Multi-institutional Survey of Radiotherapy for Octogenarian Squamous Cell Carcinoma of the Thoracic Esophagus: Comparison with the results of surgery reported in Japan

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80歳以上の胸部食道扁年上皮癌に対する放射線治療の多施設調査
－国内文献における外科治療成績との比較－

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【目的】全国8施設を対象とした，80歳以上の胸部食道扁平上皮癌に対する術前，術後照射を除く放射線治療成績の遡及的調査．これと切除成績との比較を試みる．
【対象と方法】1985年から1990年に治療が開始された全例を調査対象とし，64例が集積された．内訳は男性51例，女性13例，年齢の中央値82歳(80～93歳)，臨床病期I期5例，II期30例，III期22例，IV期7例であった．62例で通常分割照射が用いられ，57例(89%)で腫瘍に対して60 Gy以上を，外照射単独あるいは腔内照射との併用で投与されていた．59例(92%)では化学療法は併用されていなかった．これらの遠隔成績を，国立がんセンター中央病院で1985～1995年の間に行われた80歳以上の胸部食道扁平上皮癌に対する根治切除例20例，および国内4施設からの80歳以上の食道癌切除報告例34例の，計54例(I期7例，II期20例，III期19例，IV期8例)のものと比較した．
【結果】放射線治療例での5年粗生存率は4.8%，5年原病生存率は17.2%で，切除例ではそれぞれ11.1%，29.2%であり，ともに有意差は見られなかった(P>.400)．I，II期においては，放射線治療例では32/35例(91.4%)で腫瘍に対して60 Gy以上が投与され，このうち治療前のKarnofsky Performance Statusが80%以上の14例の5年原病生存率は49.0%であった．一方I，II期の切除例での5年原病生存率は47.6%であった(P=.618)．III，IV期ではいずれの治療法でも生存期間の中央値は1年未満であった．放射線治療例では，1例で食道気管瘻による晩期障害死が見られた．他の5例で晩期の食道狭窄が生じたが，いずれも保存的治療で軽快した．切除例では治療関連死が8例に見られ，重篤な術後肺炎等の頻度が高かった．
【結論】80歳以上の高齢者の胸部食道扁平上皮癌に対する放射線治療は，切除に比べて安全性に優れた治療であると考えられた．また今回の比較では，放射線治療と切除との間で生命予後の明らかな差は見られず，80歳以上では切除適応となる食道癌においても放射線治療の効果を科学的に検証することは意義があると考えられた．

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Introduction

Radical esophagectomy (RE) with thorough dissection of lymph nodes (two-, or three-field dissection) has been considered the most rational curative approach for squamous cell carcinoma of the thoracic esophagus (SqTE)[1)-4)]. Because the morbidity of this surgery can be considerable in the elderly, less invasive surgery, such as transhiatal esophagectomy or esophagectomy with a left thoracoabdominal approach, is frequently employed as an alternative in the aged[5)-11)]. However, this surgery also results in deterioration of the swallowing function[12)].

Since RT is free from surgical stress and offers a good possibility of cure in this disease, especially in patients with superficial tumors[13)], this treatment should be carefully considered for the frail elderly. Because esophageal cancer occurs mainly in the elderly, a considerable proportion of patients with this disease will be in their 80s in the near future, as the proportion of octogenarians increases. Optimization considering the risks and benefits of treating SqTE in this generation is an impending medical problem; however, there has not been a sufficient comparison of RT and RE for esophageal cancer in octogenarians. We conducted a retrospective multi-institutional survey of RT for octogenarian esophageal cancer aiming to evaluate the results in comparison with those of RE reported in the Japanese literature.

