702233

Am J Clin Oncol (CCT) 12(4): 290–294, 1989.

© 1989 Raven Press Ltd., New York

Neutron Radiation Therapy for Unresectable Non–Small-Cell Carcinoma of the Lung

A Review

File Copy 7011
Pub. # 5029
Study # 7807, 7907
Site: Lung
Modality: Ntr
Status: Pub

Glenn Stewart, M.D., Thomas W. Griffin, M.D., Brian R. Griffin, M.D., George Laramore, Ph.D., M.D., Kenneth J. Russell, M.D., Robert G. Parker, M.D., Moshe N. Maor, M.D., and Lawrence W. Davis, M.D.

Over 200 patients have been entered in five studies investigating the use of fast neutron radiation therapy in the treatment of non–small-cell carcinomas of the lung since 1983. The results of these studies have been inconsistent. Most studies did not show survival rates or local control advantages over standard photon radiation therapy. Side effects from studies employing mixed photon–neutron treatment plans or clinically oriented, high-energy cyclotrons were seen to be comparable to those of standard courses of radiation therapy, representing a considerable improvement over those studies utilizing low-energy cyclotrons for a full course of radiation therapy, which resulted in unacceptably high complication rates. A new phase III study utilizing high-energy isocentric neutron beams has been designed and implemented, and over 100 patients have been entered to date. The current status of fast neutron radiation therapy in the treatment of non–small-cell lung cancer is reviewed.

Key Words: Carcinoma of the lung—Cyclotron—Neutron radiotherapy—Non–small-cell carcinoma of the lung.

0016273

From the University of Washington, Department of Radiation Oncology, RC-08, University Hospital, 1959 N.E. Pacific Street, Seattle, Washington (G.S., T.W.G., B.R.G., G.L., K.J.R.); the University of California–Los Angeles, Department of Radiation Oncology, Los Angeles, California (R.G.P.); Department of Radiation Therapy, M. D. Anderson Cancer Center, Houston, Texas (M.N.M.); and Albert Einstein College of Medicine, Montefiore Medical Center, Department of Radiation Therapy, Bronx, New York (L.W.D.).

Address correspondence and reprint requests to Dr. Thomas Griffin, University of Washington, University Cancer Center, RC-08, 1959 N.E. Pacific Street, Seattle, WA 98195, U.S.A.

Carcinoma of the lung is a major medical problem in the United States, accounting for over 150,000 new cases of cancer per year and over 25% of all cancer deaths (1). Eighty percent of patients with carcinoma of the lung have a histologic diagnosis of non–small-cell lung cancer (NSCLC) (2). Sixty–75% of NSCLCs are unresectable at diagnosis (3), and before the advent of modern radiation therapy were considered incurable. Later, between 1965 and 1975, several studies indicated that 5–10% of patients with unresectable NSCLC were apparently cured after having received a course of radiation therapy to the chest (4–6). Although most of the deaths in this patient population were due to distant metastases, a large percentage of patients had disease that progressed locally as well.

About 10 years ago, several centers began looking at neutron radiation therapy as a potentially more effective form of treatment for patients with NSCLC than conventional photon radiation therapy. Because their radiobiologic properties differ in several significant ways from those of megavoltage photons, neutrons are theoretically superior for treating traditionally radioresistant tumors (7–9). Many of the theoretical advantages are due to the fact that fast neutrons are a form of high linear energy transfer (LET) radiation, as opposed to low LET photons. In fact, fast neutrons create 10–100 more ionizations per unit of path length than do the secondary electrons produced by high-energy photons (10). With increasing LET, the relative importance of the direct mechanism of radiobiologic damage increases. In the direct mechanism, ionization products are thought to react directly with DNA. The indirect mechanism associated with low LET irradia-

BOX No. BINDER - Collected & Copied From Shelf RTOG Publish Manuscripts
FOLDER COPIED 4-21-94 At Fermilab NTF
REPOSITORY FERMILAB NTF
Radiation Therapy Oncology group
COLLECTION RTOG Published Manuscripts (RTOG)

tion, on the other hand, is dependent on free radicals. The effectiveness of these free radicals in damaging DNA is dependent on the presence of oxygen. Thus, high LET radiation is better able to kill hypoxic cells. Because lung cancer is usually not diagnosed until the primary tumor is quite large (>1 cm^3) and because large tumors often contain areas of necrosis surrounded by hypoxic cells, lung cancer is thought to display hypoxic resistance to traditional low LET photon irradiation. Additionally, tumor repair of radiation damage (11) as well as cell cycle-associated radiation resistance are both thought to occur less often with neutrons. For all of these reasons, it was hoped that the relative biologic effectiveness (RBE) of neutrons would be greater for lung tumor cells than the RBE of 3.0–3.3 that exists for most normal tissues, thus giving an improved therapeutic ratio.

