Recent Advances in Chemoradiotherapy for Esophageal Cancer Patients

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Conservative therapies such as chemotherapy, radiotherapy, laser therapy and hyperthermia therapy have provided esophageal cancer patients with limited effects and little hope. However, since the appearance of cisplatin (CDDP), the results of chemotherapy have gradually improved in combination with radiotherapy. Ohtsu reported that the survival outcome of patients receiving CDDP/5-FU plus irradiation was almost equal to that for operative results[1]. New anticancer drugs, such as taxane, have been reported to have a high response rate, even a complete response rate. However, there has been no obvious evidence showing that adjuvant chemoradiotherapy results in better survival. In this report, an outline of chemoradiotherapy for esophageal cancer patients and prospects for the future were given.

Chemoradiotherapy

Expectations for irradiation or chemotherapies used independently in the past have not been high. However, they have somewhat improved since an appearance of cisplatin (CDDP). As shown in Table 1, Al-Sarraf[2] and Wobbes[3] found that chemoradiotherapy resulted in a significantly better prognosis than therapy with radiation alone in a randomized controlled trial (RCT). This finding showed that an improvement in the prognosis could be expected with chemoradiotherapy as standard therapy. In addition, patients undergoing chemoradiotherapy with CDDP/5-FU were reported to have approximately the same survival rate in stage II/III in Japan, which caused quite a sensation[1]. Although this result was not confirmed by RCT, it changed the conventional way of thinking, that is, to operate on any case that could be resectable.

With the development of new drugs, the results of chemoradiotherapy have improved. Results with multi-drugs, including Taxol (TXL)/CDDP are shown in Table 2. The complete response (CR) rate was relatively high ranging from13 to 48%. At the Memorial Sloan-Kettering Cancer Center, CDDP 30mg/m2 weekly/TXL 60mg/m2 96-h i.v. plus radiotherapy was recommended[14]. On the basis of this report, RCT to compare CDDP/5-FU plus radiation vs. CDDP/TXL plus radiation is going in the Radiation Therapy Oncology Group (RTOG). Based on the results of this trial, CDDP/TXL plus radiation might become standard therapy.

In addition, Nemoto *et al* reported that Nedaplatin (NDP)/5-FU plus radiotherapy showed a response rate of 96% and a CR rate of 29%[15]. Iwase and Gotoh reported that the oral anticancer drug S-1/CDDP plus radiation had a response rate of 96.6% and a CR rate of 41.4%[16]. The use of oral anticancer drugs originated in and has become quite popular in Japan. This report revealed the power of oral anticancer drugs when combined with radiation.

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Table 1. Comparison of radiotherapy and chemoradiotherapy (Randomized Controlled Trial)

Reporter (year)	Chemotherapy	Radiation dose(Gy)	Sample size	MST* (month)	p-value
al-Sarraf M[2] (1997)	none	64	62	9.3	<0.001
	CDDP/5-Fu	50	61	14.1	
Wobbes T[3] (2001)	none	55-60 (split 40)	102	7.9	0.048
	CDDP	55-60 (split 40)	104	9.6	

*median survival time

Table 2. Results of chemoradiotherapy including TXL/CDDP

Reporter	Year	Sample number	Radiation dose(Gy)	TXL (mg/m2)	CDDP (mg/m2)	5-FU (mg/m2)	CR (%)
Wright CD[4]	1997	40	58.5	100	20	800	39
Weiner LM[5]	1997	21	60	50	25	200	13
Hainsworth JD[6]	1997	29	45	200	AUC6.0	225	48
Adelstein DJ[7]	2000	40	45	175	20		23
Ajani JA[8]	2001	37	45	200	20	300 -750	31
Safran H[9]	2001	41	39.6	60	25		29
Bains MS[10]	2002	36	50.4	30 -175	30 -75		26
Urba SG[11]	2003	69	45	60	75		19
Meluch AA[12]	2003	123	45	200	AUC6.0	225	38
Goldberg M[13]	2003	27	60	20 -60	25	200 -250	18
Brenner B[14]	2004	37	50.4	10 -80	30		24

