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Status of Fast Neutron Radiotherapy for Non-Small Cell Lung Cancer[1]

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The radiobiologic properties of conventional megavoltage photon radiation and fast neutron radiation are described, and the differences that are potentially important in clinical radiotherapy are delineated. Review of the results of photon irradiation for lung cancer indicates that the principal impact of improved local control will be on long-term survival rather than median survival, which is largely determined by distant metastases. Past and present clinical neutron radiotherapeutic trials for non-small cell lung cancer are reviewed. Several nonrandomized studies seem to show a greater tumor sterilization rate than is expected for conventional photon irradiation. An ongoing randomized study by the Radiation Therapy Oncology Group compares neutron irradiation and mixed-beam (neutron/photon) irradiation with conventional photon irradiation. A preliminary analysis shows no survival differences among the three treatment arms but appears to indicate that two of the arms have a somewhat higher complete response rate than the third arm. The potential for combining fast neutron irradiation with aggressive chemotherapy is discussed. [Cancer Treat Symp 2:81–85, 1985]

The radiobiologic properties of fast neutrons differ in several significant ways from those of megavoltage photons used in conventional radiotherapeutic treatments. When a megavoltage photon interacts with matter via Compton scattering or pair production, it produces high-energy electrons (or positrons), which in turn produce a chain of secondary ionization processes (1). Fast neutrons, on the other hand, interact directly with the atomic nuclei to produce massive, slower-moving, charged particles. As they travel through matter, these particles create ten to 100 more ionizations per unit of path length than the photon-produced high-energy electrons, and it is this greater energy deposition that causes the useful radiobiologic properties of fast neutrons.

In a broad sense, there are two classes of radiobiologic damage mechanisms: indirect and direct (2). The indirect mechanism is mediated by free radicals, which are produced in the cellular cytoplasm and then diffuse to the DNA and damage it. This is the primary mechanism by which low linear energy transfer (LET) photon radiation kills cells, and it is most effective when the cells are well oxygenated, thereby producing long free radical lifetimes. With increasing LET, the relative importance of the direct mechanism increases. In this process, the ionization products interact directly with the DNA, so high-LET radiation is better able to kill hypoxic cells. For fast neutrons in particular, oxygen enhancement ratios are ~ 1.6, compared with 2.5–3.0 for high-energy photons. This effect could be clinically important for large tumors, which often contain areas of necrosis surrounded by hypoxic cells.

In addition, the type of damage inflicted by neutron radiation is less readily repaired by the tumor cells. There are two aspects to this: (*a*) reduced ability to repair sublethal damage, which is manifested by reduction of the shoulders on cell survival curves (2,3); and (*b*) reduced ability to repair potentially lethal damage (4), which could be important for cells in a resting or G_0 phase. Finally, there is less variation in radiosensitivity throughout the cell cycle than with conventional photon radiation (5). These are important radiobiologic considerations, but their applicability to a given tumor system can be determined only through clinical trials.

Over the last 15 years, several thousand patients have been treated with fast neutrons. Unfortunately, the role of this modality in the treatment of most tumors, includ-

[1]Supported in part by contract N01-CM-97282 (Division of Cancer Treatment) and Public Health Service grant CA-12441 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

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ing non-small cell lung cancer, is still in doubt. Most neutron radiotherapeutic treatments have been given using cyclotrons originally designed for physics research; hence, the treatments were less sophisticated than those given using modern linear accelerators. Also, the penetrating power of these early neutron beams was suboptimal for treating deep-seated tumors in the thorax. The majority of patients treated with fast neutrons have had advanced tumors such as head and neck cancers and high-grade gliomas of the brain for which improved local control could have a major impact on survival. Substantially fewer patients with lung cancer have received fast neutron radiotherapy. The following review of the literature outlines the results of photon irradiation to determine what might be expected from a more effective modality.

