

Results of radical and adjunctive radiotherapy of esophageal carcinoma

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Rojpornpradit P, Thitathan S, Lertsanguansinchai P, Rajatapiti P, Asavametha N, Khorprasert C. Results of radical and adjunctive radiotherapy of esophageal carcinoma. *Chula Med J* 1993 Oct; 37(10) : 631-638

A retrospective analysis of 62 patients with various types of localized esophageal cancer treated with radical or adjunctive radiotherapy was carried out; 71 per cent were males, 29.0 percent females. The median age of presentation was 61 years, ranging from 33 to 81 for the entire sample. The most common presenting symptom (90.4%) was dysphagia. The distribution of the disease by site was : upper esophagus 24.2%, mid-esophagus 64.5%, lower esophagus 11.3%. In all 62 patients, the histology of the tumors was squamous cell carcinoma. Twenty-nine per cent of the patients had well-differentiated carcinoma; in 32.3% it was moderately differentiated and in 12.9% poorly differentiated. Tumor lengths were : up to 5.0 cm 17.7%, between 5.0 and 10.0 cm 38.7%, and more than 10.0 cm 9.7%. The overall two-year survival rate was 21.0%; median survival was five months. Sex, patient age, tumor location, tumor length and histological grade was found not to influence survival. Types of surgical treatment and radiation dose were found to be significant prognostic factors in survival. Patients treated by radical surgery plus radiotherapy or radiotherapy alone had superior survival rates, i.e. 31.8% and 23.7%, respectively, compared with patients who received palliative surgery plus radiotherapy ($p < 0.05$). A TDF greater than 82 had an obviously better survival rate (30.4%) than a TDF equal to or less than 82 ($p < 0.25$). Prospects for improvement in radiotherapy were proposed.

Key words : *Esophageal carcinoma, Radiotherapy, Surgery.*

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Received for publication. September 8, 1993.

ประยุทธ์ โจน์พรประดิษฐ์, สุรีย์ ฐิตะฐาน, ประเสริฐ เลิศสงวนสินชัย, ประภัสสร รัชตะปิติ, นพดล อัสวเมธา, ชลเกียรติ ขอบประเสริฐ. ผลการรักษามะเร็งหลอดอาหารด้วยรังสี. จุฬาลงกรณ์เวชสาร 2536 ตุลาคม; 37(10) : 631-638

ได้ศึกษาผู้ป่วยมะเร็งหลอดอาหาร ย้อนหลังตั้งแต่ 1 มกราคม 2529 ถึง 31 ธันวาคม 2533 ที่มารับการรักษาที่สาขารังสีรักษา ภาควิชารังสีวิทยา จุฬาลงกรณ์มหาวิทยาลัย เป็นจำนวน 62 ราย เกณฑ์อายุผู้ป่วยอยู่ระหว่าง 33-85 ปี อายุเฉลี่ย 61 ปี อาการที่ผู้ป่วยมาพบแพทย์บ่อยที่สุดคือ กลืนลำบาก (90.4%) ผู้ชายพบ 71.0% ผู้หญิง 29.9% ตำแหน่งของมะเร็งแบ่งได้ดังนี้ ส่วนบนของหลอดอาหาร = 27.2% ส่วนกลาง 64.5% และส่วนล่างของหลอดอาหาร = 11.3% พยาธิสภาพว่าเป็น squamous cell carcinoma ทั้ง 62 คน แบ่ง histologic grade เป็น well differentiated = 29.0% moderately differentiated 32.3% และ poorly differentiated 12.9% ความยาวของมะเร็งแบ่งได้ดังนี้ ความยาวน้อยกว่าหรือเท่ากับ 5.0 ซม. = 17.7% ความยาวระหว่าง 5.0 ถึง 10.0 ซม. = 38.7% และความยาวมากกว่า 10.0 ซม. = 9.7% การรักษารังสีแบ่งได้เป็น 3 ชนิด คือ รักษาด้วย radical radiation อย่างเดียว = 50.0% รักษาด้วย radical surgery + radiotherapy = 32.3% และรักษาด้วย palliative surgery + radiotherapy = 17.1% อัตราการรอดในระยะเวลา 2 ปี ของผู้ป่วยทั้งหมด = 21.0% และระยะเวลาการรอดเฉลี่ย = 5 เดือน ผู้ป่วยที่ได้รับการรักษาด้วย radical surgery + radiation และผู้ป่วยที่รักษาด้วย radical radiation อย่างเดียว มีอัตราการรอด = 31.8% และ 23.7% ($p > 0.05$) ตามลำดับ ส่วนผู้ป่วยที่รักษาด้วย palliative surgery + radiation มีอัตราการรอดใน 2 ปี = 0% ($p < 0.025$) ขนาดของรังสีก็มีผลอย่างมีนัยสำคัญทางสถิติ ต่ออัตราการรอด ผู้ป่วยที่ได้รับรังสีโดยคิด TDF มากกว่า 82 จะมีอัตราการรอด = 30.4% เมื่อเทียบกับ 14.7% ของผู้ที่ได้รับ TDF < 82 ($p < 0.025$) ไม่พบความแตกต่างในอัตราการรอดในแง่ของอายุ เพศ ตำแหน่งมะเร็ง histologic grade และความยาวของมะเร็งได้เสนอวิธีการที่จะปรับปรุงรังสีรักษาเพื่อให้มีประสิทธิภาพมากขึ้น

