

Radiation Treatment of Esophageal Cancer

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=국문초록=

식도암의 방사선치료

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오원용 · 서창욱 · 김귀연

한국에서는 식도암의 임상적 관찰과 치료성적이 아직까지는 광범위하게 연구 및 보고되지 않았지만, 소화기계통에서 발생하는 악성종양중에서는 비교적 적지않은 것으로 알려져 있다. 의학적 지식, 진단적 설비, 방사선 치료의 적용, 외과적 수술의 진보, 그리고 최근의 화학요법의 개발등과 같은 괄목할만한 향상에도 불구하고 예후는 극히 불량하여 5년 생존율이 10%이하로서, 과거에 비하여 크게 향상되지 않은 것으로 보고되고 있다.

이에 저자들은 1970년 1월부터 1980년 12월까지 만 11년동안 식도암으로 진단되어 연세 암센터에서 근치적 목적으로 방사선 치료를 받았던 63예에 대한 철저한 추적조사를 통하여 후향성분석을 시행한 바 다음과 같은 결과를 얻었다.

1. 전 63예의 식도암 환자의 85.2%인 52예는 조직병리학적 소견에서 상피성세포암(Epidermoid Carcinoma)으로 확진되었다. 그리고 T₁인 17예를 제외한 46예(73%)의 병변은 상당히 진행되었던 예들이었다.

2. 방사선 조사선량은 일일 일회 2 Gys 가 조사되었으며 총 조사선량 50~74 Gys가 5~8주간에 조사되었다.

3. 전 63예중 28예에서 방사선 치료후 1개월만에 식도조형상을 통하여 식도암에 대한 방사선치료 효과를 평가하여 본 결과, 완전관해는 7예였으며 나머지 15예는 부분적 관해, 그리고 6예는 변화가 없었다.

4. 전 63예의 3년, 5년 생존율은 11.8%, 8.8%였으며 그리고 T₁인 17예의 3년, 5년 생존율은 24.7%, 20.8%였다.

ABSTRACT

63 patients who were irradiated with a goal of long term control among 101 patients with esophageal cancer seen during an 11 years period between Jan, 1970 and Dec, 1980 at Yonsei Cancer Center in Seoul, Korea have retrospectively analysed. 52(82.5%) among the 63 patients were

* 이 논문은 1985년 연세암센터 연구비의 보조로 이루어 졌음.

confirmed to have epidermoid carcinoma in the histology. 46 cases(73.0%) except 17 cases of T₁ were locally or far advanced extension. Tumor dose of radical radiation in the management of esophageal cancer had delivered from 50 Gy to 74 Gys. 2 Gys daily fractions, between 5 weeks and 8 weeks. After 1 month from the completion of radiation, 28 of the 63 patients had a repeat barium esophagogram for the assessment of tumor response, there had showed 7 cases of complete response and 15 cases of partial response. 45(71.4

%) patients were followed up and the remaining 18 patients were lost to follow-up within 1 year after the completion of irradiation. Actuarial overall 3 and 5 years survival rate of all 63 patients were 11.8% and 8.8%, respectively. The actuarial 3 and 5 years survival rates of 17 cases of T₁, esophageal cancer were 24.7% and 20.8%. Statistically, there was no significant difference in survival rate according to tumor location ($p > 0.05$).

Radical Radiotherapy, Esophageal Cancer

INTRODUCTION

In Korea, carcinoma of the esophagus constitutes annually less than 3% of all reported malignancy¹⁾. Generally, the patient with esophageal cancer presents with an advanced tumor at a time when obstructive symptoms have produced a significant degree of malnutrition or weight loss. Esophageal cancer behaves in a characteristic way due to the anatomy and the natural history of the diseases. The esophagus is a thin walled tube where squamous carcinomas arise, surrounded by an inner circular and outer longitudinal muscularis. There is no fibrous serosa acting as a barrier to the spread of tumor beyond the confines of the esophageal wall. Rich lymphatic networks in the submucosa and muscularis facilitate the spread of tumor circumferentially, transmurally, and longitudinally.^{2,3,7)} Distant spread of tumor within the esophagus is relatively common.^{2,7)}

