Pub # 5001
Study 77-09

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Int. J. Radiation Oncology Biol. Phys., Vol. 9, pp. 465–473
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0360-3016/83/040465-09$03.00/0
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● *Original Contributions*

RTOG PHASE I STUDY ON FAST NEUTRON TELETHERAPY FOR SQUAMOUS CELL CARCINOMA OF THE ESOPHAGUS

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From August, 1977, through January, 1981, the Radiation Therapy Oncology Group sponsored a Phase I study (RTOG 77-09) on the use of fast neutrons for treating inoperable squamous cell carcinomas of the esophagus. A total of 39 evaluable patients were treated with curative intent using either fast neutrons alone or in combination with low LET irradiation as part of a mixed beam fractionation scheme. Actuarial survival curves are presented for both the "neutrons alone" and the "mixed beam" treatment groups. There was no significant survival difference between these groups of patients. The projected survival at two years is less than 10%, which is comparable with megavoltage photon results for an unselected series of patients. The size of the primary lesion and the initial Karnofsky performance status were found to be the most important prognostic indications for prolonged survival. Sixteen of 39 patients were felt to have achieved local clearance of their tumor at some time during their follow-up with the median time until a local recurrence being 17 months. Treatment related complications and patterns of metastatic spread are discussed. In general, it appeared that the response of large tumors to neutron irradiation resulted in necrosis and fistula formation. In many cases this was accompanied by persistent/recurrent tumor within the high dose radiation volume.

Neutron teletherapy, Esophageal carcinoma.

INTRODUCTION

Although there is a decided variation in the incidence of squamous cell carcinoma of the esophagus from country to country, the results of conventional medical treatment in *unselected* series of patients are uniformly poor. In the United States, carcinoma of the esophagus constitutes 2–3% of all reported malignancies (excluding non-melanoma skin cancer); in 1980, there were ~7600 new cases diagnosed.[17] Generally, the patient presents with an advanced tumor at a time when obstructive symptoms have produced a significant degree of malnutrition or cachexia. This makes it difficult to carry out either radical surgery and/or radical radiation therapy. Moreover, the incidence of metastatic spread to either the regional nodes or beyond is ~60–80% at the time of presentation.[10,15,16]

The best reported results are those of Nakayama *et al.*[14] who quote a 5-year survival rate of 37.5% for 200 patients who completed a three stage surgical procedure combined with preoperative irradiation. Pearson[16] reports 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. However, as ~2000 patients presented with esophageal carcinoma during the period of the study, there was considerable patient selection in this

0016264

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Supported by the National Cancer Institute under core grant CA-23113 and individual facility grants CA-12441, CA-12542, CA-17465, CA-18081, and CA-19720.

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Accepted for publication 23 November 1982.

series. This work does demonstrate that for selected lesions of the upper 2/3 of the esophagus, the prognosis is better with high dose irradiation than with radical surgery because of the associated operative morbidity. Most series[2,4,7,18] of radiation-treated patients show 5-year survivals ~5%. Furthermore, Beatty *et al.*[4] report that 67% of their patients treated with radical photon irradiation developed post irradiation esophageal strictures that were associated with persistent malignancy 75% of the time. With these dismal results, it was natural to investigate the effect of combining chemotherapy with surgery and/or radiation therapy. However, the use of Bleomycin,[6] Bleomycin and Adriamycin,[11] and Vincristine, Bleomycin, and Methotrexate,[13] either alone or combined with megavoltage photon irradiation, have resulted in no significant improvement in overall survival.

Analysis of the patterns of failure indicates that although distant metastases occur in a high percentage of patients,[12] up to 80% of radiation-treated patients will develop recurrent or persistent tumor in the esophagus itself.[4] Since the primary tumors are often necrotic at the time of discovery, they could contain a significant hypoxic cell population which would make them difficult to control with conventional megavoltage photon irradiation even if high doses were used. The lower oxygen enhancement ratio of fast neutron irradiation could thus be of possible benefit for this tumor system.[19] The necrotic tumor mass could also, in principle, contain a large fraction of cells in a G_0 or resting phase and so the reduced ability of noncycling cells to repair potentially lethal damage from neutron irradiation[8] could be of potential benefit. For these reasons a Phase I clinical trial testing the efficacy of fast neutron irradiation—either alone or in combination with low linear energy transfer (LET) radiation as part of a mixed beam treatment schedule—was undertaken by the Radiation Therapy Oncology Group (RTOG 77-09). This paper constitutes the final report on local control rates, overall survival, and treatment morbidity for the patients entered onto this study.