Neutrons were first used to treat lung cancer by Eichhorn et al., who used a Soviet ^{120}U cyclotron that produced a neutron beam having a mean energy of ~6.2 MeV (12). Eichhorn et al. compared a group of patients treated with a neutron/photon combination to a similar group treated with photons alone, and based on a detailed analysis of surgical and autopsy specimens found a substantially higher fraction of sterilized tumor in the neutron/photon group (12). Autopsies showed a local control rate of 33% in patients who received photons alone, compared with a local control rate of 48% in patients who received 20% of their total dose with neutrons (13). Moreover, autopsies showed a tumor sterilization rate of 57% in those patients who received 37% of their total dose with neutrons. Because of these impressive results, several studies were initiated at cyclotron centers around the world in the late 1970s and early 1980s.

In 1983, Schnabel et al. (14) reported the results of a prospective randomized study involving 115 patients. Forty-eight patients received 18 neutron Gy in 20 fractions over 5 weeks. The neutrons were delivered with a 14-MeV deuterium–tritium (d-T) generator in Heidelberg, Germany. The 67 control patients received a dose of 54 photon Gy, using cobalt 60 in 20 fractions over 5 weeks. Unfortunately, 21 of the 48 neutron patients and 21 of the 67 photon patients received prior treatment. Also, only 30 patients in the neutron arm and 46 in the photon arm were treated according to the protocol due to equipment problems (10). There was no significant difference between the two groups in survival rate at 1 year (approximately 37%). There was also no local superiority for neutrons (Table 1). On the other hand, side effects were somewhat worse with neutrons. Although no difference was observed initially, as time went on (>200 days) there was a higher incidence of pulmonary fibrosis in neutron survivors.

TABLE 1. *Local response: Schnabel et al. (14)*

Cancer, stage	No. of evaluable cases[a]	Response, no. (%)		
		None	Partial	Complete
N	39	2 (5)	33 (85)	4 (10)
γ	53	2 (4)	40 (75)	11 (21)

[a] The remainder of the cases were not evaluable.

Osteoradionecrosis and cardiac necrosis were also more common in neutron-treated patients.

Also in 1983, Sawada et al. (15) reported the results of a small series of patients with Pancoast tumors treated at the National Institute for Radiobiological Sciences in Chiba, Japan. Eighteen patients were treated with fast neutrons from a 30-MeV d → Be reaction and had a mean survival time of 11.5 months with four long term (>2 years) survivors. It should be noted that unlike the neutrons from a d → T generator (which have a relatively uniform energy), neutrons from a d → Be generator have a spectrum of energies with a modal value of approximately 40% of the incident deuteron energy. Five patients with similar tumors treated with conventional photon irradiation exhibited a mean survival time of 4.2 months, with no long-term survivors.

In 1985, Breteau et al. (16) described 26 patients with inoperable NSCLC treated with a mixture of photons and neutrons in Orleans, France. The patients first received 40 photon Gy over 4 weeks through anterior and posterior (AP–PA) portals followed by 6.7 neutron Gy delivered in eight fractions over 2 weeks through lateral portals. The neutrons were generated by a 34-MeV proton-on-beryllium (p → Be) reaction. With follow-up times ranging from 6–26 months, local control was achieved in 21 of the 26 patients. Six cases became operable, and in three of them, examination was negative for residual tumor. Side effects included two infections in the irradiated volumes with one treatment-related death. In an additional 11 patients with Pancoast tumors treated with the same 40-photon Gy and 6.7-neutron Gy regimen, Breteau et al. reported complete pain relief in 10 with a median survival time of 9 months. No long-term survival results were published on either series of patients.