Materials and Methods

RT group

We previously carried out a review of all patients who underwent definitive RT for EC between January 1985 and December 1990 at 8 institutions in Japan (n = 362)[14)]. Sixty-four patients corresponding to the following selection criteria were analyzed: 1) age ≥ 80 years, 2) biopsy-proven SqTE, 3) had not undergone combined surgery and RT, and 4) had no history of previously treated EC. We addressed the details of the RT

Table 1　Characteristics of patients (RT)

	n	(%)	Comments
Median age	82		Range: 80-93
Gender (m/f)	51/13		
Clinical stage			Longitudinal diameter of the tumor:
I	5	(7.8%)	Median 3.0 cm (range: 3.0-3.5)
II	30	(46.9%)	5.0 cm (4.5-9.0)
III	22	(34.4%)	6.5 cm (4.0-12.0)
IV	7	(10.9%)	6.3 cm (5.5-7.5)
Location			
Iu	8	(12.5%)	
Im	47	(73.4%)	
Ei, Ea	9	(14.1%)	
Dose administered to the tumor (Sum of dose on each reference point in cases of combination with intracavitary irradiation)			
< 60 Gy	7	(10.9%)	
> = 60 Gy	57	(89.1%)	Final dose administered to the tumor
Initial treatment volume			60.0-74.6 Gy (Median 66.4)
Whole mediastinal and pericardiac (dose)	11 (34.2-50.4Gy)	(17.2%)	39.6-80.0 Gy (70.0)
Localized	53	(82.8%)	
Combination of Chemotherapy			
Yes or unknown	5	(7.8%)	
No	59	(92.2%)	
Karnofsky performance status at the start of RT			
< = 70	40	(62.5%)	
> = 80	24	(37.5%)	
Total	64	(100%)	

planning and patient outcomes, for the estimation of cause-specific survival, through additional questionnaires. Sixty-four replies were obtained (Table 1).

RE group

Of 896 surgical cases of EC at the National Cancer Center Hospital (NCCH) during the period from January 1985 to December 1995, there were 23 cases of RE for SqTE in patients 80 years of age or older. Three cases were excluded from the analyses because of preoperative RT (2 cases) and concomitant pT3N1 hypopharyngeal cancer (1 case). The remaining 20 cases were analyzed, including 2 with extra-esophageal early-stage malignancies (pT1N0 well-differentiated adenocarcinoma of the lung and solitary hepatocellular carcinoma less than 1 cm in diameter) that were completely resected simultaneously with the SqTE.

RE was performed with sampling dissection of enlarged lymph nodes only before 1987 (sampling ND, n = 8), while after 1987 a thorough two- or three-field lymph node dissection (thorough ND, n = 12) was performed.

We also reviewed the Japanese literature concerning RE for octogenarians. A total of 34 cases have been reported from 4 institutions[15)-18)] (Table 3). Surgical procedures performed at these institutions were as described.

Staging criteria

The RT group was clinically staged according to the staging criteria of the International Union Against Cancer (1987). Pathologic stage was used for the surgical patients because of inadequate clinical staging information in the literature.

Statistics

Overall and cause-specific survival were compared between the RT and RE groups. Stage I and II patients in the RT group were classified according to their Karnofsky Performance Status (KPS)[19)] at the start of the treatment (80% and above vs. 70% or below) because a significant influence of KPS on survival was observed in this generation in the previous survey[14)]. The different surgical procedures were also taken into account in the comparison with RT.

In the RE group, medical records were reviewed as to the cases in NCCH and, for the other institutions, deaths due to causes other than EC were all ascribed to the other diseases. Treatment-related death was regarded as cause-specific in both the RT and RE groups.

Survival rates were calculated using the Kaplan-Meier method, and differences in survival rates were estimated by the log rank test.

Results

Overall survival

In the RT group, 2 patients were still alive without disease

Table 2 Characteristics of patients (radical esophagectomies in NCCH)

	Thorough ND*		Sampling ND*	
	n	(%)	n	(%)
Median age	81 (Range: 80-86)		83 (80-87)	
Gender (m/f)	8/4		7/1	
Pathological stage				
I	3	(25.0%)	0	(0.0%)
II	6**	(50.0%)	5	(62.5%)
III	3	(25.0%)	2	(25.0%)
IV	0	(0.0%)	1	(12.5%)
Longitudinal diameter of the tumor:				
Median	5.0cm		7.5cm	
(Range)	(1.5-12.0)		(5.0-12.0)	
Location				
Iu	0	(0.0%)	1	(12.5%)
Im	8	(66.7%)	4	(50.0%)
Ei, Ea	4	(33.3%)	3	(37.5%)
Approach				
Right thoracotomy	12	(100.0%)	6	(75.0%)
Left thoracotomy	0	(0.0%)	2	(25.0%)
Combination of chemotherapy				
Yes	1	(8.3%)	0	(0.0%)
No	11	(91.7%)	8	(100.0%)
Total	12	(100.0%)	8	(100.0%)

