REPOSITORY Fermi Lab Neutron Therapy Facility
COLLECTION Radiation Therapy Oncology Group (RTOG) Published Manuscripts
BOX No. Binder - collected & copied from shelf
FOLDER Neutron Therapy Facility Physicians Room XGW-112

Am J Clin Oncol (CCT) 9(3): 233–243, 1986.

© 1986 Raven Press, New York

702236

Fast Neutron and Mixed Beam Radiotherapy for Inoperable Non-Small Cell Carcinoma of the Lung

File Copy
Pub. # ~~7777~~ 5011 3003
Study # 7907
Site: Lung
Modality: Part
Status: pub

Results of an RTOG Randomized Study

*G. E. Laramore, Ph.D., M.D., †M. Bauer, Ph.D., *T. W. Griffin, M.D., ‡F. J. Thomas, M.D., §‖F. R. Hendrickson, M.D., ¶M. H. Maor, M.D., *B. R. Griffin, M.D., ‡J. P. Saxton, M.D., and †L. W. Davis, M.D.

From July 1979 through March 1984 the Radiation Therapy Oncology Group conducted a randomized study comparing fast neutron radiotherapy versus mixed beam (neutron/photon) radiotherapy versus conventional radiotherapy for patients with non-small cell carcinoma of the lung. Patients were either medically or technically inoperable. One hundred two evaluable patients were placed on the study. The radiation doses were approximately 60 Gy-equivalent on each arm. Patients were stratified according to size of primary, histology, Karnofsky performance status, and age distribution. Overall local response rates as measured by serial radiographs were the same on the three arms, and an actuarial analysis showed no significant differences in either median or long-term survival. However, for the subgroup of patients exhibiting a complete or partial tumor response at 6 months there was a suggestion of improved 3-year survival on the two experimental arms (mixed beam, 37%; neutrons, 25%; photons, 12%). The p value for the difference between the mixed beam and photon curves is 0.14 (two-sided test). The incidence of major complications was higher on the neutron and mixed beam arms. These complications included four cases of myelitis which are analyzed in detail. The results are placed in the context of other published work on the use of neutrons in the treatment of lung cancer.

From the *Department of Radiation Oncology, University of Washington Hospital, Seattle, Washington, †Radiation Therapy Oncology Group, 925 Chestnut Street, Philadelphia, Pennsylvania, ‡Department of Radiation Therapy, Cleveland Clinic Foundation, Cleveland, Ohio, §Neutron Therapy Department, Fermi National Accelerator Laboratory, Batavia, Illinois, ‖Department of Therapeutic Radiology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois, and ¶Department of Radiation Therapy, M. D. Anderson Hospital, Houston, Texas, U.S.A.

Address correspondence and reprint requests to G. E. Laramore, Ph.D., M.D., Department of Radiation Oncology, University of Washington Hospital, RC-08, Seattle, WA 98195, U.S.A.

Lung cancer is now the leading cause of cancer-related deaths for both men and women in the United States. The American Cancer Society estimates that in 1985 there will be approximately 144,000 new cases and 125,600 deaths due to this disease (28). Although the numbers from different series vary somewhat, approximately 25% of cases will be of the small cell variety for which chemotherapy with or without adjuvant radiotherapy is the current treatment of choice, and approximately 75% will be of the non-small cell variety which is the subtype of interest in this paper. While there is no doubt that surgery is the primary treatment of choice for early stage, operable, non-small cell lung cancer, the majority of patients have disease that is either disseminated or too advanced locally for resection at the time of presentation. While it is clearly recognized that this disease has a propensity to distant spread, the Radiation Therapy Oncology Group (RTOG) has demonstrated that high-dose conventional radiotherapy can be effective in achieving control of disease within the thorax, and this can have a favorable impact on long-term (not median) survival (21,22).

The study the group performed (21,22) was randomized in nature and compared four photon dose fractionation schedules: (a) 40 Gy given in a "split course" fashion, (b) 40 Gy given continuously over 4 weeks, (c) 50 Gy given continuously over 5 weeks, and (d) 60 Gy given continuously over 6 weeks. Patients who received the 40 Gy dose had response rates (complete and partial) of 46% for the split course and 51% for the continuous course. The respective 2-year survival rates were 10 and 11%. Patients treated with the

0016292

higher doses of 50 and 60 Gy had respective response rates of 66 and 61% with a 2-year survival rate of 18% on both arms. The site of first failure was intrathoracic in 51% of patients receiving 40 Gy, 42% of patients receiving 50 Gy, and 35% of patients receiving 60 Gy. While these differences relating to local control were statistically significant in favor of the higher radiation doses (e.g., 40 Gy vs. 50 + 60 Gy), there was no significant difference in median survival, which ranged from 37 weeks for the 40 Gy split course treatment to 47 weeks for the 60 Gy continuous course treatment. Hence, one is led to note two important points: (a) higher doses of radiation can improve local control within the thorax, and (b) in evaluating the effect of a local form of therapy it is important to look at "long-term" survival rather than median survival which is dominated by distant failures. Simply escalating the radiation dose still further without modifying either the field geometry or the type of radiation used is not the answer since the incidence of complications graded as "severe" or greater approximately doubled in going from 50 to 60 Gy (22). While trying to improve local control might seem to be a "low-yield" approach to the treatment of inoperable lung cancer, it must be recognized that the magnitude of the problem is such that simply increasing the long-term survival by approximately 10% would have the same impact in terms of the number of lives saved as totally eliminating deaths from some of the less common tumors such as bladder cancer or esophageal cancer (28).

Fast neutron radiotherapy is currently under active clinical investigation for many different tumor systems. This paper reports the first randomized study (RTOG 79–07) testing the efficacy of this type of radiation for non-small cell lung cancer. The interest in this "new" radiation modality relates to how its radiobiological properties differ from those of megavoltage photons used in conventional radiotherapy (9,32). Fast neutrons interact directly with the atomic nuclei to produce massive, charged particles that create 10–100 more ionizations per unit path length than do the secondary electrons produced by high energy photons. It is this greater energy deposition along the secondary particle path that gives rise to the important radiobiological properties of fast neutrons.