METHODS AND MATERIALS

The study was open from September, 1977 through January, 1981 and accrued a total of 52 patients. Eligible patients had biopsy-proven squamous cell carcinomas of the esophagus that were less than 15 cm in length and had not been previously treated. They were considered ineligible if they had a prior cancer (except non-melanoma of the skin or had been free of disease for more than 8 years prior to documentation of the esophageal carcinoma), had evidence of a fistula tract on esophagram, had clinically or pathologically-positive supraclavicular or celiac nodes, or had distant metastases. Patients placed on the study also had to have a Karnofsky status ≥40 if less than 70 years old or ≥60 if between 70–75 years old. Patients older than 75 years old were automatically excluded. No patient was placed on study who had received prior irradiation to the anticipated treatment area. Informed consent was given by all patients entered on the study. The mandatory initial evaluation consisted of a history and physical examination, Hct, WBC, platelet count, blood chemistry battery including liver function tests, CXR, esophagram, and esophagoscopy and biopsy. A liver scan was required if any of the liver function tests were abnormal.

The study was nonrandomized with one of three treatment arms selected by the neutron therapy facility: (1) neutron radiotherapy given at 2 treatment fractions per week, (2) neutron radiotherapy given at 4 treatment fractions per week, or (3) mixed beam radiotherapy given at 2 neutron and 3 photon treatment fractions per week. These three different treatment methods were allowed in keeping with the somewhat diverse treatment policies and available neutron beam time at the various participating neutron treatment facilities. Patients were placed on the study by calling RTOG headquarters.

The following neutron facilities participated in the study: (1) Mid-Atlantic Neutron Therapy Association (MANTA), (2) Fermi National Acceleration Laboratory (FERMI), (3) the Texas A & M variable energy cyclotron—M.D. Anderson (TAMVEC), (4) the University of Washington in Seattle (SEATTLE), and (5) the Great Lakes Neutron Therapy Association (GLANTA). The neutron beams from these various facilities were all somewhat different in terms of their relative biological effectiveness (RBE). Table 1 summarizes the reactions used to produce the beams at the various facilities and the RBE's used in this particular protocol to scale their respective neutron doses to a photon equivalent dose. In all cases, the gamma ray contaminent was included in the measured neutron dose—i.e. $rad_{n\gamma}$.

For lesions located in the upper two-thirds of the esophagus a radiation dose of 5000 photon rad equivalent in five weeks was to be delivered to the primary, mediastinum, and supraclavicular regions followed by an additional 1000 photon rad equivalent to the primary tumor volume over one additional week. It was permissible to treat the supraclavicular region with photons alone on any of the three treatment arms since it was not possible for some of the treatment facilities to produce a single "T"—shaped field of sufficient length to encompass the entire esophagus and mediastinum. For lesions located in the lower one-third of the esophagus, a radiation dose of

Table 1. Neutron producing reaction and relative biological effectiveness (RBE) for the participating neutron facilities

Neutron facility	Neutron producing reaction	RBE
Manta	35 MeV d → Be	3.2
Fermi	66 MeV p → Be	3.0
Tamvec	50 MeV d → Be	3.1
Seattle	22 MeV d → Be	3.3
Glanta	25 MeV d → Be	3.3