*ND: Lymph node dissection, **including 2 cases of multiple primary cancer.

at 84.0 and 80.6 months at the time of this survey, and a single patient was lost to follow-up 1.2 months after RT. All but 2 cases (1.5 Gy bid.) had been irradiated with once-daily fractionation (1.6-2.0 Gy/fraction), and 57 of the 64 patients (89.1 %) were administered a total dose of at least 60 Gy (Table 1). Eleven of 64 patients (17.2%) were administered 34.2 to 50.4 Gy to the entire mediastinal and pericardiac area. In these 11 cases, a median total dose of 66.4 Gy (range 60.0-74.6 Gy) was administered to the tumor with a cone-down field, and no serious adverse effects were observed. Median survival time was 11.5 months, and 1-, 3-, and 5-year survival rates were 49.2%, 12.7%, and 4.8%, respectively.

Median survival time for the RE group was 10.0 months, and 1-, 3-, and 5-year survival rates were 48.0%, 31.3%, and 11.1%, respectively. There was no statistically significant difference in overall survival between the RT and RE groups (Fig.1, P = .462).

Table 3 Characteristics of patients (reviewed cases)

	n	(%)
Median age	82 (Range: 80-92)	
Gender (m/f)	27/7	
Pathological stage		
I	4	(11.8%)
II	9	(26.5%)
III	14	(41.2%)
IV	7	(20.6%)
Location		
Iu	1	(2.9%)
Im	21	(61.8%)
Ei, Ea	4	(11.8%)
NOS*	8	(23.5%)
Approach		
Transthoracic	17	(50.0%)
Transhiatal	9	(26.5%)
NOS*	8	(23.5%)
Total	34	(100.0%)

NOS*: Not otherwise specified.

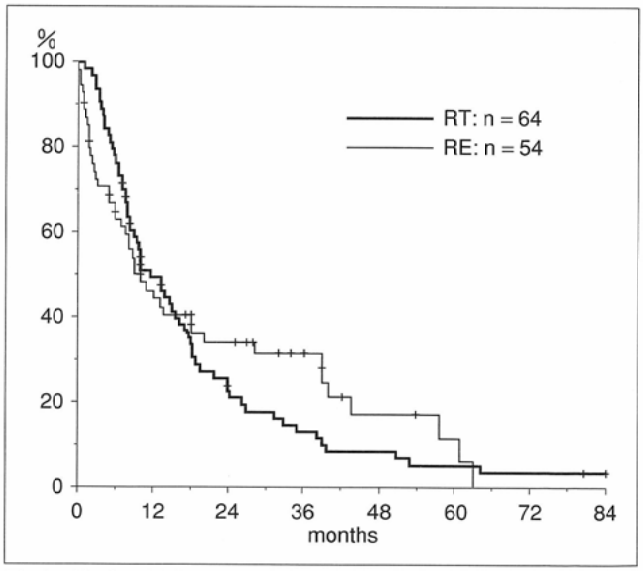

Fig.1 Kaplan-Meier estimation of cumulative overall survival. Thick and thin lines represent definitive radiotherapy (RT: n = 64) and radical esophagectomy (RE: n = 54), respectively. The difference was not statistically significant (P = .462).