In general, one can think of two classes of radiobiological damage mechanisms—"indirect" and "direct" (9). The indirect mechanism is mediated by free radicals that are produced in the cellular cytoplasm and then diffuse to the DNA or other key target areas and create damage. This is the primary mechanism by which low linear energy transfer (LET) photon or electron radiation kills cells. It is most effective when the cells are well oxygenated which gives rise to long free radical lifetimes. The oxygen also acts to stabilize the free radical damage. With increasing LET there is a higher probability that the ionization products interact directly with the DNA or other key target molecules. Thus, high LET radiation is better able to kill hypoxic cells. For fast neutrons in the energy range used clinically, the oxygen enhancement ratio is approximately 1.6 compared with 2.5–3.0 for conventional photon radiation. This could be important for large tumors where there are often areas of necrosis surrounded by cells in a hypoxic state. Such a situation may occur for lung cancers which often exhibit cavitary areas due to tumor necrosis. Tumor reoxygenation during a protracted course of radiotherapy can in principle overcome this problem but the situation in clinical practice is variable. Furthermore, the type of radiation damage caused by neutron radiation is less readily repaired by tumor cells. There are at least two aspects to this: (a) a reduced ability to repair sublethal damage, which is manifested by a reduction of the shoulders on cell survival curves (9,32) and (b) a reduced ability to repair potentially lethal damage (10), which could be important for cells in a non-cycling or G_0 phase. Finally, there is less variation in radiosensitivity across the cell cycle than with conventional photon irradiation (8). While these effects are well documented in the laboratory, their importance for any given tumor system can be determined only through clinical trials.

The present trial was ambitious in that it had two experimental arms as well as a standard control arm. One experimental arm consisted of neutron radiation alone and the other was a "mixed beam" arm which consisted of giving two neutron treatments and three photon treatments per week in doses of approximately equal biological effect. This paper is a final report on the results of this study using local control and survival as major endpoints. With any new modality it is important to document the toxicity to normal tissues, and so a special section on treatment-related morbidity is included. There were several toxicity problems associated with delivering the neutron radiation which were in part due to the rather primitive treatment facilities used in the trials but were also in part due to the unique radiobiological properties of the neutron beams. The present work will be placed in the context of other reported neutron treatment results for lung cancer and the implications for future studies discussed.

MATERIALS AND METHODS

This study was open from July 1979 through March 1984 and accrued a total of 113 patients. Initially it was intended to accrue 240 evaluable patients, but when some of the new, high-energy neutron treatment

0016293

facilities became operational, it was decided to close almost all of the existing studies that utilized the neutron generators based at physics facilities in order to keep the two patient groups separate. A second problem was that the study reported herein did not allow for *planned* chemotherapy as part of the treatment, and advances in this modality made it difficult to accrue patients who were not going to receive chemotherapy as part of their overall plan of medical management. Of the 113 patients, two had their treatment cancelled and nine were discovered to be ineligible (five with pleural effusions, two with small cell histology, one with a pancreatic primary, and one with an age greater than 80 years). This paper reports the results of treatment on the remaining 102 patients who were truly protocol eligible and on whom there are sufficient data available for analysis.

To be eligible for the study, patients had to have histologically proven non-small cell carcinoma of the lung (squamous, adeno, or large cell undifferentiated). A class V smear of the sputum for one of these histologies was acceptable in lieu of a positive biopsy. The patients could not have had prior radiation therapy to the tissue volume to be treated. There could be no evidence of distant metastases (although positive supraclavicular nodes were acceptable) and no major resection of the primary or involved nodes. The tumor volume had to be measurable in at least two dimensions on chest x-ray examination, and there could be no pleural effusion present at the time of entry onto the study. Patients also had to be <80 years old and have a Karnofsky performance status > 50. Patients were not placed on the study who had such severe underlying lung disease that they were judged not capable of tolerating the expected loss of pulmonary function with definitive radiation therapy. There could be no prior, planned, or anticipated chemotherapy although it was allowed after a documented treatment failure. Informed consent was given by all patients entered onto the study.

The mandatory pretreatment evaluation consisted of a history and physical examination, complete blood count, blood chemistry studies including liver function tests, chest x-ray films (PA and lateral), and a bone scan. A liver scan was required if any of the liver function tests were abnormal, and a radionucleotide or computed tomographic (CT) scan of the brain was required if there was any clinical suggestion of central nervous system metastases. Although not required by the protocol, the majority of patients also had CT scans of the thorax both for further evaluation of their tumor and for radiation therapy treatment planning.

Patients were staged according to the RTOG modification of the American Joint Committee for Cancer Staging and End Results Reporting system which is given in abbreviated form in Table 1. Patients had to be either technically or medically inoperable to be entered onto the study. Patients were registered and randomized by calling RTOG headquarters. The randomization was stratified according to tumor histology, size of primary tumor (0–3, >3–6, or >6 cm), and the neutron treatment facility. The following neutron treatment facilities participated in the study: the University of Washington in Seattle, WA (SEATTLE); the Great Lakes Neutron Therapy Association (GLANTA) in Cleveland, OH; the Texas A & M variable energy cyclotron facility in College Station, TX (TAMVEC) operated by M. D. Anderson Hospital; and The Fermi National Accelerator Laboratory (FERMI) in Batavia, IL. The neutron beams from these facilities were all somewhat different in terms of their relative biological effectiveness (RBE) compared with megavoltage photon irradiation. Table 2 summarizes the reactions used to produce the various neutron beams and the RBEs used in this particular protocol to scale their neutron doses with respect to each other and to convert the doses to an approximate "photon Gy equivalent." In

TABLE 1. *TMN staging system used in this and other RTOG lung cancer studies*[a]

T stage	
T_0	No evidence of primary tumor.
T_1	Tumor less than 3.0 cm in greatest diameter, surrounded by lung or visceral pleura and with no invasion proximal to a lobar bronchus.
T_2	Tumor greater than 3.0 cm in greatest diameter that is located within the pulmonary parenchyma or any size tumor extending to the hilum at bronchoscopy. Tumor not within 2 cm of the carina. Any associated atelectasis must involve less than an entire lung, and there can be no pleural effusion.
T_3	A tumor that is extrapulmonary but localized intrathoracically. It includes tumors that invade through the visceral pleura, cancers within 2 cm of the carina, or lesions with a pleural effusion having a negative cytology.
T_4	Any tumor involving the chest wall, the great vessels, the heart or esophagus. Superior vena cava obstruction with any size lesion. Pleural effusion with positive cytology.
N stage	
N_0	No nodal involvement.
N_1	Involvement of the hilar or peribronchial nodes.
N_2	Involvement of the mediastinal nodes.
N_3	Involvement of the supraclavicular nodes or scalene nodes.

[a] This is a slightly modified version of the staging system recommended by the American Joint Committee for Cancer Staging and End Results Reporting.