October 1993

Carcinoma of the esophagus is a highly fatal disease with an extremely poor prognosis. Even with the recent advances in surgery, radiotherapy and chemotherapy, long-term survival is rare. (1) Except for the classic paper by Pearson in 1966 (2) which reported a five-year survival rate of 20.0%, most other reports in western countries achieved a five-year survival rate consistently under 10% with surgery or radiation alone. (3-6) Reports of several studies combining chemotherapy with radiotherapy or surgery have suggested possibly better survival, (7-9) although the value of such therapy still remains undefined and needs further evaluation.

This study is a retrospective review of the results of radical and adjunctive radiotherapy in patients with esophageal carcinoma.

Materials and methods

During the period January 1986 through December 1990, 70 cases of various types of esophageal carcinoma without distant metastasis were referred to the Department of Radiology, Faculty of Medicine, Chulalongkorn University for radiation treatment. Of these, eight patients were excluded from the study : four patients were cases of recurrent cancer following surgery : another four patients were lost to follow up after treatment. Sixty-two patients, therefore, remained for analysis. Pathological reports on the lesions were obtained in all patients.

Table 1 lists the patient characteristics. There were 44 males (71.0%) and 18 females (29.0%). The patients ranged in age from 33 years to 85 years. The most common presenting symptom was dysphagia, which was found to affect 56 patients (90.4%)

Table 1. General characteristics of patients.

Characteristics	No.(%)
Sex	
Male	44(71.0)
Female	18(29.0)
Age	
< 60 yrs	29(46.8)
> 60 yrs	33(53.2)
Presenting symptoms	
Dysphagia	56(90.4)
Vomiting	2(3.2)
Neck node	2(3.2)
Hematemesis	1(1.6)
Sore throat	1(1.6)

The main characteristics of the tumors are shown in Table 2. Sites of the tumors were defined according to the UICC TNM Classification of Malignant Tumours (1987). (10) Fifteen tumors (24.2%) were located in the upper esophagus, 40 (64.5%) in the mid-esophagus and 7 (11.3%) in the lower esophagus. Since it was not possible to stage all tumors clinically or pathologically by the TNM staging system (11) because the system is rather complicated and depends upon the findings of several types of examination such as endoscopy, barium contrast study, computerized tomography and other imaging modalities. The tumors were, therefore, grouped

by the length of the lesion measured directly from the radiographs with magnification correction. There were 11 patients (17.7%) who had tumors equal to or less than 5.0 cm, 24 (38.7%) who had tumors measuring between 5.0 and 10.0 cm and 6 (9.7) with tumors more than 10.0 cm. The length of tumors in 21 patients (33.9%) was unknown. In all 62 patients, the histology of the tumors was squamous cell carcinoma. The tumor grades were : well-differentiated carcinoma (29.0%), moderately differentiated carcinoma 20 (32.3%), poorly differentiated carcinoma 8 (12.9%) and unknown grade 16 (25.8%).

