Preoperative Radiation for Carcinoma of the Thoracic Esophagus Involving Adjacent Organs

—A Comparative and Multivariate Analysis of Prognosis—

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Summary: Controversy remains over the comparative efficacy and subsequent prognosis for preoperative radiation for carcinoma of the esophagus involving the trachea, bronchus, and/or aorta. Results of a multi-variate analysis are reported using clinical data from 57 cases from 1981 to 1987. Based on both the survival-rate curves using the Kaplan-Meier method and the adjusted survival-rate curves using Cox's proportional hazards linear model, there was no significant difference in prognosis between patients who received preoperative radiation and those who did not. This analysis indicates that preoperative radiation at doses of 30Gy produces no clinical advantage and therefore is not the best treatment for carcinoma of the esophagus involving these adjacent organs.

Key words: thoracic esophageal carcinoma — T4 (a3) carcinoma — preoperative radiation — Cox's proportional hazards linear model — multi-variate analysis

Introduction

The prognosis for carcinoma of the thoracic esophagus remains poor despite advances in early detection and surgical management. In particular, the prognosis is the poorest for carcinoma involving one or more adjacent organs such as the trachea, bronchus and aorta. This is largely due to the significant mortality associated with tumor resection. To improve the resectability and curability for advanced carcinomas of the thoracic esophagus, preoperative radiation was introduced by Clifton et al. (1960). In

particular, since Nakayama and Kinoshita (1974), and Akakura et al. (1970) demonstrated an improved resectability and survival after preoperative radiation, this treatment has been widely accepted in Japan and other countries. However, recent reports of results from randomized controlled studies revealed that preoperative radiation did not always enhance the resectability and the survival (EORTC, 1985; Iizuka et al. 1988). Accordingly, when we now perform palliative resection or, on occasion, combined resection (Kawahara et al. 1985; Fujita et al. 1987), preoperative radiation is not used, even

for carcinoma of the thoracic esophagus involving one or more adjacent organs such as the trachea, bronchus and aorta. In contrast, many authors have described the effectiveness of preoperative radiation in conjunction with palliative resection of a carcinoma of the thoracic esophagus involving the adjacent organs (Isono et al. 1980; Iizuka, 1982). In summary, there is not yet a consensus for recommending preoperative radiation for such carcinomas. The aim of this statistical investigation was to evaluate the efficacy of preoperative radiation for carcinomas of the thoracic esophagus involving one or more adjacent organs.

Patients and Methods

During the study period from 1981 to 1987, 57 patients with histologically-confirmed squamous cell carcinoma were determined to have involvement of the trachea, bronchus and/or aorta at surgery and the resected specimens were histologically examined. The histological criteria for palliative resection were a tumor macroscopically involving an adjacent organ at surgery and microscopically exposed on the surgical margin of the resected specimen. The criteria for a combined resection was microscopic invasion into an adjacent organ.

The treatments for carcinomas of the esophagus involving adjacent organs that were examined in this study are summarized in Table 1. All patients underwent surgery. In the 27 patients who had preoperative radiation, 15 patients had only preoperative radiation, 10 patients had pre- and postoperative radiation, and 2 patients received chemotherapy in addition to preoperative radiation. A further 30 patients did not undergo preoperative radiation. Of these, 14 had surgery alone; 14 received postoperative radiation; and 2 received post-

operative radiation and chemotherapy. Preoperative radiation was not performed in the seven cases with combined resections of the trachea and/or aorta with esophagectomy. Radiation was given in dosages of 30Gy preoperatively or 50Gy postoperatively, and chemotherapy was given at dosages of more than 200 mg CDDP (Cisplatin) or more than 100 mg BLM (Bleomycin).

The patients' characteristics are summarized in Table 2. When a tumor was situated in the upper third of the thoracic esophagus between the thoracic inlet and the carina, even if only partially so; it was classified as being in the upper thoracic esophagus, because such a tumor can involve both the tracheobronchial tree and the aorta. The types on X-ray esophagograms were classified, based on the Guidelines for the Clinical and Pathological Studies on Carcinoma of the Esophagus (1976). Lymph node metastases were also classified, based on the Guidelines; "n₀" means no metastasis was found in microscopic sections of the dissected lymph nodes; "n₁₋₂" means metastasis was found in the thoracic lymph nodes (the paraesophageal or paratracheal lymph nodes); and "n₃₋₄" means me-

TABLE 1.
Treatment modalities for carcinoma of the esophagus involving adjacent organs in 57 cases of esophagectomy