0016294

TABLE 2. *Participating neutron treatment facilities, reactions used to produce the neutron beams, and RBE factors used to approximately scale the neutron doses with respect to each other and to equivalent photon doses*

Facility*	Reaction	RBE
SEATTLE	22 MeV d->Be	3.3
GLANTA	25 MeV d->Be	3.3
TAMVEC	50 MeV d->Be	3.1
FERMI	66 MeV p->Be	3.0

RBE, relative biological effectiveness.
* See text for full identification of each facility.

all cases the gamma ray contaminant is included in the measured neutron dose, i.e., $Gy_{n\gamma}$.

Patients were randomized to receive one of three treatment arms. The control arm consisted of 60 Gy in 30 fractions over 6–7 weeks, which corresponded to the arm giving the best local control in a previous RTOG randomized study (21,22). One experimental arm consisted of neutron radiation alone to a dose of 18 $Gy_{n\gamma}$ (SEATTLE dose) in 12–24 fractions over 6–7 weeks. The variation in number of fractions was allowed both because of limitations on the available treatment time at some of the facilities and also because the radiobiological properties of fast neutrons would argue that number of fractions was not an important treatment parameter compared with total dose and overall treatment time. The other experimental arm utilized "mixed beam" irradiation which consisted of two neutron treatments and three photon treatments per week in daily doses of approximately equal biological effectiveness to a dose of 60 Gy–equivalent using the RBEs specified in Table 2. This arm was included because some laboratory data (19,25) suggested an enhanced therapeutic ratio for this form of treatment over neutrons alone. Also, it was thought that given the poorly penetrating beams from the SEATTLE and GLANTA facilities, this form of treatment might offer some of the benefits of neutron irradiation without the anticipated side effects. This study is the first direct randomized comparison of neutrons alone versus mixed beam irradiation in a clinical trial.

Table 3 shows the pretreatment characteristics for the evaluable patients on each arm of the study. There was a somewhat larger number of advanced (T_3 and T_4) lesions on the neutron arm as well as more advanced nodal disease (N_2 and N_3), but these differences were not statistically significant.

Shrinking field techniques or judicious placement of field blocks were used to simultaneously deliver the specified tumor dose and to keep the spinal cord dose to the limits specified in the protocol. For the photon arm this was 45 Gy, for the neutron arm 12 $Gy_{n\gamma}$ (SEATTLE dose), and for the mixed beam arm 45 Gy–equivalent using the RBE factors specified in Table 2. Tumor doses were calculated at midplane without tissue inhomogeneity corrections for (AP-PA) fields, but lung transmission correction factors were utilized when lateral or oblique boost fields were used. The dose across the target volume could not vary by more than ±10%, and the daily fraction size was 2.0 Gy ± 10% photon or 0.6 $Gy_{n\gamma}$ ± 10% (SEATTLE) for the neutron dose. The effective energy of any photon beams used in the study had to be greater than 1 MeV, and high energy electrons were not allowed. Each port was treated daily. On the mixed beam and neutron arms it was permissible to treat the supraclavicular regions with photons *provided* that no gross disease was present. If gross disease was present, then the region had to be treated with the modality specified by the randomization arm.

The neutron facilities all utilized a fixed, horizontal beam, and so patients received their neutron treatments in a sitting or a standing position as far as the AP-PA fields were concerned. The lateral fields were generally treated in the same manner, but occasionally the patient was supine. Fixed collimators with external iron or tungsten blocks were used to shape the fields. The photon fields were all treated with the patient in the usual supine position.

Simulation films for treatment planning purposes were required as were computer isodose calculations for the central axis for both the initial and any boost fields. These were submitted to RTOG headquarters for central review. The specific design of the treatment portals was left to the discretion of the radiotherapist provided that the following criteria were met. The target volume for the lung primary had to include the radiographically visible tumor plus a 2 cm margin. For extensive lesions complicated by atelectasis or pneumonitis, the entire lung could be treated. The target volume for the lymph nodes had to include the superior mediastinum (above the carina), the ipsilateral hilum, and the inferior mediastinum (to at least 5 cm below the carina). For lower lobe lesions the inferior mediastinum had to be treated to the level of the diaphragm. The supraclavicular region had to be treated for either upper lobe primaries or if there were positive nodes in the upper mediastinum. Based upon previous RTOG studies (22), it was recognized that it was important to treat the contralateral hilum, but this could not always be accomplished without treating an unacceptable amount of normal lung (given the rather primitive field shaping techniques available at the neutron facilities). Treating the contralateral hilum was thus "encouraged" but left to the discretion of the ra-

0016295

TABLE 3. *Distribution of patient and tumor characteristics by treatment option.*

Characteristic	Photons n	Photons %	Neutrons n	Neutrons %	Mixed beam n	Mixed beam %
Histology						
Squamous cell	18	46.2	16	55.2	14	41.2
Adenocarcinoma	8	20.5	5	17.2	7	20.6
Large cell	13	33.3	8	27.6	13	38.2
Size of primary						
0–3 cm	6	15.4	2	6.9	4	11.8
>3–6 cm	19	48.7	12	41.4	16	47.1
>6 cm	14	35.9	15	51.7	14	41.2
Karnofsky status						
<80	5	12.8	5	17.2	8	23.5
80	10	25.6	9	31.0	13	38.2
90	14	35.9	12	41.4	8	23.5
100	10	25.6	3	10.3	5	14.7
T-stage						
T_0	0	0.0	0	0.0	1	2.9
T_1	7	17.9	1	3.4	2	5.9
T_2	14	35.9	9	31.0	17	50.0
T_3	11	28.2	11	37.9	9	26.5
T_4	7	17.9	8	27.6	5	14.7
N-stage						
N_0	14	35.9	10	34.5	9	26.5
N_1	10	25.6	2	6.9	10	29.4
N_2	14	35.9	14	48.3	14	41.2
N_3	1	2.6	3	10.3	1	2.9
Disease stage						
I	4	10.3	1	3.4	1	2.9
II	10	25.6	5	17.2	13	38.2
III	17	43.6	13	44.8	14	41.2
IV	8	20.5	10	34.5	6	17.6
Sex						
Male	31	79.5	23	79.3	30	88.2
Female	8	20.5	6	20.7	4	11.8
Age						
Mean	59 yr		63 yr		62 yr	
<50	9	23.1	3	10.3	5	14.7
50–70	26	66.7	22	75.9	21	61.8
>70	4	10.3	4	13.8	8	23.5

diotherapist. It is safe to assume that this was carried out more frequently for the photon fields than for the neutron fields.