Table 2. Main characteristics of tumors.

Characteristics	No.(%)
Tumor location in esophagus	
Upper	15(24.2)
Mid	40(64.5)
Lower	7(11.3)
Tumor length	
< 5.0 cm	11(17.7)
> 5.0 < 10.0 cm	24(38.7)
> 10.0 cm	6(9.7)
Unknown	21(33.9)
Tumor grade	
Well differentiated	18(29.0)
Moderately differentiated	20(32.3)
Poorly differentiated	8(12.9)
Unknown	16(25.8)

Radiation treatment could be categorized into three groups :

1) patients who were medically contra-indicated for surgery or patients whose general health was not suitable for surgery regardless of the operability of the tumors, were given radiotherapy only; they numbered 31

(50.0%). 2) patients who had undergone radical surgery (esophagectomy) with or without residual tumors numbered 20 (32.3%). 3) patients who had palliative by-pass surgery numbered 11 (17.7%). For the last two groups, post-operative radiotherapy was given. Table 3 shows the treatment methods.

Table 3. Radiation method.

Method	No.(%)
RT * alone	31(50.0)
Radical surgery + RT	20(32.3)
Palliative surgery + RT	11(17.1)

RT * = Radiation therapy.

Radiation treatment was administered with a tele-cobalt machine. The radiation technique consisted of initial anterior and posterior fields. When the tolerance of the spinal cord had been reached the radiation ports were changed to two anterior oblique wedged fields for

upper esophageal lesions, and one anterior and two posterior oblique fields for mid or lower esophageal lesions. The dose per fraction was 200-300 cGy. TDF (time, dose, fractionation factor) was used to compare the isoeffect of various radiation regimens (Table 4).

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Table 4. Radiation dose (TDF).

TDF	No.(%)
< 82	36(58.1)
> 82	26(41.9)

The survival was calculated using the product limit estimate of Kaplan and Meier. (13) Comparisons of survival were made using the log rank test. (14) a p-value of less than 0.05 was considered significant.

Results

Of the 62 patients referred for radiation treatment, 44 (71.0%) were men and 18 (29.0%) women. Sex was not found to affect the survival rate. The two-year survival rates for men and women were 20.9% and 24.3%, respectively ($p>0.05$). The most common presenting symptom was dysphagia, which was found to affect 56 patients (90.4%). The median duration of dysphagia was two months, ranging from one month to seven months. The median age of presentation was 61 years, the range being from 33 to 81. Twenty-nine patients (46.8%) were 60 years of age or younger, 33 (53.2%) were over 60 years. The survival rates for these two age-groups were 17.2% and 25.8%, respectively ($p>0.05$).

Sites of tumor were not found to be of prognostic value. The survival rates for the upper, mid and lower esophagus were 26.7%, 23.2% and 0%, respectively. Since the number of patients with lower esophageal cancer were too small to be significant, i.e. only seven patients (11.3%), they were excluded from the significance test for fear of introducing bias. Patients with a lesion up to 5.0 cm in length had a survival rate of 32.3%, while those whose tumor length was between 5.0 and 10.0 cm the survival rate was 31.7%. This difference was not statistically different. Because there were only seven patients with lower esophageal cancer, they were also excluded from significant test for the same reason. The survival rates of patients with well- and moderately differentiated carcinoma were 26.9% and 20.3%, respectively ($p>0.05$). For patients with poorly differentiated tumors, none, attained two-years of survival. The survival rate of patients who received palliative surgery plus radiation was much inferior to that of patients who had undergone radical surgery plus post-operative radiation or radiation alone, 0%, 31.8% and 23.7%, respectively ($p<0.025$). The survival of patients who received radiation alone was not statistically different from those receiving radical surgery plus post-operative surgery.