In 1986, Laramore et al. (17) published the results of a Radiation Therapy Oncology Group (RTOG) prospective study that randomly assigned 102 patients into one of three treatment arms. The control arm consisted of 60 Gy in 30 fractions over 6–7 weeks. The second arm consisted of 18 neutron Gy in 12–24 fractions over 6–7 weeks. The third arm used a "mixed beam" consisting of two neutron and three photon treatments per week in daily doses of an approximately

0016274

equal RBE to a total dose of 60 photon Gy equivalent. The specifics of the neutron generators at each of the RTOG centers participating in this study are shown in Table 2. All four of these neutron facilities, as well as those in the previous four studies, had to utilize a fixed horizontal or vertical beam. Three-year survival was 18% on the photon arm, 16% on the mixed-beam arm, and 5% on the neutron arm. These differences were not statistically significant. The overall response rate (complete and partial) was the same on all three arms, although the complete response rate was greater on the photon-only (control) arm (Table 3). Toxicities rated severe or greater occurred in 5.4% of the photon-treated patients, 14.7% of the mixed-beam patients, and 30.9% of the neutron-treated patients. These complications included subcutaneous fibrosis, pneumonitis, pulmonary fibrosis, rib fractures, and myelitis. Additionally, there were several treatment-related fatalities in the mixed-beam and neutron groups.

Most recently, in 1987, Livingston et al. (18) published results of treating patients with combination chemotherapy, neutron chest radiotherapy, and prophylactic (photon) cranial irradiation to patients with limited NSCLC. The chemotherapy included vinblastine sulfate, mitomycin-C, and cisplatin. Seven patients received their neutrons from a physics-based 22-MeV d → Be neutron generator that permitted treatment with a fixed horizontal beam only. A dose of 1.42 neutron Gy was delivered three times per week over 4 weeks for a total dose of 17 neutron Gy in 12 fractions. Four of these seven patients suffered deaths related to their combined treatment. It should be noted that autopsies on two of these patients showed no evidence of residual tumor. Forty-five patients were treated with a hospital-based 50-MeV d → Be cyclotron with an isocentric gantry, collimator rotation, and independent collimator leaf blocking. They received between 18 and 22 neutron Gy, again in 12 fractions over 4 weeks. Two patients suffered radiation-related deaths, and another four had clinically evident radiation pneumonitis. No cases of transverse myelitis occurred. Response to neutrons could be assessed in 41 of these 45 patients, as two patients had complete response after induction chemotherapy, and two had no evaluable disease radiographically. Of these 41, 12 (29%) had a complete response and 11 (27%) had a partial response, for a total response rate of 23 of 41 (56%). Despite these response rates, disease in 38 of the patients eventually progressed. Figure 1 documents the survival curve for these 45 patients. An analysis of the patterns of relapse in the first 27 patients is presented in Table 4. It should be noted that a large percentage had local failure. An analysis of failure site by neutron dose is shown in Table 5. Only one of seven patients receiving 22 neutron Gy failed in field, compared with five of 14 receiving 20.4 neutron Gy and two of six receiving 18 neutron Gy.

TABLE 3. *Complete and partial response rates for the three study arms of the 1986 RTOG study*

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

RTOG, Radiation Therapy Oncology Group.

DISCUSSION AND FUTURE DIRECTIONS

Any new radiation therapy technique must be evaluated in terms of its impact on survival, its ability to achieve local control, and its potential for side effects. In a disease such as lung cancer, which has a high rate of death due to distant metastases, it is important to look at "long-term" survival rather than median survival when evaluating the effect of a local form of therapy (17). The RTOG has shown that high-dose conventional photon radiotherapy can have a favorable impact on long term (not median) survival (19,20) (Table 6). With the exception of the small series of patients with Pancoast tumors of Sawada et al., no study has shown improved long-term survival for lung cancer patients after neutron therapy compared to standard photon therapy. This is understandable be-

TABLE 2. *Neutron generators used in the 1986 RTOG study*

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

RTOG, Radiation Therapy Oncology Group; RBE, relative biological effectiveness; GLANTA, Great Lakes Neutron Therapy Alliance; TAMVEC, Texas A & M Variable Energy Cyclotron.

TABLE 4. *Patterns of relapse in 27 patients treated with chemotherapy, neutron chest radiotherapy, and prophylactic cranial irradiation*

	Patterns of recurrence observed, no. of patients		
Total no. of patients	Local only	Local and distant	Distant only
27	16	3	8