Patients were followed every 2 months following completion of treatment for the first year, every 4 months for the second year, every 6 months for the third year, and annually thereafter. Chest x-ray films were required at each follow-up and blood chemistry studies were required every 4 months during the first year and at each follow-up visit thereafter. Pulmonary function tests were optional as were CT scans for follow-up evaluations of the tumor response. Bronchoscopy and/or biopsies were used to establish local recurrence or distant failure whenever possible.

Prior to analyzing this study, two of us (T.W.G. and G.E.L.) reviewed the beam films, isodose calculations, and treatment records for all of the patients on this study. Based upon this review, it was felt that 75 patients were treated within strict protocol guidelines, nine patients were treated with minor deviations from the protocol guidelines, 10 patients were treated with major deviations from the protocol guidelines, (nine due to too low radiation doses either because of neutron generator malfunction or having the treatment stopped because of a rapidly deteriorating condition), and six patients died during treatment. Treatment records were incomplete on two additional patients, and adherence to protocol could not be evaluated. To avoid problems with inadvertent bias due to patient exclusion, the data analysis will be carried out for the entire group of 102

0016296

patients. The impact of adherence to protocol on local/regional control and survival will be the subject of another manuscript. At the time of this analysis the average follow-up time (measured with regard to entry on the study) was 40 months.

Survival and local control rates are analyzed using the Kaplan-Meir (13) method with times being measured from the initiation of therapy. A subanalysis of the survival of patients who were treatment responders at 6 months is performed and those patients categorized according to tumor response prior to that time (2). Differences between survival curves are compared using the chi-square (log rank) test with two-sided alternatives (17,23).

TREATMENT RESULTS

The major goals of this study were to compare the methods of treatment in the three arms by evaluating the tumor response rate and survival. The evaluation of treatment related toxicity was a secondary endpoint, but because of its importance in future protocol design, a separate section of the manuscript will be devoted to this topic.

The response of the tumor was determined by serial chest roentgenograms and/or CT scans of the thorax. A complete response (CR) was defined as the disappearance of all previously measurable tumor. A partial response was defined as the reduction by at least 50% of the product of the largest perpendicular diameters of the primary lesion *and* any other indicator lesions in the treatment volume. In an attempt to avoid problems with radiation fibrosis, the *maximum* tumor response was evaluated after completing therapy. Once radiation fibrosis had developed, one could evaluate progression but generally could not otherwise determine the significance of what was occurring in the treatment volume. The maximum complete and partial response rates for the three arms of the study are shown in Table 4. Although the photon arm appeared to show the highest CR rate, this may have been due to the increased fibrosis that occurred on the two experimental arms. In spite of our best efforts to distinguish this

TABLE 4. *Maximum complete and partial response rates for the three study arms*

	Neutrons	Mixed beam	Photons
Complete response	24%	29%	44%
Partial response	31%	24%	15%
Overall response	55%	53%	59%

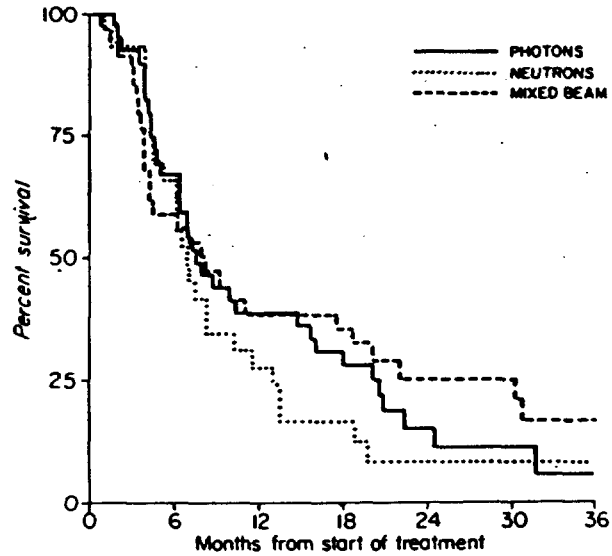

FIG. 1. Actuarial survival curves for the three treatment arms with the time measured from initiation of therapy. The photon arm is shown as the solid line, the neutron arm as the dotted line, and the mixed beam arm as the dashed line. Median survival is 7.5 months on the photon arm, 8.1 months on the mixed beam arm, and 6.9 months on the neutron arm.

from residual tumor, we may not have been completely successful. The overall response rate (complete plus partial) is the same on all three arms and is essentially the same as noted for the 60 Gy arm on a previous RTOG photon study (19,20).

Actuarial survival curves for the three arms are shown in Fig. 1. The median survival is 7.5 months for the photon arm, 8.1 months for the mixed beam arm, and 6.9 months for the neutron arm. These differences are not statistically significant. As can be seen from the figure, there appeared to be a divergence in the curves at intermediate follow-up times of 18–24 months, but the curves have essentially converged at still longer times. Three-year survival is 8% on the photon arm, 16% on the mixed beam arm, and 5% on the neutron arm. Again, these differences are not statistically significant.

Fig. 2 shows a comparison of the complete and partial responders ("best" response), combining patients from all three arms. As expected, the group of patients who achieved a complete local tumor response did significantly better with a median survival of 20.1 months compared with 9.2 months for those patients achieving only a partial tumor response. Viewed in one way, this says that aggressive local treatment is worthwhile since a complete local response means improved survival. However, this may also represent the selection of a less aggressive group of tumors or patients with other characteristics correlating with improved survival (2,29).

0016297

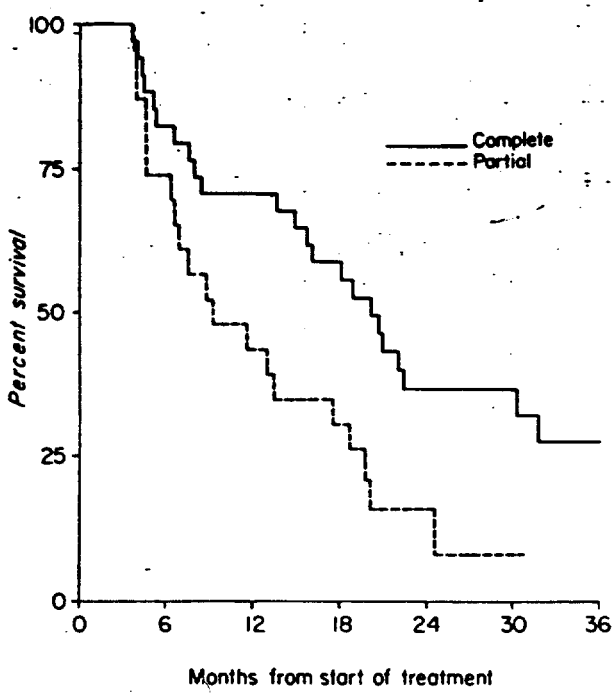

FIG. 2. Actuarial curves showing survival as a function of maximum local tumor response. The solid curve represents the subgroup of complete responders, and the dashed curve represents the subgroup of partial responders. Median survival is 20.1 months for the complete responders and 9.2 months for the partial responders. Patients from all three treatment arms have been combined in the plots.