Patients who had a TDF of up to 82 had an obviously inferior survival rate (14.7%) compared with

those with a TDF of more than 82 (30.4%), $p<0.025$.

There were two patients who survived for more than five years. Both patients had a 5.0-cm lesion, one located in the upper esophagus and the other in the mid esophagus. One patient had radiation treatment with curative intent, another had radical surgery plus post-operative radiation therapy. The radiation doses for these two patients were 60.0 Gy (TDF =99) and 61.0 Gy (TDF =109), respectively.

The overall two-year survival rate in this study was 21.0% with five months as the median survival time.

Discussion

Esophageal cancer is one of the most difficult types of cancers to cure. In spite of recent technological improvements in surgery and radiotherapy, and the availability of modern imaging techniques, the prognosis for this type of cancer continues to be poor. Overall five-year survival rates are less than 10.0% in most surgical and radiation therapy series. (3-6) The reported two-year survival rate for patients treated with radiation ranged from 4% to 28%. (4,5,15) Somewhat better survival statistics have been reported in the literature utilizing a combined modality of treatment. (7-9) Many prognostic factors have been studied. It has been shown that those having a better prognosis are females, patients whose ages less than 65 years, with the tumor being located in the upper third and being less than 5.0 cm in length. (15,16)

In this study, the overall two-year survival rate was 21.0% and the median survival duration was five months. Females had a better survival rate than males (24.3% vs 20.8%), but this difference was not statistically significant. Age of the patients could not be shown to affect survival as reported by Pearson. (15) In the present study, patients over age 60 had a surprisingly better survival rate (25.8%) than those aged up to 60 (17.2%) which is in contradiction to other reports in the literature. (15,16) However, this difference was not statistically significant. The good results of patients over 60 years emphasize to us as radiotherapists the importance of not undertreating a patient, even an aged, starved and emaciated patients who has minimal and metastatic-free disease.

Patients with lesions measuring up to 5.0 cm in length had a survival rate of 32.3%, compared with 31.7% and 0% for those whose lesions were between 5.0 and 10.0 cm, and more than 10.0 cm, respectively. Since the records on the length of lesions were not available in 33.9% of the patients, those with lesions up to 5.0 cm could have been included in this group with unknown length of tumor. A significantly better survival rate for patients with lesions up to 5.0 cm could have been obtained if the length of all the lesions had been available. Patients with both upper and mid esophageal types of cancer had a better survival rate, i.e. 26.7% and 23.2% respectively, than those with lower esophageal lesion; in the latter group, none survived for two years.

The histologic grade of cancer could not be shown to influence the survival rate. Patients with well- and moderately differentiated carcinomas had survival rates of 26.9% and 20.3%, respectively. None of the patients with poorly differentiated tumors survived for two years.

In the present series, modes of surgical treatment and radiation dose are shown to be of prognostic value. Patients who underwent radical surgery plus post-operative radiation had a better survival rate (31.8%)

than those who underwent palliative surgery plus radiation (0%). Radiation alone resulted in a 23.7% survival rate, which was not statistically different from patients who underwent radical surgery plus post-operative radiation. It should be emphasized that when comparing the results of treatment with radiation alone versus combined surgery plus radiation, it is important not to overlook the patient selection factor. In most surgical series, the patient were highly selected for operation. In contrast, patients in the group receiving radiotherapy alone are usually a combination of those who were either technically in operable or in poor general health. Thus bias could easily arise.