0016265

Table 2. Patient characteristics by treatment

	Treatment							
	Neutrons 2 fractions per week		Neutrons 4 fractions per week		Mixed beam		Total	
	#	%	#	%	#	%	#	%
Sex								
Male	6	100	2	67	23	77	31	80
Female	0	0	1	33	7	23	8	20
Age								
46–60	3	50	2	67	16	53	21	54
61–75	3	50	1	33	14	47	18	46
Karnofsky Status								
40—disabled	0	0	0	0	1	3	1	3
50—needs freq. assistance	0	0	0	0	1	3	1	3
60—needs some assistance	1	17	0	0	2	7	3	8
70—cares for self/can't work	0	0	0	0	5	17	5	13
80—some disease symptoms	3	50	1	33	10	33	14	36
90—minor signs of disease	2	33	2	67	7	23	11	28
100—no signs of disease	0	0	0	0	4	13	4	10
Weight loss								
<10%	5	83	1	33	18	60	24	62
10%–20%	1	17	2	67	8	27	11	28
>20%	0	0	0	0	4	13	4	10
Institution								
Seattle	0	0	0	0	6	20	6	15
Manta	0	0	3	100	3	10	6	15
Fermi	6	100	0	0	15	50	21	54
Tamvec	0	0	0	0	5	17	5	13
Glanta	0	0	0	0	1	3	1	3
Race								
White	4	67	1	33	20	67	25	64
Black	2	33	2	67	10	33	14	36
Location of primary								
Cervical	0	0	0	0	4	13	4	10
Upper intrathoracic	4	67	2	67	10	33	16	41
Mid thoracic	2	33	1	33	12	40	15	39
Lower	0	0	0	0	4	33	4	10
Size of primary								
3–5 cm	1	17	1	33	15	50	17	44
6–8 cm	2	33	2	67	12	40	16	41
9–15 cm	3	50	0	0	3	10	6	15
Differentiation								
Well differentiated	0	0	1	33	3	10	4	10
Moderately differentiated	2	33	0	0	14	47	16	41
Poorly differentiated	2	33	2	67	11	37	15	39
Unknown	2	33	0	0	2	7	4	10
Circumferential tumor								
Yes	0	0	0	0	14	47	14	36
No	6	100	3	100	16	53	25	64
Evidence of obstruction								
Yes	5	83	3	100	22	73	30	77
No	1	17	0	0	8	27	9	23
Extent of dysphagia								
Unrestrictured diet	2	33	0	0	7	23	9	23
Soft foods only	4	67	2	67	17	57	23	59
Liquids only	0	0	1	33	3	10	4	10
Cannot swallow	0	0	0	0	2	7	2	5
Unknown	0	0	0	0	1	3	1	3

0016266

4000 rad equivalent was to be delivered to the primary, mediastinum and epigastric regions over a four-week period followed by an additional 2000 photon rad equivalent boost to the primary tumor volume over two additional weeks. The dose per fraction was the equivalent of 500 rad_γ in the two-fractions per week neutron-only arm, 250 rad_γ in the four-fractions per week neutron-only arm, and 200 rad_γ per fraction in the mixed beam arm. That is, all arms gave the equivalent of 1000 rads per week. In the mixed beam arm, it was permissible to deliver some or all of the low LET component of the radiation dose with high energy electrons at the discretion of the treatment institution. The low LET component of the radiation could be delivered either by the primary neutron facility or by a subsidiary referring institution. Quality control was ensured by reviewing the "port films" and the treatment plans both at the primary neutron facility and at RTOG headquarters.

Patients were seen for follow-up visits every three months for the first two years after treatment and then every 6 months thereafter. At these visits, laboratory parameters, additional treatment (if any), and disease status (primary, regional lymph nodes, and other metastatic involvement) were recorded. Reporting forms were reviewed twice—once by a data manager at RTOG headquarters and once by the study data manager at the RTOG Statistical Center. Several months after patient accrual was terminated, the Statistical Center prepared a summary of the on-study, treatment and follow-up data for each patient. These data were then reviewed by one of us (GEL) who went to each of the participating institutions and compared the summarized data with the patients' actual medical records, charts, radiographic studies, etc. This procedure ensured a uniform set of criteria for the evaluation of study endpoints and perhaps provided a more consistent evaluation procedure than is usually possible with a cooperative trial. Based upon this review, it was determined that of the 52 patients entered on the study, only 39 patients were eligible and were treated in a manner appropriate for analysis. Six patients were declared ineligible (3 exceeded the maximum age limit, 1 had positive celiac nodes at laparotomy, 1 had the wrong histology—adenocarcinoma, and 1 had positive supraclavicular nodes) and seven patients were cancelled (1 died before treatment, 5 did not receive any neutron radiotherapy and in one case, there was a long-term

Table 3. T-N staging system for carcinoma of the esophagus

T-Staging	
T_1	Tumor ≤ 5 cm in length, no obstruction, no circumferential involvement, no extra-esophageal extension
T_2	Tumor > 5 cm in length, tumor of any size that is circumferential or that causes obstruction, no extraesophageal extension
T_3	Tumor of any size with extraesophageal extension
N-Staging	
Cervical esophagus: Regional nodes are cervical and supraclavicular	
N_0	Clinically negative
N_1	Unilateral mobile nodes
N_2	Bilateral mobile nodes
N_3	Fixed nodes
Thoracic esophagus: Regional nodes must be surgically staged	
N_x	Only clinical staging
N_0	No positive nodes at surgery
N_1	Positive nodes at surgery