In order to eliminate possible bias introduced by the variable time to response, Fig. 3 shows the survival as a function of treatment option for the subgroup of patients exhibiting a complete tumor response at 6 months from the initiation of treatment. Both median and 3-year survival rates are noticeably better on the mixed beam arm. Compared to the photon patients, the differences for these parameters are marginally significant at the $p = 0.14$ level (two-sided log rank test). However, the *overall* difference between the mixed beam and photon curves is significant only at the $p = 0.18$ level (two-sided log rank test).

TREATMENT-RELATED MORBIDITY

Treatment-related complications were graded according to the joint RTOG/EORTC scoring scheme for each organ system. The overall summation of the radiotherapeutic related toxicities graded severe or greater was 5.4% for the photon arm, 14.7% for the mixed beam arm, and 30.9% for the neutron arm. This shows a clear progression with increasing percent of the total dose delivered with neutrons. A summary of the types and grade of radiation complications that occurred is shown in Table 5. The numbers in parentheses indicate "fatal" complications. The incidence of subcutaneous fibrosis was clearly higher on the neutron arm. This may relate to the relatively poor depth dose characteristics of the beams from the SEATTLE and GLANTA facilities where the majority of the evaluable patients were treated (SEATTLE 75 and GLANTA 34 patients). The one case of multiple rib fractures in the treatment field likely was also due to this. The cases of myelitis all occurred on the experimental arms. While the myelitis was perhaps not immediately fatal, two of the myelitis cases on the neutron arm died within a few months of the development of symptoms and had no evidence of progressing tumor. They were thus scored as "fatal" by the study chairman.

It is instructive to review more closely the myelitis cases. The treatment details for these cases are summarized in Table 6. The patients were all treated using a "shrinking field" technique, with the initial "large" field having an AP-PA configuration that included both the mediastinum and the primary tumor. The dose to the cord was calculated for the central axis plane and is given as the first number in the second column. Then an "off-cord" boost was performed and the scattered dose to the cord given as the second number in the second column. Beam films were reviewed by the study chairman and indicated that no error in field geometry occurred—that is, the cord was not inadvertently

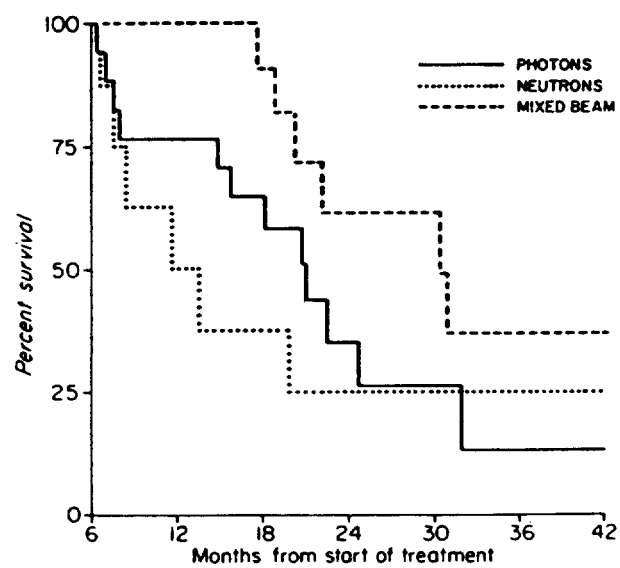

FIG. 3. Actuarial curves showing patient survival as a function of treatment option for the subgroup of patients exhibiting a complete or partial tumor response at 6 months after initiation of therapy. The median survival is 20.8 months on the photon arm, 13.4 months on the neutron arm, and 30.2 months on the mixed beam arm. The survival at 3 years is approximately 12% on the photon arm, 25% on the neutron arm, and 37% on the mixed beam arm.

0016298

TABLE 5. *Summary of radiotherapeutic complications graded severe, life-threatening, or fatal according to the joint RTOG/EORTC scoring scheme*

Complication	Photons	Mixed beam	Neutrons
Subcutaneous fibrosis	—	—	3
Pneumonitis	1	(1)*	1, (1)
Pulmonary fibrosis	1	1, (1)	2
Rib fractures	—	—	1
Myelitis	—	1	1, (2)

* Figures in parentheses indicate the number of fatal complications for each type of event.

treated in the boost fields. The summed dose to cord is also given in column 2 of the table. The length of cord irradiated in each field is given in column 3 of the table. Based upon neurological examinations, the level of the cord injury was within the central portion of the cord segment adjacent to the neutron boost, which means that the central axis doses are truly representative of the doses received by the damaged cord. The time to development of symptoms *after completion* of radiotherapy, the time to death after development of symptoms, and the cause of death are also given in the table. Case 34 (treated with mixed beam irradiation) is still alive. Radiation myelitis was diagnosed after an exhaustive evaluation that included myelograms, CT scans with metrizamide contrast, and cerebrospinal fluid analysis to rule out cord compression due to tumor. An autopsy was performed on case 69 which showed necrosis of the cord with Wallerian degeneration of the corticospinal tracts distal to the lesion and degeneration of the gracia fasciculi rostral to the lesion. The cause of death in this case was local tumor progression within the thorax.

Figure 4 shows a scattergram presentation of the spinal cord doses of the neutron-treated patients who lived 6 months or longer. The cases developing a myelitis are shown as Ms and the cases not developing a myelitis are shown as closed circles. There do not appear to be any obvious differences between the doses to the cord received by those patients who developed spinal cord injury and those who did not. Hence, this appears to be a true statistical effect relating to the susceptibility of the spinal cord to neutron radiation injury.

Figure 5 is an actuarial plot that shows the risk factor for developing a myelitis as a function of time for the patients treated on the neutron and mixed beam arms. This method of analysis scales the risk according to the decreasing number of patients present at the longer follow-up times. Note that at 18 months the risk factors are quite high, being ~40% for the neutron arm and ~10% for the mixed beam arm. The number of cases that would have developed a myelitis on this study might have been substantially greater than four if there had been better long-term survival.