In lung cancer, local control with definitive radiotherapy is not easy to assess, even with modern computerized tomography (CT) scanning techniques. It is difficult to distinguish atelectasis or radiation fibrosis from recurrent or persistent tumor. Survival is a more concrete parameter, but it must be recognized that a substantial fraction of patients die from distant metastases. Hence, there has been some uncertainty in the past regarding the role of radiotherapy for the asymptomatic patient with localized but inoperable disease. Although Smart (6) demonstrated that radiotherapy could cure lung cancer in selected patients, a randomized study by Roswit et al (7) showed that radiotherapy shifted the survival curve only slightly to longer survival times for a less-selected patient population. These early studies employed orthovoltage, and the majority of patients treated in the Roswit series received suboptimal radiation doses.

More recently, a randomized study (8,9) of 375 evaluable patients has been completed by the Radiation Therapy Oncology Group (RTOG); it demonstrates the need to exceed a 50-Gy tumor dose to achieve maximal local tumor control for non-small cell lung cancer. In this study, patients received either a total dose of 40 Gy, given continuously over a 4-week period or as a split course; 50 Gy over 5 weeks; or 60 Gy over 6 weeks. The 200 patients who received the 40-Gy dose had response rates (complete plus 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 total doses of 50 and 60 Gy had response rates of 66% (60 of 91) and 61% (51 of 84), respectively, with a 2-year survival rate of 18% in each arm. The site of first failure was intrathoracic in 58% (116) of the 200 patients receiving 40 Gy, in 45% (41) of the 91 receiving 50 Gy, and in 38% (32) of the 84 receiving 60 Gy. The median survival in all of the arms was ~ 42 weeks. These data illustrate the important point that, in evaluating the impact of improved local control in lung cancer, long-term survival must be emphasized, rather than median survival, which is largely determined by distant failure. The study indicated a higher local failure rate for the larger tumors, but for all tumor sizes, the groups receiving 50 and 60 Gy did markedly better than the groups receiving 40 Gy. Further escalation of the radiation dose would not be advantageous, since there were increased treatment-related complications when the dose was increased from 50 to 60 Gy (8).

CLINICAL NEUTRON TRIALS

When a new irradiation modality is considered, the first problem is to establish tolerance doses for the various organ systems in the treatment volume. Before patients are treated, extensive cell culture and animal studies are performed by many investigators, and relative biologic effectiveness (RBE) factors are established. The RBEs vary according to the results of the tissue studies, the end point chosen, the total radiation dose given, the fraction size used, and the particle reaction employed to produce the neutron beam. For the neutron beams and fraction sizes currently used in clinical radiotherapy, RBE is 3.0-3.3 for most tissues. However, the central nervous system is an exception to this. Since the RBE for spinal cord injury appears to be 4.0-5.0 (10), careful treatment planning is necessary when tumor masses near the spinal column are irradiated, as is often required in the treatment of lung cancer.

Another problem relates to dose reporting in the neutron therapy literature. As neutrons interact with matter, they produce γ-rays, and the amount of this contaminant varies with depth. For the 22-MeV d→Be beam used at the University of Washington, this is 8%-10% of the total physical dose at a 10-cm depth. Some centers report only the neutron component of the dose, whereas others report the total physical dose. We will adopt the latter convention and use the term $Gy_{n\gamma}$.

The first reported series utilizing neutron teletherapy to treat lung cancer was by Eichhorn et al (11), who used a Soviet ^{120}U cyclotron that produced a neutron beam having a mean energy of ~ 6.2 MeV. Because the depth-dose characteristic of this beam was poorer than that from a conventional ^{60}Co treatment unit, the investigators did not treat patients with neutrons alone but, rather, used a combination of neutron and photon treatments. A total of 20 patients received ~ 20% of the dose with neutrons (3.93 $Gy_{n\gamma}$ + 46.04 Gy_{γ}). These patients were compared with a historic group of 149 patients treated with ^{60}Co radiation alone (70.44 Gy_{γ}). The radiation was given 5 days/wk, but for most of the patients treated with both neutrons and photons, there was an interval of 3-8 days between the two forms of treatment. Assuming an RBE of ~ 3.3, the neutron-treated patients received substantially lower equivalent doses than the photon-treated patients. Nevertheless, based on histologic examination of surgical and autopsy specimens, the fraction of neutron-treated patients with sterilized tumor in the treatment volume was substantially higher, as indicated in table 1. As with any nonrandomized series,