Patients who had a TDF of more than 82 had an obviously better survival rate (30.4%) than those with a TDF of up to 82 ($p < 0.025$), regardless of the type of surgery performed. Survival rates by various prognostic factors are shown in Table 5.

Data from this study suggest that radiotherapy alone is as good in improving survival as radical surgery plus radiotherapy. However, radiation treatment must be given by a team of experienced radiotherapists.

Table 5. Survival rates by various single factors.

	No. of cases	2-year survival rate (%)	p - value
Sex			
Male	44	20.9	} NS
Female	18	24.3	
Age			
< 60 yrs	29	17.2	} NS
> 60 yrs	33	25.8	
Tumor location			
Upper	15	26.7	} NS
Middle	40	23.2	
Lower	7	0	
Tumor length			
< 5.0 cm	11	32.3	} NS
> 5.0 < 10.0 cm	24	31.7	
> 10.0 cm	6	0	
Histological grade			
Well-pifferentiated	18	26.9	} NS
Moderately Differentiated	20	20.3	
Poorly differentiated	8	0	

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Treatment

RT	31	23.7	RT/S+RT vs pS + RT } p<0.025
S + RT	20	31.8	
pS + RT	11	0	
Radiation dose (TDF)			
< 82	36	14.7	} p<0.025
> 82	26	30.4	

RT = Radiation treatment

S = Radical Surgery

pS = Palliative Surgery

In spite of these good results, improvements in radiotherapy still need to be made in the future. Firstly, tumor localization needs to be more precise by utilizing a fully three-dimensional treatment planning scheme to define the exact target volume. Radiation treatment will then be able to be delivered by conformational therapy, instead of the conventional two-dimensional method, where extremely precise dose distributions will closely follow the contours of tumors. Secondly, optimum TDF should be defined in order to obtain a better therapeutic ratio within the irradiated volume.

Conclusion

The data of 62 patients with localized esophageal carcinomas treated by radical radiation alone or surgery with adjunctive radiotherapy from 1986 to 1990 were reviewed. There were 44 males (20.9%) and 18 females (24.3%), all of whom had squamous cell carcinoma. The median age of presentation was 61 years. The most common presenting symptom was dysphagia, accounting for 90.4% of the patients. The location of the tumors were: the upper esophagus in 15 patients (24.2%), the middle esophagus in 40 (64.5%) and the lower esophagus in seven (11.3%). There were 11 patients (17.7%) whose lesions were up to 5.0 cm long 24 (38.7%) patients with lesions between 5.0 and 10.0 cm long and six (9.7%) with lesion longer than 10.0 cm. Eighteen patients (29.0%) had well-differentiated carcinoma, 20 (32.3%) moderately differentiated and eight (12.9%) poorly differentiated carcinoma. The treatment methods were: radiation alone in 31 patients (50.0%), radical surgery plus radiotherapy in 20 (32.3%) and palliative surgery in 11 (17.1%). The overall two-year survival rate was 21.0%. The median survival duration was five months. Sex, age, tumor location, tumor length and histological grade were not found to affect the survival rate. Types of surgery and radiation dose were found to be of prognostic value. Patients treated with radical surgery plus radiotherapy or radical radiation alone had a better two-year survival rate,

31.8% and 23.7% respectively, than those treated by palliative surgery plus radiotherapy which was 0% (p<0.025). The survival of patients treated by radical radiation and those treated by radical surgery plus radiotherapy was not statistically significant. A TDF greater than 82 resulted in a better survival rate (30.4%) than a TDF up to 82 (14.7%), P<0.025. Prospects for improvement in radiotherapy were discussed.

Acknowledgements

We are grateful to colleagues, past and present, for access to the case records of patients under their care.

We are indebted to Mr. Varajin Boonkong for his technical assistance; to Miss Pratum Seangurai and Miss Yanee Sutahayalai for their assistance in follow-up data collection; and to Miss Arunee Assawarakse and Mrs. Chanyar Srisuk for typing the manuscript.

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