median Survival(MO)
Steiger et al.	30	Mitomycin/5-FU/RT 3.0Gy	6/23(26)	12
Leichman et al.	21	Cisplatin/5-FU/RT 3.0Gy	5/19(26)	18
Poplin et al.	113	Cisplatin/5-FU/RT 3.0Gy	18/71(25)	12
Seydel et al.	41	Cisplatin/5-FU/RT 3.0Gy	8/27(29)	13
Forastiere et al.	43	Cisplatin/5-FU/vinblastine/RT 3.75-4.5Gy	10/41(24)	29
Kim et al.	10	Cisplatin/5-FU/vinblastine/RT 4.5Gy (1)		not reached
		Cisplatin/5-FU/RT 4.8Gy (9)	6/10(60)	

tients, and for the Southwest Oncology Group series, in which there was a 32-month median survival for such patients(Poplin E et al., 1987).

Our pathologic complete response rate(CR) of 50% is higher than those reported in other trials using concommitant cisplatin,5-FU, and lower total doses of radiation(Table 8). It might be ascribed to small sample size and method of surgery. Because transhital esophagectomy is a blind surgery,so incomplete lymph node dissection would be expected.

Pathologic CR rate is a relative term for several reasons. First, this represents the pathologist's careful examination of representative histologic sections only. Thus, if one were to keep recutting the paraffin blocks, it is likely that malignant cells would be identified in a proportion of specimens and lower the CR rate.

Another variable is the timing of the pathologic examinations in relation to completion of radiation. Evaluation at 12 weeks or longer would be optimal. Before that time, one cannot be certain that tumor cells identified in the specimen are viable, so examination of the surgical specimen before 12 weeks after radiation could result in a falsely low CR rate(Forastiere AA et al., 1993).

Significant survival advantage in pathlogic CR group was not shown in our series. This might be skewed by the relatively high early postoperative mortality and small sample size.

Undoubtedly, additional research into preoperative chemotherapy and radiation therapy is warranted regarding the value of routine esophagectomy after chemotherapy and radiotherapy.

Finally, if postoperative mortality could be compromised, preoperative chemoradiotherapy appears to be the most promising approach currently available to increase overall survival in esophageal cancer, because it induced high rate of complete pathologic response.

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