Table 4. Distribution of T and N stages for the evaluable patients on the study

	Neutrons 2 fractions per week		Neutrons 4 fractions per week		Mixed beam		Total	
	#	%	#	%	#	%	#	%
T-Stage								
T1	1	17	1	33	1	3	3	8
T2	3	50	2	67	21	70	26	67
T3	2	33	0	0	8	27	10	25
N-Stage								
NO	1	17	0	0	11	37	27	69
NX	5	83	3	100	19	63	12	31

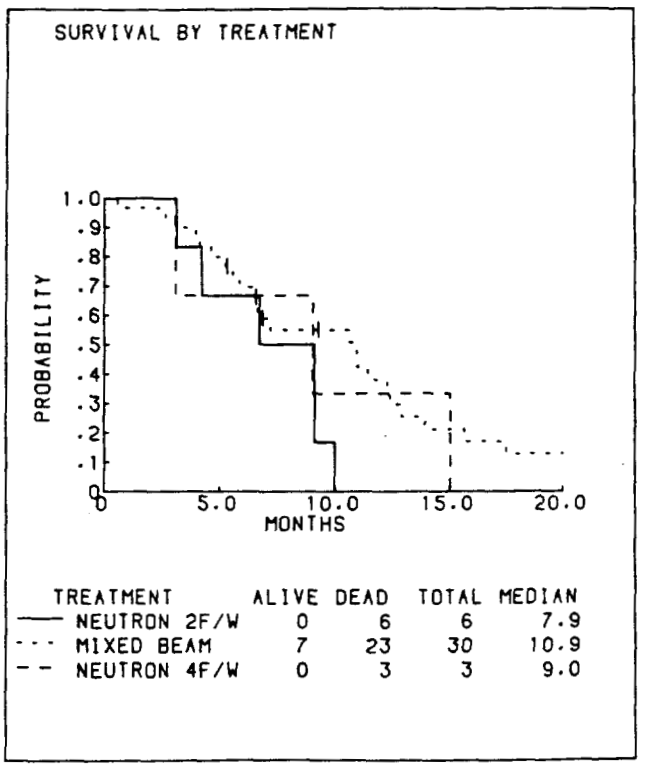

Fig. 1. Actuarial plot of patient survival for each treatment arm of the study. The solid curve represents the group of patients treated with two neutron fractions per week, the dashed curve represents the group of patients treated with four neutron fractions per week, and the dotted curve represents the group of patients treated with the mixed beam schedule.

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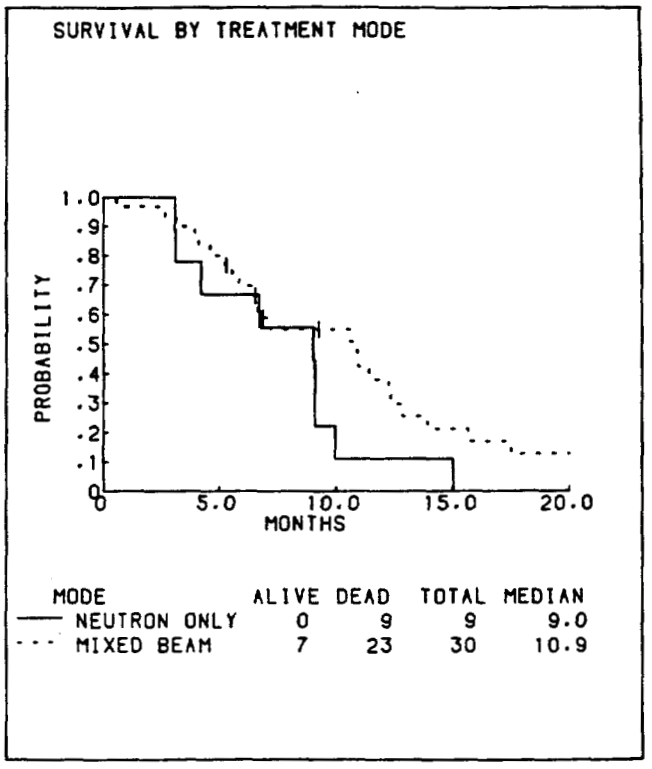

Fig. 2. Actuarial plot of patient survival comparing the "neutron only" group of patients with the mixed beam group of patients. The "neutron only" group consists of a pooled data base of the two and four treatment fractions per week and is shown as the solid curve. The mixed beam group is shown as the dotted curve.

cyclotron malfunction after only one neutron treatment had been delivered).