0016275

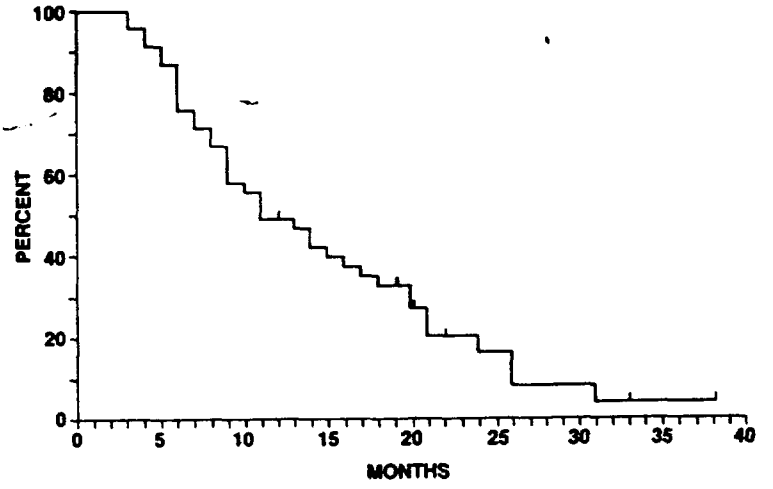

FIG. 1. Survival in 45 patients with limited non-small-cell lung carcinoma treated with chemotherapy, prophylactic cranial irradiation, and neutron chest irradiation. Disease progressed in 38 of the patients.

cause long-term survival is only possible if local control is achieved, and most work since Eichhorn's promising pilot study has not documented substantial improvement in local control with neutrons. Neither the randomized studies of Schnabel et al. nor Laramore et al. documented a local superiority for neutrons. However, the cyclotrons in both of these studies produced neutrons of relatively low energy with subsequent poor depth dose characteristics. Moreover, the fixed-beam portals employed on these machines may have compromised boost field tumor margins. The high-energy cyclotron with isocentric gantry used in Livingston's study overcomes these limitations. It produces a depth dose profile comparable to that of a 6-MeV linear accelerator (10). His local control data are more difficult to interpret due to the use of induction chemotherapy in his patients as well as the lack of randomized photon controls, but neither the response rates nor the local control rates are superior to those achieved in a previous RTOG study utilizing conventional high-dose photons (19,20). Only in the study of Breteau et al. was an impressive local control rate achieved, although follow-up time was limited, and several responders subsequently received surgery. It should be remembered that their patients were first treated with 40 photon Gy through AP–PA portals before receiving a neutron boost. This brings up an important point. Where approximately 75% of a full course of photon therapy for lung cancer may be given through AP–PA portals (i.e., 45 Gy of a total of 60 Gy), less than 50% of a full course of neutron therapy (approximately 20–22 Gy) can be given through AP–PA portals. This is because neutrons have a high RBE in central nervous system tissue, and spinal cord tolerance is reached at approximately 11–12 neutron Gy. Because the cord also receives a significant scatter dose from the "off cord" neutron boost, the AP–PA fields must be stopped after only 8–9 neutron Gy have been delivered. Cox has previously stated that the treatment volume should cover the primary tumor with a 2-inch margin as well as the entire width of the mediastinum, including both hila, from the sternal notch to at least 5 cm below the carina (21). This is often difficult to achieve in an "off cord" field, thus, there is a greater likelihood that adequate volumes get treated with sufficient radiation when a higher percentage of the total dose can be delivered through AP–PA fields. Now that high-energy, isocentric neutron facilities are available, further improvements in local control will depend on innovative treatment regimens that preferentially spare the spinal cord while covering adequate tumor volumes. Possible plans may include diagonal cross-fire fields for centrally located tumors, conformational therapy, or photon–neutron combinations similar to that used in the study of Breteau et al.

TABLE 5. *Patterns of recurrence in 27 patients treated with neutrons by neutron dose delivered*

Neutron dose, (Gy)	Total no. of patients	Dose, no. of patients (%)		
		In field	Locoregional, out of field	Distant only
18	6	2	4	0
20–20.4	14	5	5	4
22	7	1	2	4
Total	27	8 (30)	11 (40)	8 (30)

TABLE 6. *Survival rate according to photon dose*

Photon dose, Gy	2-yr survival rate, %
40	11
50	18
60	18

0016276

Finally, it appears that the high incidence of neutron toxicity observed in early trials may be avoidable. Both the randomized studies of Schnabel et al. and Laramore et al. had high complication rates on their neutron arms, but low-energy neutron generators were used. Livingston et al. also observed a high rate of serious complications in patients treated with a low-energy cyclotron; these side effects decreased dramatically when patients were treated with a high-energy machine. Breteau et al. also observed an acceptable rate of complications from their photon–neutron regimen. However, a full course of neutrons will probably always cause more radiation fibrosis than a full course of photons. Patients with a poor pulmonary reserve are thus probably best treated by photons or a photon–neutron combination.