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TABLE 1.—Comparison of tumor sterilization rates in surgical and autopsy specimens of bronchogenic carcinoma treated with photons alone or with neutron/photon irradiation

No. of patients	Dose (Gy)*		Sterilization rate
	Photons	Neutrons	
149	70.44 (9.04)	—	33%
20	46.04 (4.65)	3.93 (0.34)	50%
15	32.36 (6.51)	7.06 (0.90)	74%

* Values = average radiation doses (SD). Ref 11.

there were some differences in tumor size and histologic subtype, but the authors concluded that the combined neutron/photon irradiation appeared to be more effective than the conventional photon treatments in terms of tumor sterilization. There is a trend toward a higher rate of tumor sterilization with an increasing neutron component of the total dose. This research has been subsequently updated (12), and based solely on autopsy analyses, the groups treated in part with neutron irradiation continued to have a higher percentage of tumor sterilization in the treatment volume. As shown in autopsy studies, there was a tumor sterilization rate of 33% (149 of 429) in photon-treated patients; 48% (75 of 93) in patients receiving 20% of the total dose with neutrons; and 57% (49 of 65) in patients receiving 37% of the total dose with neutrons. Assuming equivalent groups of patients, these differences would be statistically significant.

Schnabel et al (13) have reported on a series of patients treated with the higher-energy neutron beam from a deuterium-tritium (d-T) generator (14-15 MeV). There were 116 patients in this randomized study, which compared a neutron treatment regimen of 18 $Gy_{n\gamma}$ in 20 fractions over 5 weeks with a photon treatment regimen (^{60}Co) of 54 Gy_{γ} in 20 fractions over 5 weeks. According to the Ellis nominal standard dose formula, the latter dose was comparable to the standard high-dose regimen of 60 Gy_{γ} in 30 fractions over 6 weeks that is used in the United States. Radiation therapy treatment planning was done using CT scans for tumor localization. Conventional radiographs and CT scans were performed at 3-month intervals to evaluate tumor response and pulmonary fibrosis. Because of equipment problems, only 30 patients in the neutron arm and 46 in the photon arm were treated according to the protocol. Many of these patients had received prior treatment with surgery and/or chemotherapy, so the study is not "clean" in this regard. There were no significant differences between the two treatment groups in terms of tumor control, survival (~ 37% at 1 year), or severity of pulmonary fibrosis. The incidence of treatment-related esophagitis was higher for the photon-treated patients.

A small series of patients has been treated at the National Institute for Radiological Sciences in Chiba, Japan, which utilized a 30-MeV d→Be reaction. The report by Sawada et al (14) discusses 18 patients with Pancoast's tumor treated with fast neutrons and five with similar tumors treated with conventional photon irradiation. The mean survival was 11.5 months for the neutron-treated group, compared with 4.2 months for the photon-treated group. There were no long-term survivors in the photon-treated group and four long-term survivors (2-4 years) in the neutron-treated group. The authors also noted that damage to the lung parenchyma was acceptable, provided that a shrinking-field technique was used.

There is a multi-institutional, phase III randomized study taking place in the United States to evaluate the role of fast neutron radiotherapy for inoperable, non-small cell lung cancer. This study is coordinated by the RTOG, and participating institutions include the University of Washington facility in Seattle (22-MeV d→Be reaction), the Great Lakes Neutron Treatment Association facility in Cleveland, OH (25 MeV d→Be reaction recently converted to a 42-MeV p→Be reaction), Fermi National Laboratories (66-MeV p→Be reaction), and the Texas A & M Variable Energy Cyclotron facility operated by the M. D. Anderson Hospital and Tumor Institute, Houston, TX (50 MeV d→Be reaction). Requirements for patient eligibility are histologic confirmation of disease and no prior treatment with surgery, chemotherapy, or radiotherapy. The study is ambitious in that it has three randomization arms. Patients in the control arm receive high-dose photon radiation to 60 Gy_{γ} in 30 fractions over 6-7 weeks. Patients in the two experimental arms receive neutron radiation alone to 18 $Gy_{n\gamma}$ in 12-24 fractions over 6-7 weeks and mixed-beam radiation, which consists of two neutron treatments and three photon treatments per week in biologically equal daily doses. A total dose equivalent to 60 Gy is given in this arm. The neutron doses specified here are for the Seattle facility, and the neutron doses at the other facilities are scaled appropriately. For order-of-magnitude comparisons, the RBE for the Seattle facility is assumed to be ~ 3.3. Shrinking-field techniques are used in the areas of clinical involvement (primary tumor and nodes), and the dose to the spinal cord is kept at a safe level (< 10 Gy_{γ}).