There have been several papers analyzing reported cases of myelitis induced by photon irradiation (1,11,15,24,31). Phillips and Buschke (24), using a cutoff time of 18 months after completing treatment and using the Ellis (NSD) formulation, concluded that a 1,500 ret dose was probably safe for the cord. This

TABLE 6. *Treatment details for cases developing radiation myelitis*

Study arm	Case number	Cord dose	Length of cord irradiated (cm)	Time to development of symptoms (mo)*	Time to death after symptoms (mo)	Cause of death
Neutrons	36	12.87 Gy_{nr} 0.32 Gy_{nr} 13.19 Gy_{nr}	19.5 9	11.5	5	Myelitis
Neutrons	69	11.27 Gy_{nr} 0.69 Gy_{nr} 11.96 Gy_{nr}	16 9	9.5	1.5	Tumor
Neutrons	91	10.69 1.12 11.81 Gy_{nr}	18 12.5	7.5	4	Myelitis
Mixed beam	34	4.52 Gy_{nr}/32.91 Gy_{γ} 0.31 Gy_{nr}/0.36 Gy_{γ} 4.82 Gy_{nr}/34.91 Gy_{γ}	16 8	10.5	NA	NA

NA, not applicable.
* Time *after* completion of treatment.

0016299

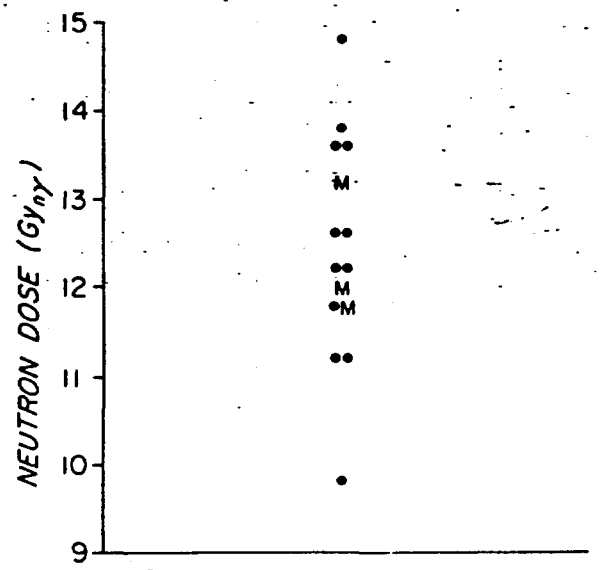

FIG. 4. Scattergram showing the maximum radiation doses ($Gy_{n\gamma}$) received by the spinal cord for those patients treated on the neutron arm who lived 6 months or longer after completing treatment. The cases ultimately developing a myelitis are shown as M's and the cases not developing a myelitis are shown as closed circles.

corresponds to approximately 47 Gy/25 fractions/5 weeks. They also implicitly recognized the dangers in using the Ellis formula for neural tissue and warned against "non-standard" treatment regimes for fields involving the cord. Holdorff (11) emphasized the variable nature of the latency period for cord damage and noted that most cases of a complete myelitis were fatal within 6–12 months of their onset. This is in keeping with our experience. This author established an NSD of 1,530 ret for the development of an incomplete myelitis of the thoracic cord which corresponds to approximately 48.7 Gy/25 fractions/5 weeks. Lambert (15) showed a tolerance curve for the thoracic spine that establishes 49 Gy/24 fractions/5 weeks as a "safe" dose. These numbers are all remarkably similar. There also appears to be a consensus that the tolerance of the cervical cord is somewhat higher than that of the thoracic cord, being of the order of 50–55 Gy/25–28 fractions/5–5.5 weeks.

The neutron dose established for the spinal cord in this study was based upon both animal model data (3,7,30,33) and clinical data from previous neutron pilot studies involving irradiation of the cervical cord (16,20). Bradley et al. (3) compared the effects of neutron and photon radiation on rabbit spinal cord using the neutron beam from the MANTA facility (35 MeV d->Be reaction). They found that paraplegia occurred only after neutron doses >25.2 $Gy_{n\gamma}$ or photon doses ≥ 67.2 Gy corresponding to an RBE for spinal cord injury of approximately 2.7. Geraci et al. (7) tested the effect of the SEATTLE beam on mouse spinal cord and found that the latent period for injury correlated strongly with the dose given. They found six cases of injury after doses of 9 $Gy_{n\gamma}$ in mice living longer than a year, but as they used single fractions in their study, they concluded that this corresponded to an RBE of approximately 1.75. Zook et al. (33) tested the beam from the MANTA facility on dog spinal cords using a fractionation scheme of four treatments per week for 5 weeks, which corresponded reasonably well with the scheme used clinically. They found that a high incidence of myelitis occurred only after neutron doses of ≥26.25 $Gy_{n\gamma}$ and photon doses ≥ 78.78 Gy corresponding to an RBE of approximately 3.0. Also, they did not observe any myelitis events at doses of 11.67 or 17.5 $Gy_{n\gamma}$. Stephens et al. (30) studied Rhesus monkeys using the beam from the TAMVEC facility using a fractionation scheme of nine treatments over 29 days. They only found injuries at doses ≥ 14.25 $Gy_{n\gamma}$ and did not find any definite injuries even for photon doses as high as 59.4 Gy.

Prior to beginning this study, the only data on neutron induced myelitis in humans related to the cervical cord. Laramore et al. (16) reported on five cases that occurred in patients with oropharyngeal primaries who received approximately 15 $Gy_{n\gamma}$ to the cord in 20 fractions over 5 weeks at the SEATTLE facility but noted that patients with primaries in other head and neck sites who received similar cord doses did not exhibit such problems. Ornitz et al. (20) reported on two cases

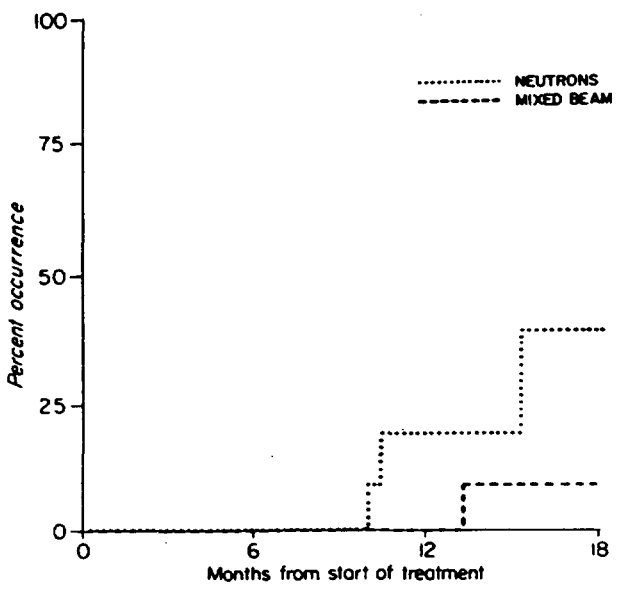

FIG. 5. Actuarial curves showing the risk of developing a myelitis as a function of time after initiating treatment for the neutron and mixed beam patients treated on this protocol. The calculations take into account the decreasing number of patients at risk for the longer follow-up times.