Table 2 summarizes the characteristics of the 39 patients at the time of entry on the study. Thirty patients were treated with the mixed beam schedule and nine patients were treated with neutrons alone. The lesions were staged according to the most recent recommendations of the American Joint Committee for Cancer Staging and End Result Reporting,[1] which is shown in Table 3. The T-N staging distribution of the evaluable patients is shown in Table 4.

RESULTS

The major endpoints to be determined by the study were survival, complication rates, and tolerance of the surrounding normal tissue to neutron or mixed beam irradiation. Review of the patient treatment records showed that of the 39 evaluable patients, 10 had been treated strictly according to the protocol guidelines, 20 were judged in "minor deviation", and 9 were judged in "major deviation." Of the major deviations, 1 occurred because of an overextended time course (because of a bowel infarction during therapy), 4 had inadequate radiation fields (typically inadequate treatment of the mediastinum and/or supraclavicular region), 3 had violations both in the time course and in the specified field coverage, and 1 patient died before radiation therapy could be completed. To ensure against introducing a bias into the study, all of these patients are included in the following analysis. The time axes of all plots in this section are measured from the data radiation treatments were initiated.

Figure 1 shows a Kaplan-Meier[9] actuarial plot of patient survival as a function of the method of treatment. Note that the majority of patients were treated on the mixed beam arm and that only a small number of patients were treated on either "neutron only" arm. Based upon the logrank test, there is no statistically significant difference among the three curves.

Figure 2 shows a similar plot of patient survival with the "neutron only" patients pooled together. Median survival was 10.9 months for the mixed beam group and 9.0 months for the "neutron only" group. Even with this pooling of patients, the numbers are too small for the difference between the curves to be statistically significant using the logrank test. The projected one-year survival rates were 11% for the "neutron only" group and 38% for the mixed beam group.

Since this was a nonrandomized Phase I study, we felt it was important to try and isolate prognostic variables which could be useful in designing future studies. A

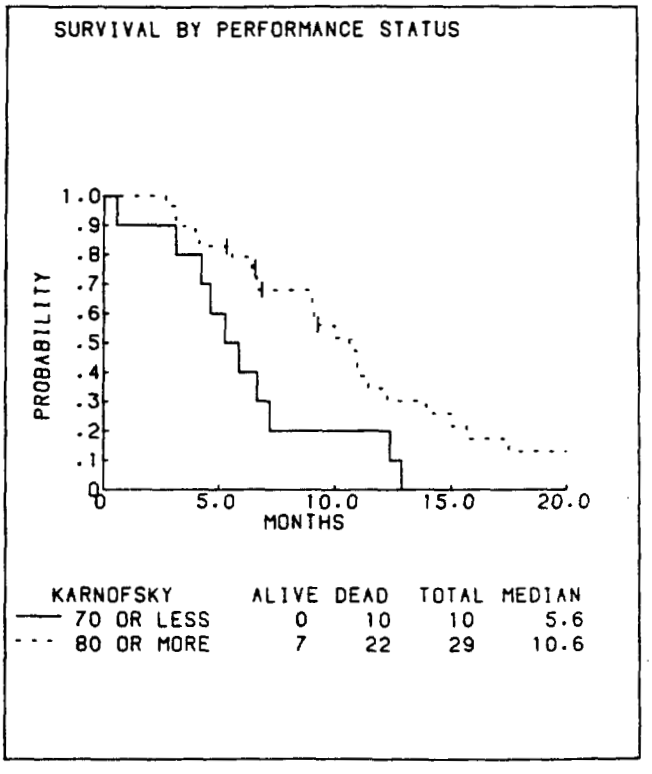

Fig. 3. Actuarial plot of patient survival according to Karnofsky performance status at time of entry on the study. The solid curve represents the group of patients with Karnofsky performance status ≤ 70 and the dotted curve represents the group of patients with Karnofsky performance status ≥ 80. The "neutron only" and mixed beam patients are combined in this plot.