In spite of recent advanced in medical knowledge, diagnostic facilities, radiotherapy appliances and surgical techniques esophageal cancer, still ranges among the tumors with a higher unfavorable prognosis and the overall 5 year survival rate has not changed essentially over the past three decades.³⁾ The poor prognosis for esophageal cancer following radiotherapy has recently been highlighted by Earlam and Cunha-Medlo¹²⁾ in there reviews of series reported in the world literature. In the result of review, the actuarial 5 years survival rate after radical irradiation have been less than 10% unfavorably. On the other hand,

Pearson reports¹⁹⁾ an overall 5 year survival of 17% for a group of 288 patients treated definitively with irradiation and an overall 5 year survival of 11% for a group of 432 patients treated with radical surgery.

Until now, radiation therapy as primary treatment has been used extensively in the management of patients with cancer of the esophagus. It has demonstrated an ability to cure a small minority of patients. Cure is likely to be limited to the patients who have lesions less than 5 cm in length and have minimal, if any involvement of lymph nodes. This study constitutes the first report on local response of radiation, overall survival, and comparison of survival rate by T stage in Korea and want to discuss treatment modalities for the improvement of survival rate in esophageal cancer.

METHODS AND MATERIALS

The total number of cancer patients have seen about 6,000 for the 11 years between Jan, 1970 and Dec, 1980. Among the total 6,000 patients, 406 cases were GIT cancer (6.7%) and 101 of 406 cases have irradiated for esophageal cancer (1.68 %). But only 63 cases who irradiated with radical aim and therefore were included in this study (Table 1).

All 63 patients were clinically and histologically diagnosed by the following methods and

Table 1. Treatment Modality of Cancer in the Esophagus(1970~1980)

Treatment Modality	No. of Patient
Radical XRT	63
Palliative XRT	4
XRT+radical esophagectomy	2
XRT+bypass surgery	14
XRT+chemotherapy	6
No or incomplete XRT	12
Total	101

Table 2. Tumor Location and T₁ Stage of Cancer in the Esophagus

Tumor Site	T ₁	T ₂	T ₃	M ₁	Total(%)
UPPER	2	3	3		8(12.7)
MID	8	25	3	4 ⁺	40(63.5)
LOWER	7	6	2		15(23.8)
Total(%)	17(27)	34(54)	8(13)	4(6)	63(100)

T₂N_xM₁(4)⁺

determined the significance of staging (TNM) as esophageal cancer.

Careful history taking and physical examination.

Full laboratory investigations.

X-ray examination of chest. Chest CT scann.

Esophagogram, Esophagoscopy with biopsy.

Indirect laryngoscopy and bronchoscopy.

Whole body bone and liver scann.

Mediastinoscopy and laparoscopy or laparotomy.

Age and Sex Distribution (Fig. 1)

All 63 patients who have irradiated with radical aim ranged between 30 years and 80 years of age. Of them, 55 cases (87%) show over 50 years of age and among all 63 patients in which radical irradiation of the esophagus was carried out there were 59 males and 4 females. Much more frequency in males than females in sex ratio.

Primary Site and T Stage (Table 2)

The location of primary tumor in esophageal cancer was determined with esophagoscopy finding, esophagogram and chest CT scann. In the result of tumor location, upper third (cervical esophagus) of 8 cases (12.7%), middle third (thoracic esophagus) of 40 cases (63.5%) and lower third of 15 cases (23.8%) in the esophagus showed. Clinically tumor staging for the knowledge of tumor extension by AJC was only possible T staging. On T staging, 17 cases (27%) of T₁, 34 cases of T₂(54%), 8 cases of T₃(13%) and the remaining 4 cases of M₁(6%) was showed. All cases except 17 cases of T₁(73%) were locally or far advanced and inoperable status in the extension of esophageal cancer.