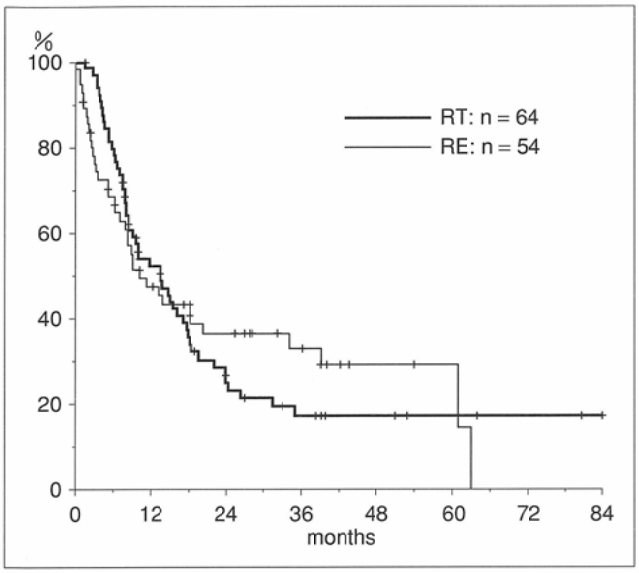

Fig.2 Kaplan-Meier estimation of cumulative cause-specific survival. Thick and thin lines represent definitive radiotherapy (RT: n = 64) and radical esophagectomy (RE: n = 54), respectively. The difference was not statistically significant (P = .720).

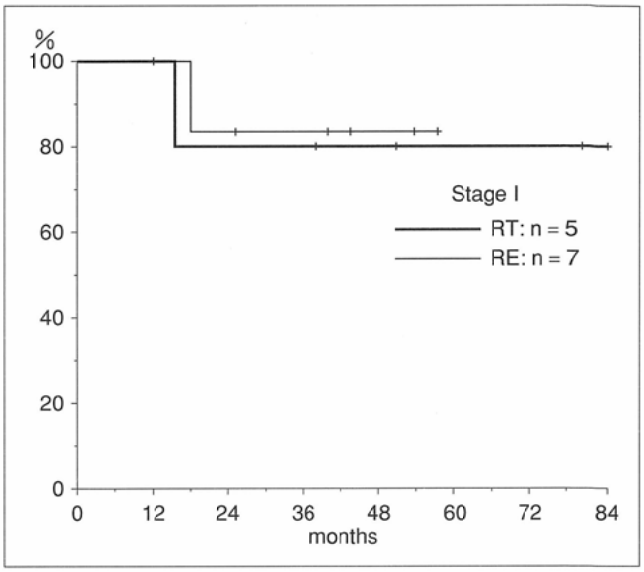

Fig.3 Cause-specific survival in stage I cases (radiotherapy (RT): n = 5, radical esophagectomy (RE): n = 7). The difference was not statistically significant (P=.784).

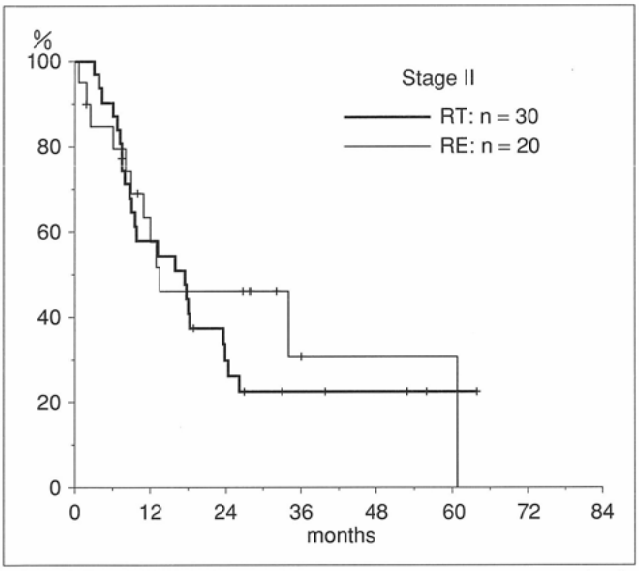

Fig.4 Cause-specific survival in stage II cases (radiotherapy (RT): n = 30, radical esophagectomy (RE): n = 20). The difference was not statistically significant (P = .933).

