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RADIATION THERAPY ONCOLOGY GROUP

NON-RANDOMIZED STUDY OF NEUTRON THERAPY IN THE TREATMENT OF CARCINOMA OF THE ESOPHAGUS

77-09

closed

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INDEX

Schema

1.0 Introduction

2.0 Objectives

3.0 Patient Selection

4.0 Work-Up

5.0 Registration

6.0 Radiation Therapy Program

7.0 Endpoints

8.0 Additional Therapy

9.0 Study Parameters

10.0 Follow-Up Schedules

11.0 Pathology

12.0 Statistical Considerations and Forms

13.0 Patient Consent

References

Appendix I - Staging

Appendix II - Karnofsky Performance Status

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Protocol For Neutron Therapy

Esophageal Carcinoma

CHOOSE

Fast Neutrons - 2 fractions/week
6000 rad equivalent/6 weeks

~~Fast Neutrons - 4 fractions/week~~ Not a CTF option
~~6000 rad equivalent/6 weeks~~

Mixed Beam - 2 neutron and 3 photon fractions/week
6000 rad equivalent/6 weeks

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1.0 INTRODUCTION

This study is a non-randomized pilot study to evaluate the effectiveness of Fast-Neutron Radiation Therapy for carcinoma of the esophagus. The results will be compared with the uniformly poor results with current treatment modalities and will be used to design subsequent clinical trials using fast neutrons.

Esophageal carcinoma accounts for about 3% of all carcinomas (1). The incidence varies among countries. Estimated new cases of esophageal carcinoma in the United States in 1973 were 6,800 (2). The 1947 U.S. cancer survey reported an incidence of 8.3 per 100,000 population for males and 1.9 for females. The highest incidence is between 60 and 70 years. The male to female ratio is between 3:1 and 5:1.

The prognosis in squamous carcinoma of the esophagus is discouraging regardless of the mode of treatment; this is, in spite of advances in surgical and radiotherapy techniques. Dr. Nakayama reported only 301 survivors at 5-years' follow-up (3). Esophageal cancer, nevertheless, remains localized at the primary site in a majority of cases. Consequently, an improved method of local treatment should result in an increased survival rate or as a minimum, improved local control. Fast-neutron radiotherapy has been proposed as a means of improving the local control rate.

1.1 Results with Conventional Treatment Modalities

A review of the literature shows the uniformly poor results of present treatment methods in the management of esophageal cancer.

In addition to the results of Nakayama cited above, Smithers' review in 1957 reported only 135 survivors (1). An exception is the result reported by Pearson of Edinburgh of a 20% 5-year survival in 99 patients treated with radical megavoltage irradiation (4-6).

The experiences of the M.D. Anderson Hospital and the University of Texas Medical Branch are similar to those reported from other institutions, of 491 patients with esophageal carcinoma seen at the M.D. Anderson Hospital, between 1944 and 1970, only 5.3% were alive at 5-years' follow-up, of 191 patients treated definitively the absolute 3-year survival rate was 11.5%. Seventy percent of the patients were treated with definitive radiotherapy, either primarily or for residual or recurrent disease. The absolute 3-year survival rate of these patients was 11.4%.

Table I compares the 5-year survival of surgery and radiotherapy and Table II summarizes the results of preoperative radiotherapy by Nakayama (3).

In a series reported by Seymour and Petit 27 patients were treated and 9 of them were alive at 3-years' follow-up (7). Eight of the nine lived 7.8 to 13.6 years and one was lost to follow-up.

FIVE-YEAR SURVIVAL: SURGERY AND RADIOTHERAPY

Table I:

	Cervical Esophagus	Upper Half Thoracic	Lower Half Thoracic	Total
Surgery	4/19 (21%)	11/135 (8%)	31/275 (11%)	46/429 (11%)
X-ray Treatment	14/46 (30%)	12/73 (16%)	6/50 (12%)	32/169 (19%)

0015858

FIVE-YEAR SURVIVAL: PREOP. RADIOTHERAPY

Table II:

	Preop. Radiotherapy + Surgery	Surgery Only	Radiotherapy Only
Nakayama (3):	3/8 (37.5%)	4/21 (19.1%)	6/77 (7.7%)

1.2 Rationale

The rationale for fast-neutron radiotherapy is related to the hypoxic-cell problem. Numerous radiobiological studies have shown that hypoxic cells are 2.5 to 3.0 times more resistant to the effects of X and Gamma irradiation than are well-oxygenated cells. While the cells in most normal tissues are well oxygenated, most solid tumors have hypoxic regions which have outgrown their vascular supply. It has been postulated that these cells remain viable and provide a focus for local recurrence. With neutron irradiation, radiosensitivity is less dependent upon the state of oxygenation. As a result, fast-neutron irradiation may be more efficient in the treatment of bulky tumors than X or Gamma irradiation.