Histologic Types (Table 3).

52 cases (82.5%) of all total 63 patients were

Table 3. Histologic Type of Cancer in the Esophagus(1970~1930)

Histologic Type	No. of Patient	%
Epidermoid	52	82.5
Adenosquamous	1	1.6
Unconfirmed	10	15.9
Total	63	100.0

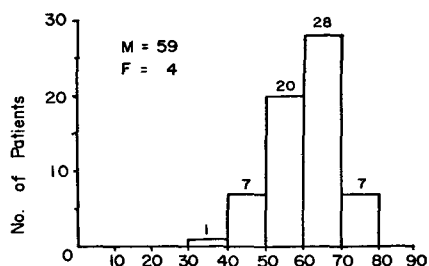


Fig. 1. Age and Sex Distribution of Cancer in the Esophagus.

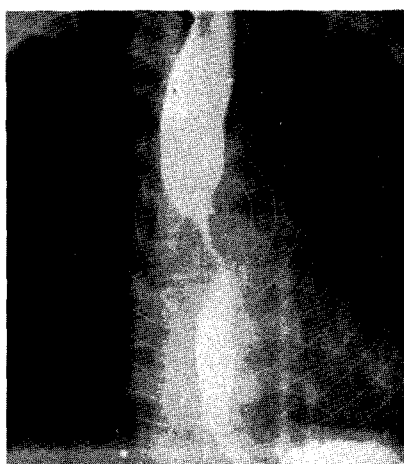
confirmed to be epidermoid carcinoma on esophagoscopy biopsy but 10 cases were of unknown histology and 1 case of adenosquamous carcinoma. 10 cases of unknown histology were failed to determine pathologic types in spite of the application of diagnostic procedures, but irradiated under the suspicion of carcinoma because of definitive involvement of the esophagus on barium study.

Radiation Techniques

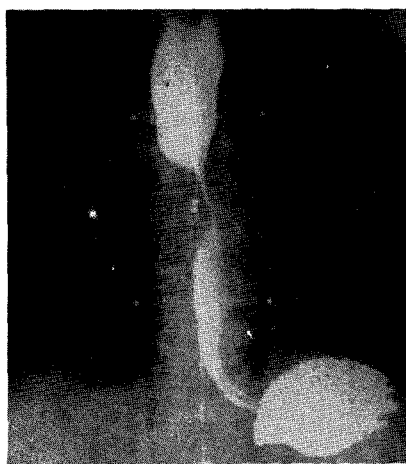
Radiation sources: ⁶⁰Co was used in 24 patients and 13 MeV Linear accelerator in the remaining 39 patients. Radiation fields (Fig. 2a,b): The length of the field of radiation was decided by

Table 4. Radiation Portals of Cancer in the Esophagus

Portal	Upper	Mid	Lower	Total
Full arc rotation	—	6	2	8
AP+PA	—	—	2	2
AP+PA 2 or 4 oblique	6	18	8	32
AP+PA rotation	—	14	2	16
AP+PA 2 pair wedge 45°	1	—	—	1
4 OBLIQUE	1	2	1	4
Total	8	40	15	63



2-a



2-b

Fig. 2-a and 2-b. Radiation fields using the shrinking field techniques of cancer in the esophagus.

the length of the lesion. Usually, both the primary tumor and the most common areas of regional lymphatic spread are included. At first, field sizes of all patients extended to at least 5~8 cm from the upper and lower borders of the tumor using the shrinking field technique. After a dose of 36~44 Gys in 4~5 weeks to large fields encompassing the primary tumor and areas of potential spread, the portals are reduced and an additional 14~30 Gys in 2~3 weeks were delivered to the primary tumor with minimal margins.