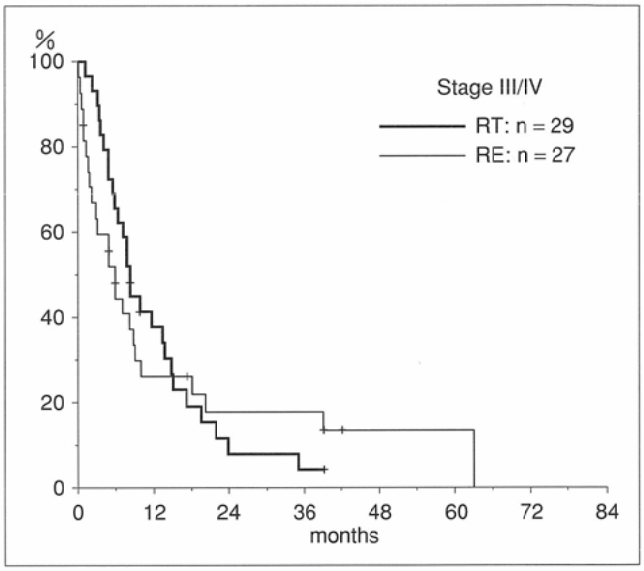

Fig.5 Cause-specific survival for stage III/IV cases in the radiotherapy (RT) group (n = 29) and in the radical esophagectomy (RE) group (n = 27). The difference was not statistically significant (P = .951).

Cause-specific survival

In the RT group, 16 patients died of causes other than EC. Eleven of these patients had no evidence of residual or recurrent EC based on imaging or autopsy findings at the time of death. One-, 3-, and 5-year survival rates were 52.2%, 17.2%, and 17.2% for RT, and 51.1%, 32.9%, and 29.2%, respectively, for RE (Fig. 2, P = .720). Cause-specific survival within a stage also was not different between the RT and RE groups (Figs.3, 4, and 5, p >.50).

Relationship between cause-specific survival and KPS in stages I and II

Among 35 stage I and II patients in the RT group, a cumulative dose of ≥ 60 Gy was administered to the tumor in 32 (91.4%), using conventional fractionation (1.6-2.0 Gy/fraction, 5 fractions per week) with or without intracavitary irradiation (Table 4). Two patients of KPS ≤ 60% were administered 51.4 Gy as planned, and one patient 89 years of age (KPS = 70%) was administered 40.0 Gy because of his refusal of further treatment. Chemotherapy was used for 2 patients, and others were treated with RT alone.

One-, 3-, and 5-year survival rates for patients receiving a total dose of 60 Gy/6 weeks or more were 65.3%, 31.9%, and 31.9%, respectively, and 78.6%, 49.0%, and 49.0%, respectively, for 14 patients with KPS ≥ 80%. Survival for patients

Table 4 Background of patients' performance status (Stage I and II)

	RT (administered ≥ 60 Gy)			RE
	KPS ≥ 80	KPS ≤ 70	Total (RT)	Total
I	4 (28.6%)	1 (5.6%)	5 (15.6%)	7 (25.9%)
II	10 (71.4%)	17 (94.4%)	27 (84.4%)	20 (74.1%)
Total	14 (100.0%)	18 (100.0%)	32 (100.0%)	27 (100.0%)

KPS: Karnofsky performance status.

whose KPS was 80 or above treated with RT was almost identical with that of RE (Fig.6).

Relationship between cause-specific survival and the extent of node dissection

We selected from stage I and II nine patients that underwent a thorough ND in NCCH. In comparison with patients in the RT group who received a cumulative dose of ≥ 60Gy, RE with thorough ND appeared to offer a better outcome (P = .06) than RT, but no difference was observed between the remaining 18 cases of RE and the RT group (Fig.7).

Complications

In the RT group, an 82-year-old woman with stage III disease died of tracheoesophageal fistula 11.5 months after treatment. This was considered a treatment-related death because there had been complete tumor resolution. Five patients suffered from benign esophageal stricture or ulcers that were successfully treated with conservative therapy.

Of 12 patients at NCCH that underwent esophagectomy and a thorough ND, one patient suffered from mechanical ileus that was surgically treated. There were also three patients with anastomotic leak, one with pneumonia, and one with postoperative delirium that were conservatively treated. No treatment-related deaths were observed. Two of the 8 patients that underwent sampling ND at NCCH suffered postoperative pneumonia, and one patient died 1.9 months after RE.

There were 8 operative deaths among the 34 reviewed cases. Other complications among the reviewed cases included anastomotic leak, electrocardiogram abnormalities, pneumonia, delirium, and postoperative liver and renal dysfunction.