TXL is not covered by insurance in our country, but taxotere (TXT) is. Therefore, we decided to perform a phase I/II study of TXT/S-1[17]. In this study, the patients were given S-1 (60mg/m2/day) orally from days 1 to 14, and TXT (20mg/m2 in level 1, 25mg/m2 in level 2, and 30 mg/m2 in level 3) intravenously on days 1 and 8. The patients received radiation in 2.0 Gy daily fractions from days 1 to 21, for a total of 30 Gy. They were given a seven-day rest after the first course, and then treated with the same regimen from days 28 to 49. The phase I study was completed for 10 cases. All patients completed the treatment schedule, with no treatment-related deaths and no grade 4 adverse events being observed. As for hematotoxicity, one case experienced grade 3 leukopenia and grade 2 neutropenia. A non-hematotoxic adverse event (grade 3

anorexia) was observed in one patient. The response rate evaluated by Response Evaluation Criteria In Solid Tumors (RECIST) was 66 % (CR in two cases, PR in four cases). We assumed that the recommended dosage of TXT and S-1 was 30mg/m2 and 60mg/m2, respectively, combined with a radiotherapy dose of 60Gy. This combination therapy may be superior to other treatments because of its lower rate of adverse events and higher response rates. We are continuing this study to Phase II in order to generate data on the response rate and adverse event rate in a greater number of patients with esophageal cancer.

Adjuvant therapy

With surgical treatment, only local control can be obtained. Therefore, further improvement in the prognosis of postoperative cancer patients requires the combined modality therapy. A report by Nakayama in 1960 regarding the preoperative irradiation for esophageal cancer patients brought the introduction of combined modality therapy[18]. The concept of preoperative irradiation is to minimize the residual tumor to contribute to improvement of the patient's prognosis. Then, in 1988, Iizuka *et al* reported the superiority postoperative irradiation over pre-and post-operative irradiation for survival in RCT (Japanese Clinical Oncology Group; 8201 study[19]. This finding changed the focus of the combined modality therapy all at once from pre-and postoperative irradiation to postoperative irradiation. However, there was criticism at that time, that the superiority of combined radiotherapy could not be proven.

Like surgery, irradiation is a local treatment, and there was no clear evidence in RCT that it improved the survival rate of postoperative patients, as shown in Table 3. In fact, patients receiving adjuvant irradiation therapy had a decreased incidence of recurrence in local regions, but an increased incidence of recurrence in distant organs[21),23]. Experimentally, we found that irradiation to inoculated tumor enhanced lung

Table 3. Outcome of randomized controlled trial for adjuvant radiotherapy

Reporter (year)	Sample size	Timing	Radiation dose (Gy)	p-value
Launois B[20] (1987)	124	before	40	n.s.
Gygnoux N[21] (1987)	208	before	33	n.s.
Teniere P[22] (1991)	221	after	45-55	n.s.
Fok M[23] (1991)	130	after	49-53	n.s.
Nygaard K[24] (1992)	186	before	35	P=0.009
Arnott SJ[25] (1992)	176	before	20	n.s.
Zieren[26] (1995)	68	after	30.6	n.s.

n.s.: not significant

Table 4. Outcome of randomized controlled trial for adjuvant chemotherapy

Reporter (year)	Sample size	Time	Drugs	p-value
Roth JA[28] (1988)	39	before & after	CDDP/VDS/ BLM	n.s.
Nygaard K[24] (1992)	186	before	CDDP/BLM	n.s.
Pouliquen X[29] (1996)	120	after	CDDP/5-Fu	n.s.
Ando N[30] (1997)	205	after	CDDP/VDS	n.s.
Kelsen DP[31] (1998)	440	before	CDDP/5-Fu	n.s.
Ando N[32] (2003)	242	after	CDDP/5-Fu	n.s

metastasis[27].

As for adjuvant chemotherapy, there had been no evidence of its usefulness, as shown in Table 4. Only one report from Ando *et al*[32] (JCOG 9204 study) revealed improvement of the disease-free survival rate with a p value of 0.036. However, there was no significant improvement in the overall survival rate.

When we have used chemotherapies together with irradiation, the survival has been better than with irradiation therapy only, as mentioned above. Therefore, chemoradiotherapy method may become the mainstream form of adjuvant therapy in the future. Even now, however, there have been few reports of RCT, although Boseset *et al*[33] reported that CDDP together with irradiation therapy as an adjuvant therapy extended disease free-survival significantly.

In western countries, pre-operative chemoradiotherapy method is used widely, but a metaanalysis revealed that while pre-operative chemoradiotherapy improved the survival of postoperative patients, the results of RCT did not show a significantly better survival rate[35]. In addition, sub-analysis showed that only an adenocarcinoma group and a concomitant administration group receiving chemotherapy with radiotherapy experienced significant improvement (Fig.1). However, a recommended kind of protocol was missing. In addition, an increase in postoperative complications has always been a problem with preoperative irradiation.