Radiation portals (Table. 4): As it shows in Table 5, radiation portals and the direction of beams in the techniques of treatment in esophageal cancer were varly individualized, respectively. 8 among the total 63 patients were treated with a cobalt 60 teletherapy unit by full 360° rotation

therapy technique at a source tumor distance (S.T.D.) of 80 cm. The remaining 49 patients except 4 cases using alone 4 oblique and 2 cases using alone anterior and posterior, parallel opposed techniques in the portal were given 36~44 Gys of tumor dose via two parallel opposed portals with a wide field, and then the remaining 14~30 Gys tumor dose was delivered via oblique, full 360° rotation or 2 pair of wedged portals to the small field of the primary site.

Radiation dose (Table 5): At the Yonsei Cancer Center, total tumor dose of 50~74 Gys, in daily 2 Gy fractions, for 5~8 weeks was delivered using the shrinking field technique. At first, after a dose of 36~44 Gys, daily 2 Gys fractions, 4~5 weeks to large fields encompassing the primary tumor and areas of regional lymph nodes, and then the

Table 5. Radiation Dose of Cancer in the Esophagus

Tumor Dose(Gy)	T ₁	T ₂	T ₃	M ₁	Total(%)
50~60	5	3	3	2	13(20.6)
60~70	12	29	4	1	46(73.0)
70~80	—	2	1	1	4(6.4)
Total	17	34	8	4⁺	63(100.0)

T₂N_xM₁(4)⁺

Table 6. Local Response of 28 Patients at One month Follow-up after Irradiation

Stage	CR	PR	SD	PD	Total
T ₁	4	6	1	—	11
T ₂	3	7	3	—	13
T ₃	—	1	2	—	3
M ₁ ⁺	—	1	—	—	1
Total	7	15	6	—	28/63

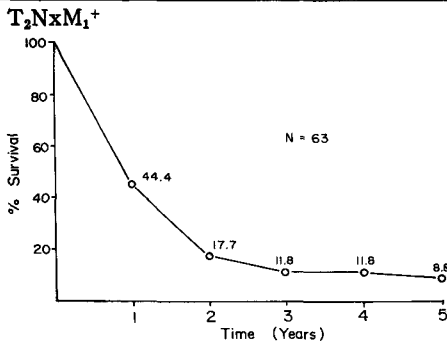


Fig. 3. Actuarial Overall Survival of Cancer in the Esophagus(1970~1980).

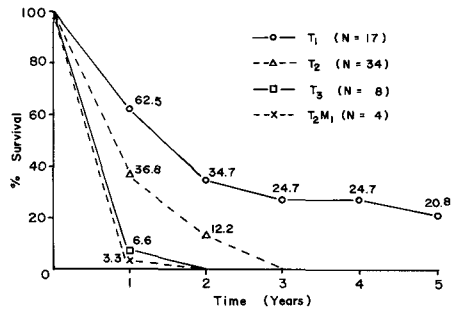


Fig. 5. Actuarial Survival by Stage(T) of Cancer in the Esophagus(1970~1980).

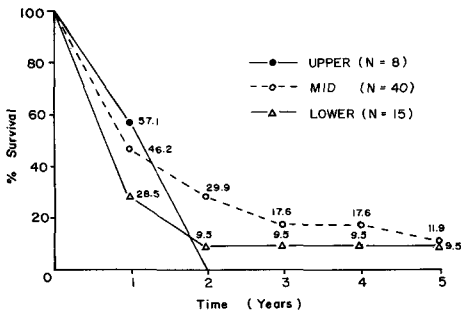


Fig. 4. Actuarial Survival by Tumor Location of Cancer in the Esophagus(1970~1980).

portals were reduced and an additional 14~30 Gys in 2~3 weeks delivered to the primary tumor within minimal small fields.

RESULTS

Radiation Response (Table. 6)

28 of the 63 patients were checked with a repeat barium esophagogram for the assessment of tumor response at 1 month after the completion of radical irradiation. 7 cases showed complete response and 15 cases partial response.