Squamous carcinoma of the esophagus is among the more suitable tumors for a fast-neutron trial because: (1) the local control with conventional methods are low; (2) the tumors are frequently ulcerated or necrotic, and should contain a significant hypoxic compartment; (3) local recurrences usually occur within two years, allowing an early evaluation of results.

0015859

1.3 Anatomy and Staging

The staging system to be used is the TNM classification of the American Joint Committee (1976) (see Appendix I). The point of origin of the tumor is based on the center of the bulk of the lesion as demonstrated on the esophagram. Patients with lesions presenting in the postcricoid region will be included; however, patients with tumors showing encroachment on the end of the pyriform sinus, or arytenoids, or pharyngeal wall at the arytenoid level are excluded, unless the greater bulk of the tumor is shown to lie within the cervical esohpagus. Facilities may elect to exclude patients with tumors of a selected esophageal region, but this must be submitted, in writing, to RTOG Headquarters.

2.0 OBJECTIVES

2.1 To determine if local control of the primary is improved compared to traditional treatment methods.

2.2 To determine the tolerance of surrounding normal tissue and complication rates.

2.3 To determine the incidence of distant metastases.

2.4 To determine the survival rate.

2.5 To determine the quality of survival as reflected by the Karnofsky Performance Status.

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3.0 SELECTION OF PATIENTS

Patients considered for the study will be those with histologically-proven squamous-cell carcinoma of the esophagus.

3.1 Eligible Patients

3.11 Eligible patients who have an untreated squamous carcinoma of the esophagus.

3.12 No prior cancer, except of skin, unless disease-free for 8 years.

3.13 The lesion must be a biopsy-proven squamous-cell carcinoma.

3.14 Patients with tumors originating in the following sites will be admitted to the study:

a) Upper one-third (postcricoid or cervical)

b) Middle one-third

c) Lower one-third

3.15 The patient must understand the provisions of the study, and sign the investigational treatment consent forms.

3.2 Ineligibility Criteria

Patients are ineligible for the following reasons:

3.21 A histological diagnosis other than squamous-cell carcinoma.

3.22 Lesions greater than 15 cm in length (esophagram, measurements corrected for magnification).

3.23 Presence of fistula or sinus tract on esophagram.

3.24 Clinically or pathologically-positive supraclavicular, or celiac nodes, or distant metastases.

0015861

3.25 Patients with a simultaneous or previous primary cancer, other than skin carcinoma, within the past 8 years.

3.26 Previous radiotherapy to areas within the projected-treatment protocols.

3.27 Patients who have, in the opinion of the study radiotherapists, an associated or unrelated illness which would interfere with diagnosis, treatment, or subsequent evaluation. (Karnofsky <40% - see Appendix II) Patients with more than 20% weight loss.

3.28 Patients over 70 years of age will generally be excluded. Patients up to 75 years of age, however, may be included if they are in good physical condition (Karnofsky >60% - see Appendix II) and the referring physician and the study chairman agree.

4.0 WORK-UP

4.1 History and physical exam

4.2 Hemoglobin or hematocrit, WBC, platelet count

4.3 SMA-12

4.4 Liver scan, if liver function studies are abnormal

4.5 Chest X-ray

4.6 Esophagram

4.7 Esophagoscopy and biopsy

5.0 REGISTRATION

There will be no randomization in this study. Sequential, eligible patients should be treated according to one of the study arms. To place a patient on study, call RTOG Headquarters at (215-574-3150) between 9:00 a.m. and 5:00 p.m., ET, Monday through Friday and give the following information:

a) Protocol name

b) Institution

c) Patient name

d) Treatment

A study-case number will be assigned which will be confirmed by mail.

6.0 RADIATION THERAPY PROGRAM

6.1 Treatment Modalities

6.11 Neutron radiotherapy only given at 2 fractions per week.

6.12 Neutron radiotherapy only given at 4 fractions per week.

6.13 Mixed-beam radiotherapy consisting of 2 neutrons and 3 photon fractions per week.

6.2 Treatment Volume and Dose

6.21 Upper 2/3 primaries, a dose equivalent of 5000 rad photons in 5 weeks to the supraclavicular area and mediastinum, followed by an additional boost to the primary tumor to a total equivalent dose of 6000 rad in 6 weeks. Lower 1/3

primaries, an equivalent dose of 4000 rad photons in 4 weeks to the epigastric area and mediastinum, followed by a boost to the primary tumor to a total equivalent dose of 6000 rad in 6 weeks.