Discussion

Transthoracic esophagectomy with thorough two- or three-field lymph node dissection is thought to be the most appropriate therapy for this disease. Nevertheless, this surgery in the frail elderly frequently leads to cardiopulmonary complications or anastomotic leakage. Consequently, some surgeons have proposed that less aggressive surgery with a transhiatal or left thoracoabdominal approach may be preferable for the frail elderly[5),11),20)]. Adam et al. reported a 10.7% mortality rate for elective esophagectomy with left thoracolaparotomy among octogenarians, and 12 of 31 (38.7%) patients suffered from moderate to severe post-operative complications such as anastomotic dehiscence, aspiration pneumonia, atrial fibrillation, and/or confusion[5)]. The operative mortality for esophagectomy

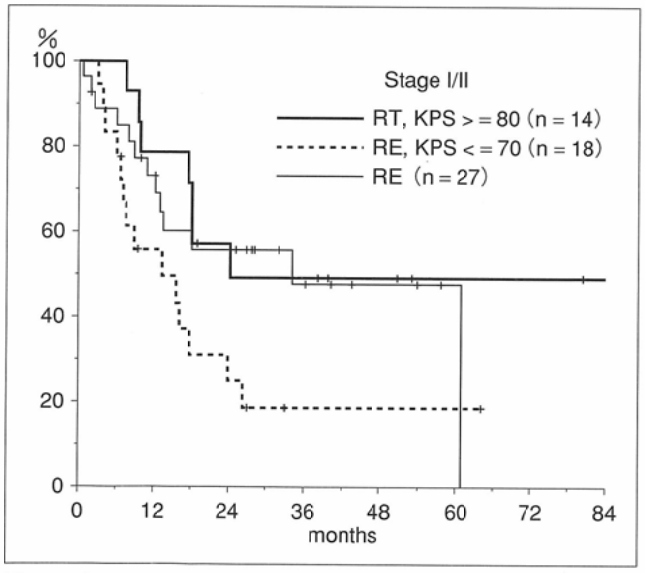

Fig.6 Cause-specific survival in stage I/II cases in the study groups. In the RT group receiving ≥ 60 Gy, patients with a ≥ 80% Karnofsky Performance Status (KPS) prior to RT had significantly better survival than those with a ≤ 70% KPS (P = .041) and almost identical survival with those in the RE group (P = .618).

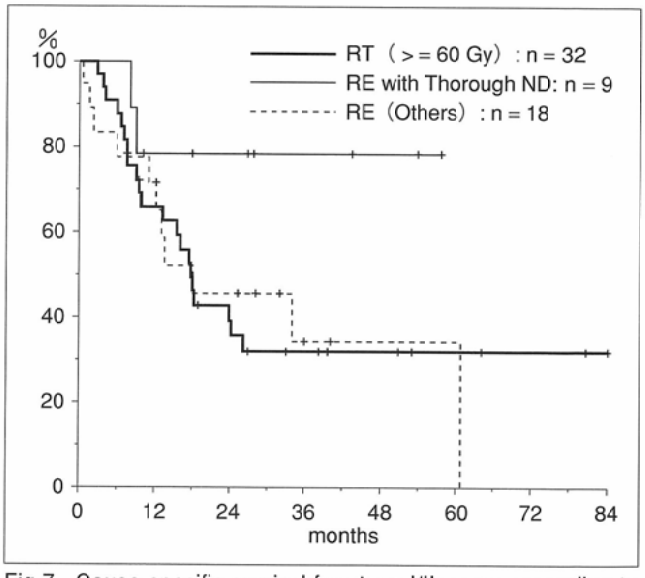

Fig.7 Cause-specific survival for stage I/II cases, according to treatment procedures. Patients who underwent a thorough lymph node dissection (ND) (n = 9, including 3 stage I cases) had a somewhat better outcome (P = .060) than those treated with ≥ 60 Gy of RT (n = 32, including 5 stage I cases). The curves for the remaining 18 RE patients (including 4 stage I) and RT patients were essentially superimposable (P = .962).

in the septagenarian has been reported to range from 7.8% to 32%[6),11),20)-23)], and, in addition, alterations in the integrity of the digestive tract may be followed by serious nutritional problems[24),25)]. In the RE group, 8 of 54 patients (14.8%) died of treatment-related death, and post-operative pneumonia, arrhythmia or delirium were not uncommon. The overall operative mortality of 14.8% in octogenarians in this review compares favorably with these figures considering the difference in patients' ages.