Survival Rate (Fig. 3~5)

45 of the 63 patients (71.4%) who were irradiated with radical aim for esophageal cancer have been followed up at the time of this study. Actuarial overall 3 and 5 year survival rates by Kaplan and

Meier (life table) method are 11.8% and 8.8%, respectively. Actuarial 3 and 5 year survival rates according to tumor location in the esophagus are shown as the following: 8 cases of upper third of cancer in the esophagus have died, all within 2 years after the end of irradiation. On the other hand, actuarial 3 and 5 year survival rates of middle third and lower third cancer of the esophagus are shown as 17.6%, 9.5% and 11.9%, 9.5% respectively. But statistically, there is no significant difference in survival rate according to tumor location. ($p > 0.05$). And also, actuarial 3 and 5 year survival rates of 17 cases of T_1 , esophageal cancer are 24.7% and 20.8% while 34 cases of T_2 are died all within 3 years of the end of irradiation and the remaining 8 cases of T_3 and 4 cases of M_1 died within 2 years of the end of radical irradiation.

DISCUSSION

Since the initial report of the technique of radium bouginage by Jean Giusez in 1909^{8,9)}, there have been major technical advances and the development of high energy machines in radiation therapy that have contributed to improved survival for patients with esophageal cancer. Until now, advocacy of primary irradiation of esophageal cancer by many investigators based upon considerations of tumor histology (squamous cell ca), early advanced or inoperable carcinoma in most cases (no fibrous serosa acting as a barrier) and knowledge of the acute morbidities of esophageal surgery and irradiation.^{2,3,8,16,18)}

Treatment volume, total tumor dose and fractionation are major determinants of response and cure in radiation therapy and are issues that remain unsettled in the management of patients with esophageal cancer.^{3,4)} The majority of radiation oncologists report the use of limited treatment volumes as advocated by Pearson,^{19,23)} in which the primary esophageal lesion is irradiated with approximately 5 cm of margin lateral to clinically defineable abnormalities. Because of,

tumor involvement have been documented 4 to 8 cm beyond the margins of primary tumor despite microscopically uninvolved intervening regions of esophagus. Generally, radiation volume or radiation field if possible, must encompass the tumor and the surrounding areas of potential spread (mediastinal structures including regional paraesophageal lymph nodes). In the Princess Margaret Hospital,⁴⁾ both large and small field areas were compared to survival and both showed an optimum area of about 120 cm², but neither of these findings was statistically significant. Because of the wide variation in radiation dosage, only patients receiving 5,000 rads in 5 weeks were considered and it was then noted that the large field correlated well with survival. An optimum size of 100~140 cm² was identified. On the other hand, total tumor dose, fraction size and duration of therapy have widely varied by many other investigators. Most investigators^{3,5)} consider radical therapy to be any dose regimen equivalent to or exceeding the administration of 5,000~6,000 rads to the tumor in standard, 180 or 200 rad fractions, over a 5~6 weeks period. The highest dose regimen reported comes from Stanford³⁾ University, where preoperative tumor doses of 6,600 rad were administered in 250 to 275 rad fractions over a period of 7 weeks. Lower doses were administered to clinically uninvolved areas in the mediastinum and epigastrium. These high doses were felt to have contributed to the 33% incidence of postoperative mortality and were responsible for an additional 12.5% mortality rate from pneumonitis and carditis beyond the 30 day postoperative period. On the other hand, in a clinical and histologic study of the effects produced with Betatron by W.B. Seaman and L.V. Ackerman,⁶⁾ they came to the conclusion that the tolerance of the normal esophageal wall to radiation of this energy was in the region of 6,000 rads given in 6 weeks. Therefore, the total tumor dose should not exceed 6,000 rads in 6 weeks or its equivalent in a longer or shorter time. Analysis of the PMH experience⁴⁾ indicated maximum survival with dose

regimens whose modern normal standard dose (NSD), based upon the formulation proposed by Ellis was 1602~1714 rets (mean 1679 rets). This translates into a dose of 5,000 rad given in 20 fractions over 4 weeks. This dosage regimen was also advocated by Pearson and subsequently, by Newaishy et al in Edinburgh of Scotland.^{13,14,23)} The lack of 5 year survivors in the PMH experience suggests that this dose may be inadequate for local control in the majority of esophageal tumors but may approximate tolerance of surrounding normal tissues. At the Yonsei Cancer Center, tumor dose of 50~74 Gys, daily in 2 Gys fractions, 5~8 weeks was delivered in using the shrinking field technique.