6.3 Dosimetry Data

6.31 Neutron-only radiation will consist of two or four fractions per week with 500 and 250 rad photons equivalent dose, respectively, delivered per fraction. Neutron doses considered equivalent to 250 and 500 rad photons irradiation are:

	250 Rad	500 Rad
MANTA	78 Rad	156 Rad
NAL	80 Rad	160 Rad
SEATTLE	75 Rad	150 Rad
TAMVEC	80 Rad	160 Rad

At least 90% of the total dose will be delivered by neutrons.

6.32 Mixed-beam irradiation will consist of 3 photon and 2 neutron fractions per week of 200 rad each fraction. Neutron doses considered equivalent to 200 rad photon irradiation are:

MANTA	63 Rad
NAL	65 Rad
SEATTLE	60 Rad
TAMVEC	65 Rad

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At least 30% of the total dose will be delivered with neutrons.

6.33 Fraction size may vary by plus or minus 10% to correct for missed treatments, errors in dosage calculations, etc., but corrections beyond this degree must be made by giving additional fractions.

6.34 Localization films will be obtained at the start of treatment and for boost fields and will be submitted for review.

6.35 Photon irradiation must be delivered with megavoltage equipment of 4 MeV or greater or cobalt 60.

6.36 Tumor doses should not be specified to midplane.

6.37 Doses should not be corrected for increased lung transmission. If these corrections are calculated, this information should be submitted to RTOG Headquarters.

7.0 ENDPOINTS

7.1 Primary endpoints will be:

7.11 Survival time with an evaluation of the mode and cause of death.

7.12 Control of cancer within the irradiation field.

7.2 Secondary endpoints will include an evaluation of the complication frequency, the quality of survival as determined by the Karnofsky Performance Status, and the incidence of distant metastases.

8.0 ADDITIONAL THERAPY

8.1 Instrumentation (including dilatation) is permitted, but should be postponed until mucosal healing is complete (2-3 months).

8.2 No additional cancer therapy (surgery or chemotherapy) is allowed unless there is evidence of treatment failure.

8.3 For local recurrence, additional surgery or chemotherapy is permitted as dictated by the clinical situation.

8.4 For distant metastases, additional surgery, radiotherapy or chemotherapy is permitted as dictated by the clinical situation.

9.0 STUDY PARAMETERS

9.1

	Time of Study			
Study Parameters	Prior To Therapy	During Therapy	At Follow-Up	Every 6 Months
History and Physical Exam	X	X	X	
CBC	X	X	X	
Liver Functions (SMA-12)	X			X
Liver Scan	X[a]			X[a]
Esophagram	X		X	
Chest X-ray	X			X
Esophagoscopy	X			

[a]If liver functions are abnormal.

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9.2 Weekly evaluation during treatment.

9.21 Patient weight.

9.22 WBC, platelets, hemoglobin, and hematocrit.

10.0 FOLLOW-UP SCHEDULES

10.1 Follow-up examinations will be reported at 3 monthly intervals for 2 years and 6 monthly intervals for the subsequent 3 years, giving a total follow-up of 5 years.

10.2 Parameters to be evaluated at each follow-up visit are:

10.21 Esophagram

10.22 Patient weight

10.23 WBC, platelets, hemoglobin, (or hematocrit)

10.24 Chest X-ray and liver function studies at 6, 12, 18, and 24 months

10.25 Status of primary tumor

10.26 Evidence of nodal or distant metastases

11.0 PATHOLOGY

The lesion must be an epidermoid carcinoma. In addition to his own microscopic description and diagnosis, the pathologist is requested to grade the tumors as: Low grade (well differentiated), intermediate (moderately differentiated), and high grade (undifferentiated). Slides should be submitted to RTOG Headquarters for submission to the referee pathologist.

12.0 STATISTICAL CONSIDERATIONS AND FORMS

Assuming a 10% three-year survival rate with present treatment methods and a 25% three-year survival rate with fast-neutron radiotherapy, 45 evaluable patients must be enrolled ($p = 0.05$). Assuming 10 patients to be excluded as inevaluable, a sample size of 55 patients will be required. The estimated duration of patient accrual is 2 years.