0016268

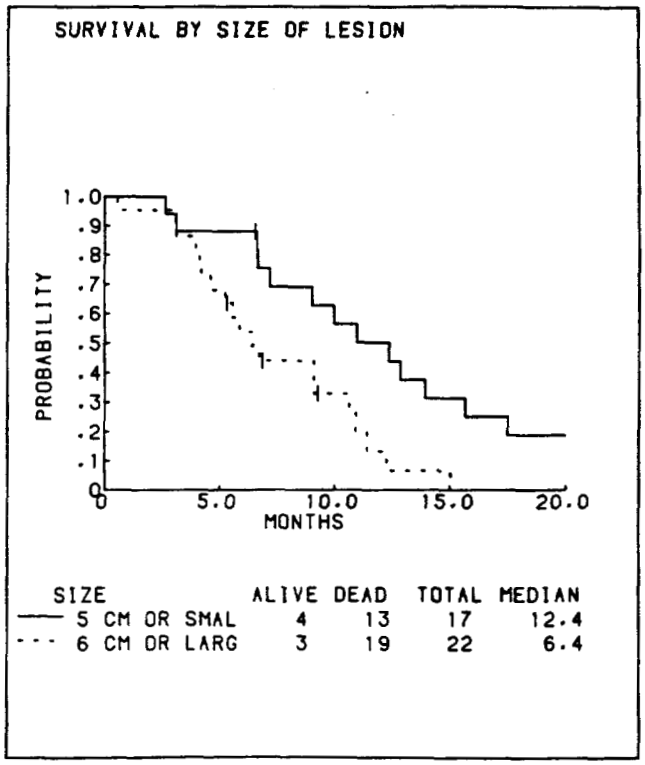

Fig. 4. Actuarial plot of patient survival according to length of esophagus involved with tumor at the time of entry on the study. The solid curve represents the group of patients having a lesion ≤ 5 cm in extent and the dotted curve represents the group of patients having a lesion ≥ 6 cm in extent. The "neutron only" and mixed beam patients are combined in this plot.

stepwise Cox model[3,5] was used to select the relevant parameters. A model was fit and variables were added one at a time until no additional variable was significant at the $p = 0.05$ level. Two variables were found to be significant: (1) Karnofsky performance status (70 and below vs. 80 and above) and (2) size of primary lesion (5 cm or smaller vs. 6 cm or larger). A plot of survival according to Karnofsky performance status is shown in Figure 3. The median survival is almost a factor of 2 larger for the subgroup of patients with Karnofsky performance status ≥80. A plot of survival according to the length of the lesion is shown in Figure 4. Again, the median survival is almost a factor of 2 larger for the subgroup of patients having a lesion ≤5 cm in size.

A total of 16 patients seemed to have had clearance of their primary tumor at some time during their follow-up. Three of these were in the subgroup treated with 2 neutron fractions per week, 1 was in the subgroup treated with 4 neutron fractions per week, and 12 were in the subgroup treated with the mixed beam schedule. Clearance was determined by either having no evidence of disease on an esophagram (i.e., a smooth mucosa without irregularities) or an endoscopic examination with a negative biopsy. Clearly this is a difficult tumor site to assess and it is not too surprising that 7/16 (44%) of these patients ultimately exhibited a proven failure at the primary site.

Figure 5 shows an actuarial plot of the disease-free interval for the 16 patients who exhibited clearance of their tumor. Here "disease-free' refers only to the status of the primary tumor. Patients who died with no evidence of tumor at the primary site were considered censored observations (as opposed to failures) at the time of their death. All of the "tick marks" on the neutron curve and all but one on the mixed beam curve represent these patients. At the time of this analysis, only three patients are alive and free of disease at respective follow-up times of 36, 22 and 9 months.

Treatment reactions were classified on a scale of 1–5 as "mild," "moderate," "severe," "life threatening," or "fatal." Very few acute reactions were reported. In the mixed beam arm, there was one severe esophageal reaction, one fistula classified as mild, and one mild lung reaction. In the four-fractions per week neutron arm, there was one case of severe nausea and vomiting and three cases of mild skin reactions. No acute reactions were reported in the two-fractions per week neutron arm.