In the clinical course and tumor response following irradiation of the esophageal cancer, the squamous epithelium of the esophagus has approximately the same radiosensitivity as that of the oral mucosa.^{6,7)} De-epithelization leads to clinical symptoms of esophagitis that begin in 1 to 2 weeks after the start of treatment and, in some patients, can be severe.^{6,7)} Tumor response usually begins at 2 to 3 weeks. Improvement in swallowing and relief of tumor pain can help in making the discomfort of esophagitis more tolerable. There is a suggestion that modern high energy x-ray treatment produces an improvement when compared to the natural history of the disease. In addition, between 60% to 80% of irradiated patients⁸⁾ will have their dysphagia partially or completely report of A.M. Mandard et al,¹⁰⁾ 12 of 52 patients receiving radiation doses of 5,000 rad or more, on the rate of 1,000 rad/5 fractions/1 week, 23% presented no residual esophageal cancer at autopsy, and complete disappearance of local tumor of esophageal carcinoma after irradiation, its possibility may reach 33%(18/54) if the dose exceeds 5,000 rad, on the rate of 1,000 rad/5 fractions/1 week, by Z.Y. Yang et al¹¹⁾.

W.D. Rider¹²⁾ has noted that 5,000 rad administered in 4 weeks controls approximately 80% of small squamous cell carcinomas in the esophagus but that tumor size and spread curtail the effe-

ctiveness of irradiation. Unfortunately, only 28 of the 63 patients with radical irradiation at the Yonsei Cancer Center were given a repeat barium esophagogram at 1 month after the completion of irradiation. They showed 7 cases of complete response and 15 cases of partial response but did not change the remaining 6 cases. Because of incomplete follow up at 1 month after irradiation, we can't make a comparison between tumor response and tumor dose. And so, we can not decide on the optimum dose in esophageal cancer and this needs further study.

Although until now, there has been no controlled study of survival rate between radiation and surgery alone in the management of esophageal cancer. In a critical review of a large collection of published series (49 literatures) by Earlam and Cunha-Melo^{14~15)}, overall survival rate of esophageal cancer is very poor. They conclude there is little discernable difference between less than 10% of 5 years cumulative survival from radiation alone series and the results for surgery alone except 21% of 5 year survival from 1956 to 1963 (123 patients) and 17% of 5 year survival from 1949 to 1967 (288 patients) in the experience of radiation alone by Pearson in Edinburgh of Scotland^{19~21)}. Unfortunately, only 45 of all 63 patients (71.4%) who were irradiated with radical aim of esophageal cancer at the Yonsei Cancer Center for 11 years from Jan, 1970 to Dec, 1980 have been able to be followed up at the time of this study (Dec, 1984). The remaining 18 patients were lost within 1 year after the completion of irradiation. And so, overall 1 year survival of all on irradiated patients was may be over calculated but 3 and 5 year overall survival were similar to many other results as 11.8% and 8.8%, respectively.