0016300

who received 15.43 $Gy_{n\gamma}$ in 28 fractions over 7 weeks at the MANTA facility.

Given these clinical and laboratory data, it was thought that limiting the dose to the thoracic cord in this study to 12 $Gy_{n\gamma}$ was safe. Only case 36 had a dose that somewhat exceeded this (including the scattered component from the boost field). However, it must be noted that subsequent work by Hórnsey et al. (12) using the beam from a 16 MeV d->Be reaction (HAMMERSMITH) determined that the RBE for spinal cord injury was approximately 4.5–5.0 (relative to ^{60}Co for the treatment scheme used in this protocol). When this was learned, the allowable dose to the cord was reduced to 10 $Gy_{n\gamma}$ and no further injuries occurred.

All of the myelitis injuries that occurred in this study were in patients treated at the SEATTLE facility who received their radiation treatment in 0.67 $Gy_{n\gamma}$ daily doses on a 4-day-a-week basis. Thus, they constitute a uniform data base. If one assumes that the threshold dose for photon irradiation to the thoracic cord is 50–55 Gy in conventional fractionation schedules, then the RBE for spinal cord damage is in the range of 4–4.6 for the particular neutron fractionation schedule used in this study. Using this RBE, the mixed beam patient (also treated at the SEATTLE facility) had a dose to the cord of 54–57 Gy–equivalent. The conclusions reported here are specific for low energy neutron beams produced by d->Be reactions, and it is expected that the RBEs for spinal cord damage from the new clinical facilities using a high energy p->Be reaction will be somewhat lower. This is in keeping with the FERMI experience (4) where an extensive review showed no problems for cord doses in the range of 13–14 $Gy_{n\gamma}$.

DISCUSSION

This study was launched with the hope that fast neutron radiotherapy would provide a means of improving local control for patients with inoperable non-small cell lung cancer, and that this in turn would improve "long-term" survival. Earlier neutron pilot studies seemed to support this view. Eichhorn et al. (6) compared a group of patients treated with a neutron/photon combination to a similar group treated with photons alone and, based upon a detailed analysis of surgical and autopsy specimens, found a substantially higher fraction with sterilized tumor in the neutron/photon group. Moreover, delivering a higher portion of the total dose with neutrons seemed to correlate with increased tumor sterilization. An updated work (5) confirmed this with autopsies on 149/429 photon-treated patients showing a local control rate of 33%, autopsies on 75/93 patients receiving 20% of their total dose with neutrons showing a local control rate of 48%, and a topsies on 49/65 patients receiving 37% of their tot dose with neutrons showing a tumor sterilization ra of 57%. Schnabel et al. (27) reported on a randomiz study comparing 116 patients treated with either c rative doses of photon irradiation or with neutron r diation from a d-T generator. This was not a "clear study because many patients had received prior surge and/or chemotherapy. They did note no difference b tween the treatment groups in terms of tumor contr survival at 1 year (37%), or severity of pulmonary brosis. A small series of patients has been treated the NIRS facility in Chiba, Japan. The report by S. wada et al. (26) discusses 18 patients with Pancoa tumors treated with fast neutrons and five patients wi similar tumors treated with conventional photon i radiation. The mean survival was 11.5 months for t neutron-treated group compared with 4.2 months f the photon-treated group. There were no long-term survivors in the photon group, but four patients in th neutron group lived 2–4 years.

The present study did not show any improvemen in the local tumor response rate for the neutron an mixed beam arms. There was also no improvement i either median or "long-term" survival. However, i the subgroup of patients who exhibited a complete partial tumor response at 6 months, there appeared be an improvement in long-term (i.e., 3-year) surviv for the mixed beam group. This difference was at t marginally significant level ($p = 0.14$) and its clinic implication is uncertain.

Previous studies (21) show the dependence of su vival on T-stage, N-stage, and size of lesion; therefor with the relatively small number of patients in our s ries, it is not possible to make a detailed compariso with previous works. However, the overall survival a pears to be comparable with the previous RTOG ph ton experience. At 2 years, survival for our study rang from a high of approximately 25% for the mixed bea arm to a low of approximately 8% for the neutron arm These numbers are comparable to the 2-year surviv rate of 18% noted for the previous RTOG photon grou that received 60 Gy.

The treatment-related complications were higher o the experimental arms, and this was discussed in deta in the previous section. The problem of spinal cor tolerance is of particular concern since, when treatin the mediastinal nodes, one generally uses AP-PA field that also include the spine. In the case of photon i radiation, 45 Gy out of a "usual" dose of 60 Gy ca be given in this manner, leaving the other 15 Gy to delivered through boost fields that pass through norm lung tissue. This latter dose is safe and usually will n cause pulmonary complications in the absence of pri

0016301

chemotherapy. In the case of neutron irradiation, current protocols limit the spinal cord dose to 8–8.5 $Gy_{n\gamma}$ out of a planned total dose of approximately 20 $Gy_{n\gamma}$. It is not possible to deliver 12 $Gy_{n\gamma}$ through normal lung without causing significant fibrosis which can mean that the field geometry is somewhat compromised. Adequate chemotherapy to treat areas of microscopic disease may be the solution to this, and the synergism of various chemotherapeutic regimes with fast neutron radiotherapy is currently under active investigation. However, caution must be exercised if the regimes contain agents such as bleomycin or mitomycin-C that have their own inherent pulmonary toxicity. Current plans are to establish the tolerance neutron dose for normal tissues of the thorax using the higher energy neutron beams from the new treatment facilities and then to re-examine the question of a new randomized study comparing neutron and photon irradiation for non-small cell lung cancer.

Acknowledgment: This work was supported by the National Cancer Institute under core grant CA-23113 and individual facility grants CA-12441, CA-17465, CA-18081, and CA-19720.