12.1 Forms to be Submitted - Initial Evaluation Form

12.11 Will be submitted when a patient is placed on study.

12.12 Appropriate diagrams of the primary tumor with accurate measurements of dimensions (supplied by RTOG Headquarters).

12.13 Copy of the pathology report to be appended.

12.14 A pathology slide is to be forwarded to RTOG Headquarters for review by the consultant pathologist.

12.15 Copy of the treatment plan, localization films, and isodose distributions, if done, will be forwarded for permanent filing.

12.2 Treatment Forms will be submitted at the completion of radiotherapy.

12.3 Follow-up Examination Forms will be submitted as specified in Section 10.0.

12.4 Death of Patient Form.

13.0 PATIENT CONSENT

All institutional, National Cancer Institute, state and federal regulations, concerning informed consent will be fulfilled.

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REFERENCES

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4. Pearson, J.G.: The value of radiotherapy in the management of esophageal cancer. Amer. J. Roentgenol., Rad. Ther. and Nucl. Med. 105:500-513, 1969.
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6. Pearson, J.G.: Value of radiation therapy. JAMA 227:181-183, Jan. 14, 1974.
7. Seymour, E.Q. and Pettit, H.S.: An evaluation of long-term survivors treated for cancer of the esophagus with preoperative x-ray therapy. Radiology 106:423, 1973.

0015870

APPENDIX I

STAGING

Esophagus

The following regions are defined and the tumor is assigned to the region in which the bulk of it is situated.

(1) Cervical esophagus

This commences at the pharyngo-esophageal junction and ends at the thoracic inlet, approximately 10 cm from the upper incisor teeth.

(2) Intra-thoracic esophagus (excluding Region 3)
This may be divided into two sites, namely:

a) The upper thoracic portion, extending from the thoracic inlet to the lower border of the sixth thoracic vertebra, approximately 26 cm from the upper incisor teeth.

b) The mid-thoracic portion, extending from the lower border of the sixth thoracic vertebra to the lower border of the eighth thoracic vertebra, approximately 31 cm from the upper incisor teeth.

(3) Lower esophagus

This portion, 10 cm in length, commences at the lower border of the eighth thoracic vertebra and ends at the cardiac orifice, approximately 40 cm from the upper incisor teeth.

The regional lymph nodes are as follows: Cervical esophagus-cervical lymph nodes include the supraclavicular nodes. Intra-thoracic esophagus-the intra-thoracic lymph nodes are included. (The intra-abdominal lymph nodes and the scalene nodes will be considered as distant metastases).

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(American Joint Committee, 1976)

Stage I

T1 N0 M0 T1 NX M0	Tumor in any region of the esophagus that involves 5 cm or less of esophageal length, produces no obstruction, has no extra-esophageal spread, does not involve the entire circumference, and shows no regional lymph node metastases or remote metastases.

Stage II

T1 N1 M0 T1 N2 M0 T2 N0 M0 T2 N1 M0 T2 N2 M0 T2 NX M0	Any tumor of any size of the cervical esophagus that has not extended outside the esophagus, with regional lymph node metastases that are not fixed, and without remote metastases; or a tumor more than 5 cm in size without evidence of extra-esophageal extension, without regional lymph node involvement, or with regional lymph node involvement without fixation, without distant metastases.
	Any intra-thoracic esophageal carcinoma of any size involving either the upper and mid-thoracic region or the lower thoracic region without evidence of extension outside the esophagus, without regional lymph node metastases, without evidence of distant metastases, and which produces obstruction or involves the entire circumference of the esophagus; or any tumor which involves more than 5 cm of esophageal length without evidence of extra-esophageal spread and without regional lymph node metastases.

Stage III

Any T3 Any N3 (cervical esophagus) Any N1, 2, or 3 (thoracic esophagus)*	Any esophageal cancer at any level with: 1. Distant Metastases 2. Extra-esophageal Extension 3. Fixed Lymph Node Metastases
Any M1	Any intra-thoracic esophageal carcinoma, including either the upper and mid-thoracic region or the lower thoracic region with any positive findings in regional lymph nodes.

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*Regional lymph nodes of either thoracic esophageal region cannot be properly assessed preoperatively. Any Stage I or II lesions of the thoracic esophagus which are found to have microscopic evidence of metastases to the regional lymph nodes become Stage III.

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APPENDIX II

R.T.O.G. (KARNOFSKY) PERFORMANCE STATUS

100	Normal; no complaints; no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self; unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospitalization is indicated, although death not imminent.
20	Very sick; hospitalization necessary; active support treatment is necessary.
10	Moribund; fatal process progressing rapidly.
0	Dead.

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