In the reports by many investigators, the following factors influenced the prognosis in carcinoma of the esophagus^{16,17)}. The prognosis for women is significantly better than the prognosis for men. Tumor location in the esophagus is a significant prognostic factor since the survival rate for the patients with upper or lower third lesion is con-

siderably better than the survival rate for patients with middle third cancers. Tumor size as measured by the length of the tumor on the esophagogram is also an important prognostic indicator. On the other hand, age, race, cell type and grade of tumor, lymph node and extramural invasion (complete or incomplete) and potential immunological change in nodes are interrelated with survival. Among 63 patients receiving radical irradiation, 8 cases of upper third, 40 cases of middle third, the remaining 15 cases of lower third of cancer in the esophagus were showed. Although no difference in survival between middle third and lower third of the esophagus and worst in survival of upper third in the esophagus, statistically there is no significant difference in survival rate according to tumor location of esophageal cancer ($p > 0.05$). But favorably, actuarial 3 and 5 years survival rate of 17 cases of T₁, esophageal cancer in the comparison of survival rate according to tumor size or T₁ stage are 24.7% and 20.8%, respectively. Interestingly, favorable 3 and 5 years survival rate of 17 cases in the T₁ esophageal cancer is similar to the favorable result of J.P. Pearson¹⁹⁻²¹) More interestingly, 2 among 7 cases showing complete response of T₁ esophageal cancer, they are now alive in 9 years 1 month and 6 years 6 months on Dec, 1984 (time of this study). It suggest the possibility of complete cure in early T₁ esophageal cancer using radical irradiation alone.

Still now, what are the reasons for the poor results in survival of esophageal cancer in spite of advances in the techniques and machines for radical radiotherapy and aggressive surgical resection? Pearson¹⁹) noted the following as reasons for failure:

- 1) widely disseminated disease.
- 2) debilitated patients.
- 3) localized treatment of surgical resection.
- 4) recurrence within the fully irradiated volume.
- 5) death due to treatment itself.
- 6) death from causes unrelated to the cancer or its treatment. On the other hand, he suggests the

possibility of further improvement as the followings:

- 1) prevention (a reduction in the combined consumption of alcohol and tobacco).
- 2) earlier diagnosis.
- 3) reduction of operative mortality.
- 4) systemic treatment of chemotherapy.
- 5) better radiotherapy.

It has been of particular interest since reports of encouraging results with several management techniques at a meeting of the American Radium Society in 1968 led to expectations that a period of rapid advance in the radiation management of esophageal cancer was underway. Reports²⁵) were presented by John T. Goodner of Memorial Sloan-Kettering, Komei Nakayama of Tokyo Women's Medical College, J.G. Pearson of Edinburgh, W.G. Ryder of Princess Margaret Hospital, Toronto, and V.P. Lollins of Baylor University. To confront these reasons of failure to radical treatment in esophageal cancer, multimodality regimens combining surgery, chemotherapy and newer radiation techniques are being developed. On the other hand, the new diagnostic and therapeutic techniques now available offer exceptional opportunities to design, implement and evaluate trials of new approaches incorporating these and other emerging medical technologies. New therapeutic techniques include high LET radiation (neutrons, heavy ions, pi mesons), hyperthermia, radiosensitizers, altered time-dose fractionation, and afterloading radionuclides (iridium-192, cobalt-60, californium-252). New diagnostic techniques include cross-sectional imaging, computed tomographic dosimetry, pericolic arteriography and gallium scanning. However, for the improvement in survival of esophageal cancer, at first, it need to determine the operability the following diagnostic methods:

- 1) standard or optimal diagnostic work-up for the evaluation of patients in esophageal cancer.
- 2) esophagogram and azygogram.
- 3) combined mediastinoscopy and celiotomy (exploratory-lapa).

- 4) Gallium-67 scanning.
- 5) pretreatment staging by CT.

By many investigators, it is contended that radiation therapy is superior to surgical excision in the treatment of cancer of the upper two-thirds of the esophagus and but surgery is still the treatment of choice for lesions of the lower-third. if possible. If tumor volume is clinically less than 5 cm (T₁) in length shall be need to randomized study between radiation and surgery alone, afterward. If tumor volume is more than 5 cm (T₂ or T₃), combined multimodality of the treatment in esophageal cancer must be try. But if impossible to radical treatment, only palliative treatment with radiation, bypass surgery or both are possible.

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