REFERENCES

1. Abbatucci JS, Delozier T, Quint R, Roussel A, Brune D. Radiation myelopathy of the cervical spinal cord: time, dose, and volume fractions. *Int J Radiat Oncol Biol Phys* 1978;4:239–48.
2. Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. *J Clin Oncol* 1983;1:710–9.
3. Bradley EW, Zook BC, Casarett GW, Mossman KL, Rogers CC. Effects of fast neutrons on rabbits—II. Comparison of pathologic effects of fractionated neutron and photon exposures of lung and spinal cord. *Int J Radiat Oncol Biol Phys* 1979;5:795–802.
4. Cohen L, ten Haken RK, Mansell J, Yalavarthi SD, Hendrickson FR, Awschalom M. Tolerance of the human spinal cord to high energy p(66) Be(49) neutrons. *Int J Radiat Oncol Biol Phys* 1985;11:743–9.
5. Eichhorn HJ. Results of a pilot study on neutron therapy with 600 patients. *Int J Radiat Oncol Biol Phys* 1982;8:1561–5.
6. Eichhorn HJ, Lessel A, Matschke S. Comparison between neutron therapy and ^{60}Co gamma ray therapy of bronchial, gastric, and oesophagus carcinomata. *Eur J Cancer* 1974;10:361–4.
7. Geraci JP, Thrower PD, Jackson KL, Christensen GM, Parker RG, Fox MS. The relative biological effectiveness of fast neutrons for spinal cord injury. *Radiat Res* 1974;59:496–503.
8. Gragg RL, Humphry RM, Thomas HT, Meyn RE. The response of Chinese hamster ovary cells to fast-neutron radiotherapy beams III. Variations in RBE with position in the cell cycle. *Radiat Res* 1978;76:283–91.
9. Hall EJ. *Radiobiology for the radiologist.* 2nd ed. Hagerstown, MD: Harper & Row, 1978.
10. Hall EJ, Kraljevic U. Repair of potentially lethal radiation damage: comparison of neutron and x-ray RBE and implications for radiation therapy. *Radiology* 1976;121:731–4.
11. Holdorff B. Dose effect relationships in cervical and thoracic radiation myelopathies. *Acta Radiol Oncol* 1980;19:271–7.
12. Hornsey S, Morris CC, Myers R, White A. Relative biological effectiveness for damage to the central nervous system by neutrons. *Int J Radiat Oncol Biol Phys* 1981;7:185–9.
13. Kaplan EL, Meir P. Non-parametric estimation from incomplete observation. *J Am Stat Assoc* 1958;53:457–81.
14. Kim YH, Fayos JV. Radiation tolerance of the cervical spinal cord. *Radiology* 1981;139:473–8.
15. Lambert PM. Radiation myelopathy of the thoracic spinal cord in long term survivors treated with radical radiotherapy using unconventional fractionation. *Cancer* 1978;41:1751–60.
16. Laramore GE, Blasko JC, Griffin TW, Groudine MT. Fast neutron radiotherapy for advanced carcinomas of the oropharynx. *Int J Radiat Oncol Biol Phys* 1979;5:1821–7.
17. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966;50:163–70.
18. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *JNCI* 1959;22:719–48.
19. Nelson JSR, Carpenter RE, Parker RG. Response of mouse skin and the C3HBA mammary carcinoma of the C3H mouse to x-rays and cyclotron neutrons: effect of mixed neutron-photon fractionation schemes. *Eur J Cancer* 1975;11:891–901.
20. Ornitz RD, Bradley EW, Mossman KL, Fender FM, Schell MC, Rogers CC. Clinical observations of early and late normal tissue injury in patients receiving fast neutron irradiation. *Int J Radiat Oncol Biol Phys* 1980;6:273–9.
21. Perez CA, Stanley K, Graham G, Hanson W, Rubin P, Kramer S, Brady LW, Marks JE, Perez-Tamayo R, Brown GS, Concannon JP, Rotman M. Impact of irradiation technique and tumor extent in tumor control and survival of patients with unresectable non-oat cell carcinoma of the lung: report by the Radiation Therapy Oncology Group. *Cancer* 1982;50:1091–9.
22. Perez CA, Stanley K, Rubin P, Kramer S, Brady L, Perez-Tamayo R, Brown GS, Concannon J, Rotman M, Seydel HG. A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable, non-oat cell carcinoma of the lung: preliminary report by the Radiation Therapy Oncology Group. *Cancer* 1980;45:2744–53.
23. Peto R, Peto J. Asymptotically efficient rank invariant test procedures. *J R Stat Soc (A)* 1972;135:185–206.
24. Phillips TL, Buschke F. Tolerance of the thoracic spinal cord. *Am J Radiol* 1969;105:659–64.
25. Rasey JS, Carpenter RE, Nelson NJ, Parker RG. Cure of EMT-6 tumors by x-rays or neutrons: effect of mixed fractionation schemes. *Radiology* 1977;123:207–12.
26. Sawada K, Fukuma S, Seki Y, Tanaka F, Ishida I, Matsumura K, Nakamo M, Iida K, Sata S, Umegaki Y, Tsunemoto H, Morita S. Clinical experience in patients with Pancoast's tumor treated by fast neutron radiotherapy. *Gan No Rinsho* 1983;A7:111–4. (English abstract).
27. Schnabel K, Dari S, Hover KH, Scher KE. Radiation therapy of bronchogenic carcinoma with a neutron generator. In: Kärcher KH, Kogelnik HD, Reinartz G, eds. *Progress in radio-oncology II.* New York: Raven Press 1982:139–44.
28. Silverberg E. Cancer statistics, 1985. *CA* 1985;35:19–35.
29. Simon R, Makuch RW. A non-parametric graphical representation of the relationship between survival and the occurrence of an event: application to responder vs. non-responder bias. *Stat Med* 1984;3:35–44.
30. Stephens LC, Hussey DH, Raulston GL, Jardine JH, Gray KN, Almond PR. Late effects of 50 MeV d->Be neutron and cobalt-60 irradiation of rhesus monkey cervical spinal cord. *Int J Radiat Oncol Biol Phys* 1983;9:859–64.
31. Wara WM, Phillips TL, Sheline GE, Schwade JG. Radiation tolerance of the spinal cord. *Cancer* 1975;35:1558–62.
32. Withers HR. Biological basis for high LET radiotherapy. *Radiology* 1973;108:131–7.
33. Zook BC, Bradley EW, Casarett GW, Fisher MP, Rogers CC. The effects of fractionated doses of fast neutrons or photons on the canine cervical cord. *Radiat Res* 1981;88:165–79.

0016302