Preoperative radiation	27 cases
Preoperative radiation	15
Pre- and postoperative radiation	10
Preoperative radiation and chemotherapy	2
Non-preoperative radiation	30 cases
Surgery alone	14 (5*)
Postoperative radiation	14 (2*)
Postoperative radiation and chemotherapy	2

* Combined resection of the adjacent organs

tastasis was found in the distant lymph nodes (the cervical or abdominal lymph nodes). The quantity of dissected lymph nodes reflects the intensity of the required lymph node dissection. With regard to operative risk and the systemic condition of each patient, the criteria indicating a high risk for an operation included; respiratory hypofunction with $\%FEV_{1.0} < 50\%$ or with $FVC < 1500 \text{ ml/m}^2$, cardiac infarction within the previous 6 months, severe arrhythmia, anginal attacks, renal hypofunction with creatinine clearance $< 50 \text{ ml/min}$, active hepatitis, liver cirrhosis, diabetes mellitus requiring insulin and severe emaciation (Yamana et al. 1986).

The backgrounds of these patients were examined for any differences between the preoperative radiation group and the non-preoperative radiation group using the chi-squared test and Fisher's exact method when a cell contained less than five cases. The survival curves were drawn using the Kaplan-Meier's method. Next, 13 factors were evaluated for their independent contribution to the prognosis using Cox's proportional hazards linear model. A survival curve was then estimated for each group after a normalizing adjustment of the other 12 factors. All the statistical analyses were performed using the SAS (Statistical Analysis System, 1985) program on a HITAC M240H main-frame computer at the National Cancer Center, Tokyo (Harrell, 1983).

Results

The 57 patients who underwent combined or palliative resections for carcinomas of the thoracic esophagus involving the trachea, bronchus and/or aorta were examined to investigate the role of background factors which might influence the survival. There were 27 patients in the preoperative radiation group and

30 patients in the non-preoperative radiation group. As shown in Table 2, there were no differences in sex, age distribution, cancer location, length on the esophagogram, lymph node metastasis, distant organ metastasis, chemotherapy or operative risk between the preoperative radiation group and the non-preoperative radiation group. However, in the preoperative radiation group, there were significantly more cases that involved a tumor of the spiral type ($p=0.011$), significantly more cases with aortic involvement ($p=0.014$), significantly more cases having palliative resection ($p=0.008$), and significantly more cases having less than 20 lymph nodes dissected ($p=0.001$).

The survival curves for the preoperative and the non-preoperative radiation groups from the Kaplan-Meier analysis are shown in Fig.1. There was no significant difference between the two curves.

Next, the 13 background factors of the 57 patients were examined by Cox's proportional hazards linear model. No significant differences in the survival rates were shown for 12 factors including sex, age distribution, location of the tumor, tumor length on the esophagogram, tumor type on the X-ray esophagogram, involved organs, lymph node metastasis, distant organ metastasis, modality of resection (combined resection vs. palliative resection), number of the dissected lymph nodes, chemotherapy, or preoperative radiation (preoperative radiation vs. non-preoperative radiation) (Table 3). However, one factor had a significant relationship to survival rate. Patients at low risk for surgery had a higher survival rate than did those at high risk for surgery ($p=0.004$).

To show the independent effect of preoperative radiation, modified survival curves were calculated and plotted (Fig. 2) under the condition that all other var-

iables were set to their mean values. As a result, no overall significant difference was demonstrated between the preoperative radiation group and the non-pre-

operative radiation group, although the non-preoperative radiation group had a slightly higher survival rate.

TABLE 2.
Distribution of 12 factors in cases with preoperative and non-preoperative radiation

	Preoperative radiation	Non-preoperative radiation	p-value
Sex			
male	25	28	0.653
female	2	2	
Age			
<70	19	22	0.887
≥70	8	8	
Location			
upper	17	13	0.923
middle and lower	10	17	
Length on X-ray			
<8cm	9	13	0.887
≥8cm	18	17	
X-ray type			
spiral	19	11	0.011
others	8	19	
Involved organ			
tracheobronchus	5	15	0.014
aorta (+tracheobronchus)	22	15	
Lymph node metastasis (n)			
n0, n1-2	16	14	0.637
n3-4	11	16	
Distant organ metastasis (m)			
(-)	16	28	0.706
(+)	1	2	
Resection			
combined	0	7	0.008
palliative	27	23	
Dissected lymph nodes			
<20	20	9	0.001
≥20	7	21	
Chemotherapy			
(+)	2	2	0.653
(-)	25	28	
Operative risk			
low	25	26	0.388
high	2	4	

TABLE 3.