To date, most of the 114 patients entered in this study are being treated at the Seattle (75 patients) and GLANTA (34) facilities. Because the study is ongoing, the results are presented in coded format. A preliminary analysis of the complete and partial response rates for the three arms is shown in table 2. Two arms show a

TABLE 2.—Preliminary analysis of complete and partial [illegible] for neutron protocol RTOG 79-07*

Response	Treatment arm	
	A	B
Complete	34%	20%
Partial	26%	37%

* Analysis is blinded.

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somewhat higher complete response rate than the other arm, but this is not statistically significant.

One of us (TWG) has independently reviewed the x-ray studies (conventional and CT scans) for the 75 patients treated at the University of Washington (25 in each arm). The maximum tumor response during the first 4 months after completion of radiation therapy was evaluated. There was complete response in four patients in the photon arm, eight in the mixed-beam arm, and 12 in the neutron arm. Any ambiguous density was assumed to be tumor rather than atelectasis or fibrosis.

Actuarial survival curves for the three arms are shown in figure 1. Although there initially appeared to be a divergence in the curves at intermediate follow-up times of 18-24 months, the curves have subsequently come together. The overall median survival for all patients in the study is 7.5 months. Long-term survival ranges from 7% on treatment arm A to 14% on treatment arm C. This difference is not statistically significant. Figure 2 shows a comparison of the survival curves for the complete responders and the partial responders for all three treatment arms. As expected, survival in the patients who achieve complete local response is significantly better, with a median survival of ~ 20.3 months, compared with ~ 11.6 months for those who achieve only partial response.

The overall complication rate also appears to be somewhat higher in the experimental arms: 50.0% in the photon arm, 63.3% in the mixed-beam arm, and 63.9% in the neutron arm. If only the severe or life-threatening complications are considered, the incidence is 7.9% in the photon arm, 23.3% in the mixed-beam arm, and 19.4% in the neutron arm. There have been two fatal complications in the mixed-beam arm and one fatal complication in the neutron arm. The higher complication rates associated with present neutron treatments are partially due to the primitive facilities and low-energy beams that have been utilized.

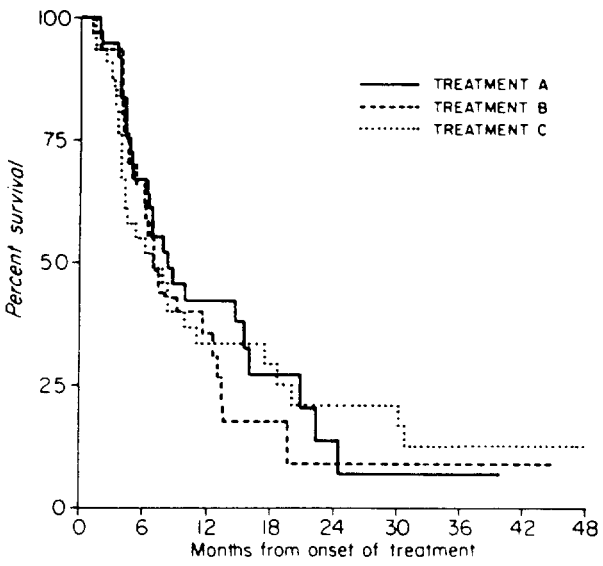

FIGURE 1.—Actuarial survival curves for 3 treatment arms of neutron protocol RTOG 79-07. 12 of the 38 patients on treatment arm A are alive (median survival, 8.4 mo); 7 of the 30 patients on treatment arm B are alive (median survival, 7.1 mo), and 9 of the 36 patients on treatment arm C are alive (median survival, 7.0 mo).