The authors have used various regimens. EFP treatment that combined Etoposide (ETP) /5-FU/CDDP with irradiation showed 50% of response rate, but an adverse event of grade 3/4 frequently occurred. In addition, we investigated the usefulness of the above therapy as an adjuvant therapy using the matched pair algorism technique, but the regimen did not contribute to any more improvement in the survival rate than surgery only[35]. Since then, the concept of biochemical modulation (BCM), the use of one medicine (modulator) to enhance the effect or reduce the adverse events of another medicine (effector) has become popular. The use of low dose FP (CDDP/5-FU) treatment has spread particularly in Japan. As for the use of low dose FP with irradiation therapy for esophageal cancer patients, there have been a few comparative adverse events, and the response rate was 57.1% in our results. Furthermore the percentage of CR cases

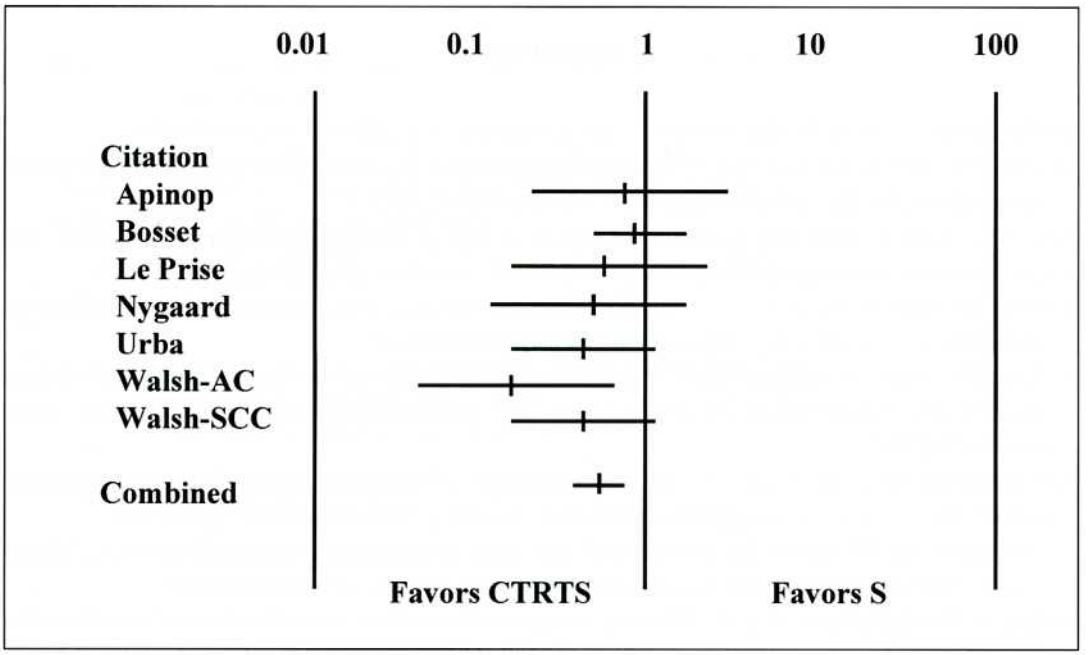

Fig. 1. Meta-analyses of pre-operative chemoradiotherapy[35]

Three years survival rate (An odds ratio;0.06, 95%Confidence interval;0.47-0.92, p=0.016)
AC: Adenocarcinoma, SCC: Squamous cell carcinoma
CTRTS:chemotherapy,radiotherapy,surgery, S: surgery

21.4% (not published). However, the therapy did not contribute to improvement of the survival rate when we used it as an adjuvant therapy.

In recent years, combination chemotherapy plus irradiation including one of the so-called new drugs has been used for the treatment of esophageal cancer, and improvement of the response rate and efficacy as a surgical adjuvant therapy are expected. Now the authors are carrying out a phase I/II study of TS-1/TXT plus irradiation, the results of which were mentioned above. In addition, as a general rule, we begin the postoperative adjuvant therapy three months after surgery. The aim of this protocol is to raise the success rate by starting under good general condition, and to improve the survival rate.

To date, standard regimen has not been decided on because no RCT have revealed significant improvement in survival. In the future, large-scale RCTs are needed to improve the survival rate of the postoperative esophageal cancer patients.

CONCLUSION

At present, chemotherapy for esophageal cancer patients is categorized where we cannot expect the prolongation of survival, but useful for improvement of a symptom at present. To overcome this situation, the development of new medicines, large-scale RCT to determine standard regimen and sensitivity tests to so-called order-maid treatment is required.

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