Analysis of data using Cox's proportional hazards linear model for 57 cases

Variable	Beta	Standard Error	Chi-Square	P-value	Relative Risk
Sex	0.47	0.61	0.59	0.442	1.60
Age	-0.21	0.35	0.34	0.560	0.81
Location	0.43	0.36	1.45	0.228	1.54
Length	0.36	0.36	1.01	0.316	1.44
X-ray type	0.40	0.36	1.25	0.264	1.50
Involved organ	0.52	0.36	2.11	0.147	1.68
N	0.14	0.38	0.13	0.723	1.15
M	1.39	0.74	3.54	0.060	4.02
Resection	-0.32	0.46	0.49	0.483	0.72
Dissected LN	-0.10	0.36	0.07	0.785	0.91
Chemotherapy	0.35	0.59	0.34	0.558	1.42
Risk	1.71	0.59	8.49	0.004	5.55
Preop. radiation	-0.63	0.43	2.18	0.140	0.53

Fig. 1. Survival curves for preoperative and non-preoperative radiation groups (Kaplan-Meier method).

Fig. 2. Adjusted survival curves for preoperative and non-preoperative radiation groups (Cox's proportional hazards linear model).

Discussion

This investigation was undertaken to evaluate the effectiveness of preoperative radiation for carcinoma of the thoracic esophagus involving one or more adjacent organs such as the trachea, bronchus, and/or aorta. There was no significant difference between the survival curves for the preoperative radiation and non-preoperative radiation groups when analyzed statistically by the Kaplan-Meier's method.

However, patients with very advanced tumors invading the aorta were more

frequently in the preoperative radiation group. In contrast, patients who had not received preoperative radiation underwent more radical operations, such as combined resections of adjacent organs or wide lymph node dissections, than did the patients who had received preoperative radiation. Therefore, testing of the unique contribution to survival of preoperative radiation was included, using a multi-variate analysis with Cox's proportional hazards linear model.

As seen in Table 3, only one operative risk factor deleteriously affected survival; while the other 12 factors, including pre-

operative radiation, were unrelated to survival. In other words, preoperative radiation did not enhance the survival of patients with carcinomas involving the trachea, bronchus and/or aorta, but actually seemed to decrease their survival. This was demonstrated by the adjusted survival curves for the preoperative radiation and non-preoperative radiation groups (Fig. 2).

During the past 20 years, preoperative radiation has been commonly used, as it is considered to enhance both the resectability and the survival. Since randomized control studies revealed that the effectiveness of preoperative radiation is questionable (EORTC, 1985; Iizuka et al. 1988), preoperative radiation is only rarely employed usually for carcinomas of the esophagus involving one or more adjacent organs such as the trachea, bronchus and aorta, that are difficult to resect. The present analysis has shown that preoperative radiation is not always effective even for carcinomas of the esophagus involving the adjacent organs. Randomized trials are needed to further investigate this problem.

Several authors have reported that in 25 to 46% of cases with carcinoma of the esophagus involving adjacent organs who have undergone preoperative radiation, the tumors disappeared from the adventitia of the resected esophagus (Isono et al. 1980; Iizuka, 1982; Yagasaki and Kato, 1985). Such cases were excluded from the present study on histological criteria. The actual survival rates for those that received preoperative radiation may have to be re-evaluated more fully, in consideration of the preoperative disappearance of the tumors from the adjacent organs or the adventitia of the esophagus. However, local recurrence is possible in one-third of cases that have received preoperative radiation, even if the tumors disappeared from the adventitia of the esophagus (Fujita, 1984). Yagasaki et al.

(1985) have also reported that even if the tumors disappeared from the adventitia or the adjacent organs after preoperative radiation, the survival rate of the patients was not improved. Accordingly local therapies, such as radiation, for these cases must be viewed as ineffective, mainly due to the involvement of the adjacent organs often with widespread lymph node metastasis and/or distant organ metastasis. The present statistical analysis supports this view.

With regard to a recommended treatment for carcinoma of the esophagus involving one or more adjacent organs such as the trachea, bronchus and aorta, the following may be proposed. When the combined resection of the trachea or aorta is performed during the esophagectomy, preoperative radiation should not be used, because the margin of the tumor becomes unclear and postoperative wound healing is suppressed by the radiation. Moreover, even if combined resection of these organs cannot be performed and surgery results in palliative resection of the tumor, radiation is unnecessary preoperatively, although postoperative combined treatment should be administered.

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