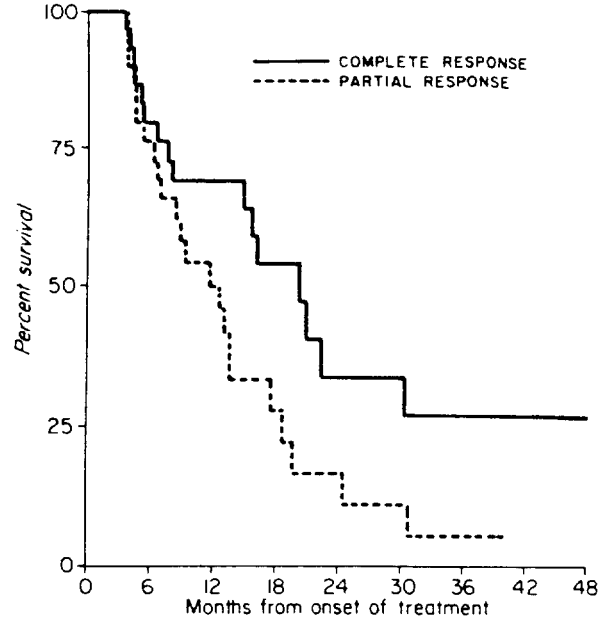

FIGURE 2.—Actuarial curves showing survival as function of local tumor response for neutron protocol RTOG 79-07. Patients from 3 treatment arms are included in plots. 13 of the 29 patients who had complete response are alive (median survival, 20.3 mo), and 7 of the 30 patients who had partial response are alive (median survival, 11.6 mo).

SUMMARY AND FUTURE DIRECTIONS

There has been only a limited amount of clinical research to test the applicability of high-LET neutron radiotherapy for inoperable carcinoma of the lung, partly because of the known high rate of distant metastases, which is felt to dominate median survival statistics in protocols testing one local modality against another. Review of the photon radiotherapy data for non-small cell lung cancer indicates that there might be some improvement in *long-term* survival if better local control could be achieved, so a neutron protocol (RTOG 79-07) was designed to test this hypothesis. To date, however, this study has shown only some suggestion of improved local control with fast neutron irradiation and no evidence of improved survival. This higher local control rate is in agreement with the results of previous pilot studies (11-14). However, the higher complication rates in pa-

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tients receiving therapy with neutrons alone or mixed-beam radiation are reason for concern.

The next generation of neutron treatment facilities is nearing completion in the United States. Treatment at three of these facilities will be based on cyclotrons utilizing 42- and 48-MeV p→Be reactions and will have isocentric capability. These machines will have depth-dose characteristics comparable to those of 6-MeV linear accelerators and will be able to give radiation treatments of at least equal levels of sophistication. A fourth machine will be based on the d-T reaction. The cyclotron units will be located at the University of Washington Hospital, M. D. Anderson Hospital and Tumor Institute, and Wadsworth Veterans Administration Hospital (University of California, Los Angeles). The d-T unit will be based at the Fox-Chase Hospital, Philadelphia, PA. These new units should greatly reduce the morbidity previously associated with neutron treatments.

However, the question of distant metastases must still be addressed. Recently, the Southwest Oncology Group has developed a pilot study (SWOG 83-67) testing the feasibility of combining fast neutron radiotherapy with aggressive chemotherapy for non-small cell lung cancer. This protocol consists of one cycle of induction chemotherapy with alternating sequences of vinblastine/mitomycin and vinblastine/cisplatin, followed by fast neutron radiotherapy of 17 $Gy_{n\gamma}$ in 12 fractions over 4 weeks, followed by repetition of the cycle of chemotherapy. The patients also receive 30 Gy of prophylactic cranial irradiation with megavoltage photons. This is primarily a toxicity study, and thus far, the main acute side effect is nausea related to the chemotherapy. However, with longer follow-up times, two of seven patients have had probable treatment-related pneumonitis; this indicates the need for reduction of the radiation dose to normal lung tissue when chemotherapy is given. This study is probably the forerunner of the next generation of neutron studies in the United States. We are hopeful that the combination of aggressive chemotherapy with improved local control will make a significant impact on the future treatment of inoperable lung cancer.

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