In conclusion, the theoretical advantages of using neutrons and the early promising work of Eichhorn have not yet resulted in significant clinical improvements for patients with lung cancer. However, the introduction of high-energy, clinically oriented cyclotrons has resulted in acceptable levels of side effects so that neutrons may now be more widely employed in new protocols seeking to improve the outlook of patients with NSCLC. Over 100 patients have been entered and randomly assigned in a study comparing neutron treatment on these new isocentric machines with photon radiation therapy. A definitive answer should be available in a year or two to the question of whether or not fast neutron radiation therapy can improve the results of treatment for NSCLC.

Acknowledgment: This work was supported in part by the National Cancer Institute under grants CA-12441, CA-22133, and contract CA-97282.

REFERENCES

1. American Cancer Society. *Cancer facts and figures, 1987.* New York: American Cancer Society, 1987:1–31.
2. Cox JD, Stanley K, Petrovich Z, et al. Cranial irradiation in cancer of the lung of all cell types. *JAMA* 1981;245:469–72.
3. Perez CA, Pajak TF, Rubin P, et al. Long-term observations of the patterns of failure in patients with unresectable non–oat cell carcinoma of the lung treated with definitive radiotherapy. *Cancer* 1987;59:1874.
4. Brady LW, Cander L, Evans GC, Faust DS. Carcinoma of the lung: results of supervoltage radiation therapy. *Arch Surg* 1965;90:90–4.
5. Bucalossi P, Ravasi G, Bozzetti F, Milani F. Treatment of bronchogenic carcinoma with surgery and radiotherapy: the experience of the National Cancer Institute of Milan. *Cancer Chemother Rep* 1973;4:101–7.
6. Guttmann R. Results of radiotherapy in cancer of the lung classified as inoperable at exploratory thoracotomy. *Cancer* 1964;17:37–41.
7. Elkind MM, Swain RW, Alescio T, et al. Oxygen nitrogen recovery and radiation therapy. In: *Cellular radiation biology, 18th symposium on fundamental cancer research, M. D. Anderson Hospital and Tumor Institute.* Baltimore: Williams and Wilkins, 1965:442–61.
8. Thomlinson RH, Gray LH. The histologic structure of some human lung cancers and the possible implications for radiotherapy. *Br J Cancer* 1955;9:539–49.
9. Withers HR, Peters LJ. Radiobiology of high LET irradiation: neutron irradiation. In: Karchen KL, Kogelnik HD, Meyer HJ, eds. *Progress in radio-oncology.* New York: Theime-Stratton Inc., 1980:1–7.
10. Laramore GE, Pajak TF, Griffin TW. Status of fast neutron radiotherapy for non–small cell lung cancer. *Cancer Treat Symp* 1985;2:81–5.
11. Hall EJ, Kraljevic U. Repair of potentially lethal damage: comparison of neutron and x-ray RBE and implications for radiation therapy. *Radiology* 1976;121:731–5.
12. Eichhorn JH, 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.
13. Eichhorn JH. Results of a pilot study on neutron therapy with 600 patients. *Int J Radiat Oncol Biol Phys* 1982;8:1561–5.
14. Schnabel K, Vogt-Moykopf I, Berberich W, Abel U. Vergleich einer Neutronen-mit einer photonenbestrahlung des bronchialkarzinoma. *Strahlentherapie* 1983;159:458–64.
15. Sawada K, Fukuma S, Seki Y, et al. Clinical experience in patients with Pancoast's tumor treated by fast neutron radiotherapy. *Gan No Rinsho* 1983;A7:111–14.
16. Breteau N, Destembert B, Sabattier R, Schlienger M. An interim assessment of the experience of fast neutron boost in glioblastomas, rectal and bronchus carcinomas in Orleans. *Strahlentherapie* 1985;161:787–90.
17. Laramore GE, Bauer M, Griffin TW, et al. Fast neutron and mixed beam radiotherapy for inoperable non–small cell carcinoma of the lung: results of an RTOG randomized study. *Am J Clin Oncol* 1986;9(3):233–43.
18. Livingston RB, Griffin BR, Higano CS, et al. Combined treatment with chemotherapy and neutron irradiation for limited non–small cell lung cancer. *J Clin Oncol* 1987;5:1716–24.
19. Perez CA, Stanley K, Graham G, et al. 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 RTOG. *Cancer* 1982;50:1091–9.
20. Perez CA, Stanley K, Rubin P, et al. 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 RTOG. *Cancer* 1980;45:2744–53.
21. Cox J. Non–small cell lung cancer. *Chest* 1986;89:284S–8S.

0016277