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Letter to the Editor

A Question in Evaluation of Mixed Beam (Neutron/Photon) Therapy

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IN THE Proceedings of the 3rd Meeting on Fundamental and Practical Aspects of the Application of Fast Neutrons and Other High-LET Particles in Clinical Radiotherapy, published as a supplement to the *European Journal of Cancer*, a paper by Griffin *et al.* [1] presents data indicating the superiority of mixed beam (neutron/photon) therapy over all neutron or all photon therapy for cervical adenopathies ($P<0.025$) and primary tumors of the head and neck region. In this report, the responses of 33 cervical adenopathies and 40 primary tumors treated with neutrons between 10 September 1973 and 13 May 1977 are compared with the responses of 80 cervical adenopathies and 84 primary tumors treated with mixed beam during this time period. This 2:1 majority of mixed beam to neutron patients seems odd since the "mixed beam option was added" only in the last $2\frac{1}{2}$ years of the 4-year clinical trial, whereas neutron-only treatments were done in all 4 years. There is no indication in the report that mixed beam treatment was the predominant modality during the last 2 years of the trial. To further illustrate this point, Berry *et al.* [2] reported that between September 1973 and May 1975, out of 36 cervical adenopathy patients treated at the University of Washington, 26 were neutron and 10 were mixed beam. Subtracting these data [2] from those given in the Proceedings report [1] indicates that during the last 2 years of the trial 70 cervical adenopathies were treated with mixed beams and only 7 were treated with neutrons alone. This result would seem incompatible with the assertion that both the mean and maximum follow-up times were equivalent for the two treatment schemes [1]. The numbers are still more puzzling since one month after the Proceedings report, Laramore *et al.* [3] reported that 27 out of 48 University of Washington oropharyngeal cancer patients were treated with neutrons alone. This suggests that oropharyngeal cancer patients, which comprise 38% of all the primary head and neck tumor patients, accounted for 68% of all the head and neck patients treated with neutrons alone. Why was there a predilection to treating oropharyngeal cancer patients with only neutrons? More recently Laramore *et al.* [4] have also reported that 16 cancers of the oral cavity were treated with neutrons and 10 with mixed beams during this time period. Adding the 27 oropharynx patients treated with neutrons to the 16 oral cavity patients treated with neutrons gives a total of 43 primary tumors treated with neutrons. This figure is already larger than the 40 cases reported in the Proceedings [1], not including the 39 primary tumors of the nasopharynx, hypopharynx, larynx and maxillary sinus.

To further explore this problem, I have examined the University Hospital patient records with respect to head and neck patients treated with neutrons at the University of Washington between September 1973 and June 1977. I was able to examine the records of 119 primary tumor patients as compared to the 124 cases reported in the Proceedings, and also I was able to examine the records of 103 cervical adenopathy patients, as compared to 113 cases reported in the Proceedings. Based on the evaluation of the Hospital records, the distribution of these patients among the various treatment schemes is shown in Table 1. These data show that, in contrast to the Proceedings report, 64 adenopathies and 65 primary tumors were treated with neutrons and 39 cervical adenopathies and 54 primary tumors were treated with mixed beans. The validity of these numbers is supported by the fact that the distribution between mixed beam and neutron patients for cervical adenopathies treated prior to 1975 is identical to that reported by Berry *et al.* [2], as well as that for all oropharyngeal cancers reported by

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Table 1. Distribution of patients according to treatment schemes

Treatment	Primary head and neck cancers*	Cervical adenopathy†
1 No. of patients receiving neutrons to primary or node sites	65	64
2 No. of patients receiving mixed beams (neutron/photon) to primary or node sites	54	39
3 No. of patients receiving neutrons to primary or node sites and photons to prophylactic sites	29	33
4 No. of patients receiving mixed beams (neutron/photon) to primary or node sites plus No. of patients receiving neutrons to primary or node sites and photons to prophylactic sites (i.e., 2 plus 3 above)	83(84)‡	72(80)‡
5 No. of patients receiving neutrons to primary or node sites and not receiving photons to prophylactic sites (i.e., 1 minus 3 above)	36(40)§	31(33)§

*Oral cavity (31 patients), oropharynx (48 patients), hypopharynx (16 patients), larynx (11 patients), nasopharynx (8 patients), maxillary sinus (4 patients).

†Patients with primary tumors of the oral cavity (22 patients), oropharynx (38 patients), hypopharynx (13 patients), larynx (11 patients), submaxillary gland (1 patient), parotid gland (1 patient), nasopharynx (7 patients), and maxillary sinus (1 patient); 9 patients had undetermined primary sites.

‡Values in parentheses are the numbers of mixed beam (neutron/photon) patients reported by Griffin *et al.* [1, 5].

§Values in parentheses are the numbers of neutron patients reported by Griffin *et al.* [1, 5].

Laramore *et al.* [3], and is similar to that reported for cancers of the oral cavity by Laramore *et al.* [4]. Only if one characterized mixed beam patients as those patients receiving neutron treatments to the primary tumor (29 patients) or involved nodes (33 patients) *and* those *also* receiving photon treatments to prophylactic sites, can one arrive at the 2:1 majority of mixed beams to neutrons-only patients reported by Griffin *et al.* [1]. Since photon treatments of prophylactic sites were done throughout the trial, this could explain how the follow-up times of the mixed treatment patients reported by Griffin *et al.* [1] are similar to the follow-up times of the neutron patients. However, neutron patients receiving photons to prophylactic sites cannot be considered mixed beam patients since both photons and neutrons were not delivered to the same site.

Therefore, the concept that mixed beam treatment is superior to neutrons alone, based on University of Washington patient data, needs to be carefully re-examined. This is extremely important since the superiority of mixed beams over all neutron or conventional photon therapy appears to be the only significant improvement so far suggested from the use of neutrons in cancer therapy in the United States [1, 5–7].

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Dr. Joseph P. Geraci's Letter to the Editor was sent to

K. BREUR, G. W. BARENDSEN and J. J. BROERSE
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who offer the following comments:

DR. GERACI's Letter to the Editor was sent for comment to us as editors of the supplement of the *European Journal of Cancer* containing the Proceedings of the 3rd Meeting on Fundamental and Practical Aspects of the Application of Fast Neutrons and other High-L.E.T. Particles in Clinical Radiotherapy. As organisers of that Meeting we had invited representatives from all centres in the world, known to have treated more than a hundred patients with fast neutrons, to report on their experiences. The group from the University of Washington (Seattle) had treated more than two hundred patients in pilot studies. Their experience was presented in a paper by Dr. Griffin *et al.*, containing interesting data. As editors we had neither reasons nor means to analyse the data in the way Dr. Geraci did.

As clinical and experimental investigators in the field of fast neutron therapy, it is our opinion that the available data from Houston and Seattle were not quite convincing with regard to biological advantages of a mixed beam therapy and that differences with neutrons alone could be attributed to differences in dose fractionation schemes and dose distribution. For the same reason the High-L.E.T. Therapy Group of the E.O.R.T.C. decided not to include an arm with mixed beam treatments in their trials, but to compare neutrons alone with photon treatment to establish differences in biological effects between both agents, using five daily fractions per week in both arms. The influence of a worse dose distribution in the neutron-treated patients unfortunately can not be eliminated, but by careful planning it is tried to reduce this factor. Carefully planned controlled studies are needed to establish the value of mixed beam treatments.

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