The frequency of late complications was much higher. Approximately 50% of the treated patients had one or more serious late effects—graded "severe" or worse. Most of the serious late effects were local in nature, i.e., fistula or other esophageal complications. However, there were also several lung reactions—i.e., radiation pneumo-

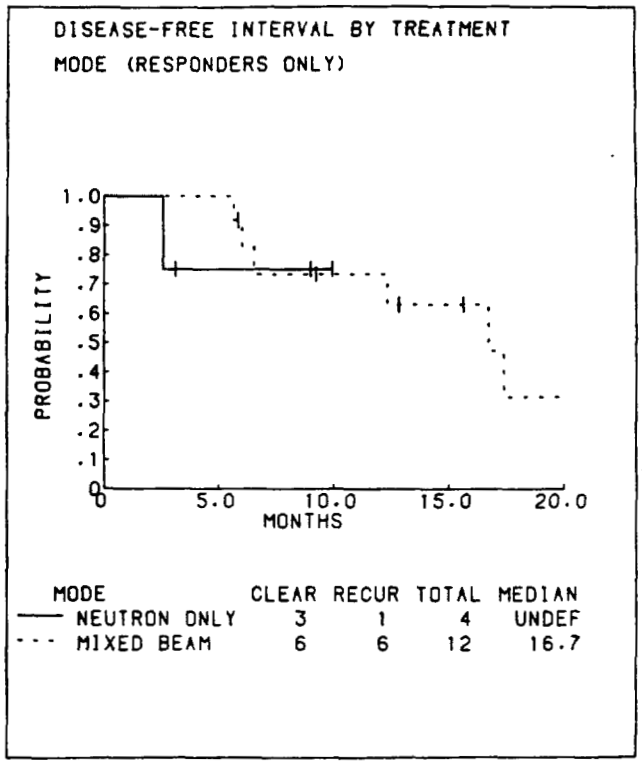

Fig. 5. Actuarial plot of tumor control at the primary site as a function of time after initiating treatment for the 16 patients who exhibited a clearance of their disease. The "neutron only" group is a pooled group of the two and four treatment fractions per week arms and is shown as the solid curve. The mixed beam group is shown as the dotted curve.

0016269

Table 5. Summary of major endpoints for evaluable patients

Patient no.	Survival (days)*	Duration of local clearance (days)†	Site(s) of distant failure	Complications
Neutron 2 fractions per week				
36	299	299+	—	Life threatening fistula
4	273	77	Gastric node	—
46	273	0	Second primary (colon)	Life threatening fistula
26	202	0	—	Moderate skin, mild larynx
2	127	0	—	—
38	94	94+	Left adrenal gland	Life threatening-lung, heart, arteries
Neutron 4 fractions per week				
10	451	0	—	Acute nausea, vomiting, mild skin
8	271	271+	Lung	Life threatening fistula, severe esophagus, mild skin
24	93	0	—	Mild skin
Mixed beam				
11	1065+	1065+	—	Severe lung
40	651+	651+	—	—
44	606+	502	Lung	Moderate esophagus
37	525	522	—	Severe esophagus
22	470	470+	—	Severe lung, moderate heart, arteries, mild skin
45	418	0	Lungs, pericardium, abdominal para-aortic nodes	Fatal fistula
9	386	386+	—	Severe larynx
31	371	371	—	Severe lung, moderate esophagus, skin
14	368	0	Bone (femur and ribs)	Severe esophagus
13	343	0	Lung, thyroid, parathyroid, fundus of gallbladder, lymph nodes of diaphragm, pericardial lymphatics	—
23	329	0	Liver and supraclavicular nodes	Mild lung, larynx life threatening fistula
25	328	0	—	Severe esophagus
16	319	181	Lung	Life threatening esophagus
48	278+	278+	—	—
50	216	0	—	Severe esophagus
49	206+	0	—	Severe esophagus
28	200	170	—	Moderate lung
3	199	0	Mediastinal nodes, subcutaneous nodules	Severe esophagus
51	197+	197	Second primary (squamous cell carcinoma of anus), liver, celiac nodes	—
20	193	0	Cervical, scalene nodes	Life threatening fistula, severe esophagus
12	176	176+	Lung	—
6	167	0	—	Mild fistula
52	160+	0	—	Life threatening esophagus
19	158	0	Bone, liver, paraaortic nodes	—
27	139	0	—	—
29	124	0	Bone (skull), subcutaneous lesions	Mild skin
21	119	0	—	—
33	94	0	Lungs, right adrenal gland, paratracheal nodes	—
32	80	0	Lung	—
35	17	0	—	—

*"+" indicates that the patient was last reported alive.
"0" indicates persistent primary disease; "+" indicates that patient was last reported locally free of disease.