Radiotherapy empirically treats the gross tumor with a 3 to 5 cm margin to deliver a curative dose without significant morbidity. However, lymph nodes in the upper mediastinal and pericardiac area are often outside the treatment volume. The target of such radiotherapy is similar to the less aggressive esophagectomy. The safety of RT for aged patients has been verified in many anatomical sites, including the thorax[14),26)-29)]. Zachariah et al.[26)] reported that only mild to moderate mucositis was noted in patients aged 80 years or older treated for intrathoracic malignancy, and concluded that radiotherapy was highly effective and well tolerated by the oldest old. Similar to our previous report[14)], Pignon et al. reported that there were no age-related differences in the incidence of acute and late adverse reactions after radical radiotherapy for esophageal cancer[29)]. In the RT group, one of the 64 (1.6%) patients died of treatment-related death, and 5 (7.8%) patients suffered from benign esophageal stricture. Severe cardiopulmonary complication was not observed. These results suggest that RT was equally safe for patients in their 80s suffering from SqTE. Furthermore, about 17 percent of patients were administered 34.2 to 50.4 Gy to the entire mediastinal and pericardiac area, and no serious adverse effects were observed in this series. This demonstrates that RT may have a tumoricidal effect on microscopic metastases over a wider area than less aggressive esophagectomy.

In contrast, there was no obvious survival advantage for RE as compared with RT for octogenarians in this study. Adam[5)] reported an absolute 5-year survival rate of 17% in their series of 31 patients, including 23 patients with adenocarcinoma mainly located in the lower third of the esophagus and cardia[30)]. Our survey demonstrated an actuarial 5-year survival rate of 5.4% in the RT group. However, a significant proportion of the RT group might be poor surgical candidates, and therefore the 5-year cause-specific survival rate of 17.2% might be a more appropriate value to use in comparing outcome with RE. This concept is supported by the fact that RT for patients with stage I and II disease and with favorable KPS (≥ 80%) resulted in equal survival compared with RE. Okawa et al. have reported a promising result of radiotherapy for superficial esophageal carcinoma[13)]. The benefits of radiotherapy, freedom from surgical stress, and alterations in gastrointestinal integrity should be carefully considered in the octogenarian for whom there are significant risks associated with RE.

Al-Sarraf[31)] and Heskovic[32)] et al. reported better survival with combined chemoradiotherapy than with RT alone. However, the safety of such combined-modality therapy was not elucidated for the frail elderly. Although Conti[33)] and Kimmick[34)] et al. reported that standard chemotherapy should be considered for the elderly with sufficient physiological function, 59 (92.2%) patients in our review had not undergone additional chemotherapy. Furthermore, RE with thorough dissection of lymph nodes for selected patients with stage I and II disease resulted in the best long-term survival in this series. Age-related infirmity cannot be assessed by chronological age alone[35)], and appropriately selected candidates may enjoy extended survival, similar to that of younger patients, with intensive treatment. Further improvement in overall rates of cure and post-treatment quality of life will require developing adequate selection of treatment, including adjuvant regimens or intensive surgery that specifically addresses the relationship between the hardiness of the elderly and the safety of treatment.

On the other hand, since both RT and RE resulted in less than 1 year of median survival for patients with advanced disease, treatment for advanced SqTE should be weighed against short-term quality of life. RT may play an important role because of its favorable response rate[14)] without surgical stress.

The stage of disease in the RT and RE groups was not in agreement because of the inadequacy of clinical staging information for the surgical cases. In addition, there are other problems including publication bias, selection bias, and the limitations of a retrospective survey and literature review with a limited number of cases. Furthermore, local-regional control and nutritional status were not surveyed in consideration of the heterogeneity of follow-up data. These limitations may obscure the actual risks and benefits of the two treatments. Therefore, we can only conclude through this study that the rationale for the recommendation of radical esophagectomy for octogenarian SqTE cannot be considered conclusive. Since the mean age of patients with SqTE in Japan continues to rise, development of appropriate cost-effective treatment for elderly patients is important. Convincing evidence in favor of one or the other strategy for patients in their 80s with SqTE is necessary. To this end, a prospective study of RT for octogenarians with medically resectable SqTE would be informative and justifiable.

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