0016210

nitis. There was one instance of a radiation pericarditis that occurred on the two-fractions per week neutron arm. A more detailed analysis of the late morbidity and discussion of the neutron tolerance doses of various normal tissues will be presented in a future paper.

Table 5 summarizes the major endpoints for the evaluable patients including survival, duration of local control, sites of distant metastases, and treatment complications. Note that in patients where no local control of tumor was achieved, it is a moot point to assign a local complication such as a fistula to the method of treatment, since it equally well could be a natural result of tumor growth. However, the treatment may have hastened the development of this complication and so we have classified it as a treatment related effect. Within each treatment group the patients are ordered according to duration of survival.

DISCUSSION

We have reported the results of a Phase I study (RTOG 77-09) testing the efficacy of fast neutron radiotherapy for inoperable squamous cell carcinomas of the esophagus. Three different schemes were allowed: 1) neutrons 2 fractions per week; 2) neutrons 4 fractions per week; or 3) neutrons 2 fractions per week and low LET irradiation 3 fractions per week (mixed beam schedule). In all cases, the radiation dose delivered to the primary tumor volume was 6000 rad equivalent as detailed earlier in the paper. The numbers of patients in each arm of the study were small, but there was no obvious difference in either tumor control of morbidity among the different arms. The projected survival at two years is certainly *less than 10%*. This survival rate is essentially the same as that reported by several groups using megavoltage photon irradiation to treat *unselected* series of patients. Wara *et al.*[18] describe a series of 129 patients with squamous cell carcinomas of the esophagus treated primarily with radiation therapy. Only 103 completed their planned course of therapy; this subset of patients had a median survival of 7.0 months and a survival rate at 2 years of 8%. Elkon *et al.*[7] describe a series of 50 patients treated with curative intent using megavoltage photons; only one of these survived 3 years. At two years, their surviving fraction was about 15%. Beatty *et al.*[4] describe a series of 176 patients treated radically with surgical resection and/or radiation. Even though some preselection probably went into this series, their 2-year survival rate was only about 20%.

Separating out the question of local control from overall survival, 16/39 (41%) of our patients were felt to have had local clearance of their tumor at some time during their follow-up. However, this tumor site is exceedingly difficult to evaluate and 7/16 (44%) of these were ultimately proven to have either a recurrence or a persistence of their primary tumor. Even though several endoscopic examinations and biopsies returned only necrotic tissue without evidence of tumor cells, subsequent examinations often would show evidence for tumor. Hence, the 9/39 (23%) patients who either died NED or who are still alive and apparently NED, likely represent an overestimate of the fraction of patients who truly had their primary tumor controlled. Autopsies were performed on 13 patients and in 9 cases, there was positive tumor at the primary site in conjunction with necrosis and denudation of the esophageal mucosa. In the other 4 patients, fistulas were found without any evidence for residual tumor. It should be noted that the majority of our patients had quite advanced tumors which would be more prone to fistula formation. In addition, tumor infiltration under normal esophageal mucosa could account for some of the observed mucosal denudation.

However, in spite of compelling radiobiological arguments for the use of high LET neutron irradiation for squamous cell carcinomas of the esophagus, this study showed no obvious benefits compared with the results of megavoltage photon irradiation for similar patient groups. Since approximately 50% of our patients had significant morbidity related at least in part to treatment, simply escalating the radiation dose is not the answer. Clinical trials are underway with heavy ions and pi-mesons, which offer the theoretical advantage of combining high LET irradiation with more precisely defined dose localization. This may well reduce the treatment morbidity while allowing for even higher radiation doses to be delivered to the primary tumor volume. However, for advanced tumors, the response to radiotherapy often is necrosis and fistula formation regardless of the radiation modality used. Early detection of esophageal tumors will likely continue to be the most important factor in improving patient survival. Future follow-up studies should probably be limited to patients with fairly early disease.

0016271

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0016272