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FAST NEUTRON RADIATION THERAPY

Results of phase III randomized trials in head and neck, lung, and prostate cancers

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The results of phase III trials comparing neutrons to photons for head and neck squamous cell cancers, non-small cell lung cancers, and prostate adenocarcinomas are reviewed, with emphasis given to the most recent U.S. National Cancer Institute sponsored randomized clinical studies in which fast neutrons were delivered using modern, hospital-based, high-energy, isocentric-capable cyclotrons. In locally advanced squamous cell head and neck cancers, neutrons showed no convincing advantage over photons. Fast neutron radiotherapy may have provided a therapeutic benefit in selected patients with inoperable non-small cell lung cancers. For locally advanced prostate adenocarcinomas, neutron therapy resulted in significantly superior clinical and histological loco-regional tumor control, which may translate to improved survival with additional follow-up. In general, severe late complications were more frequent with neutrons, especially in patients treated on older physics laboratory-based equipment. Even with modern state-of-the-art neutron generators, careful beam collimation and treatment planning are required to minimize side effects.

Fast neutron radiotherapy was first introduced into clinical use by Robert Stone and colleagues at the Lawrence Berkeley Laboratory in the 1930s (1). Although dramatic responses were noted in patients with advanced malignancies, there were few long-term survivors, and an unacceptably high incidence of severe late radiation sequalae was reported. These observations discouraged further clinical investigation of fast neutron therapy for approximately two decades. Subsequent basic science experiments, aided by the development of mammalian cell culture techniques, provided more precise data regarding neutron dose and radiobiological effect (RBE), and determined that many of the earliest neutron-treated patients had been seriously overdosed (2).

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With a greater understanding of its physical and radiobiological properties, fast neutron radiation was reintroduced for cancer therapy in the 1960s by Catterall and co-workers at Hammersmith Hospital (3). Early results were highly encouraging, and a major multinational effort was initiated to more fully assess the potential impact of fast neutrons in the clinical management of cancer patients. In the United States, fast neutron radiotherapy was begun in the 1970s using beams from modified physics facilities. Subsequently, the National Cancer Institute (NCI) undertook a multimillion dollar initiative to build several hospital-based, high-energy, isocentric-capable cyclotrons for neutron clinical trials, with these machines entering service in the mid 1980s (4).

The largest number of patients evaluated on randomized studies comparing fast neutrons to standard photon radiotherapy have been those with squamous cell head and neck cancers, non-small cell lung cancers, and prostate adenocarcinomas. The last of the NCI sponsored multicenter phase III trials for patients with these tumors who were treated on the new, state-of-the-art neutron generators were closed to further accrual in March, 1991. This report provides an overview of the randomized clinical experience

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with fast neutron radiotherapy for patients with tumors arising from these three sites.

Head and neck squamous cell cancer

More head and neck (H&N) squamous cell cancer patients have been entered on neutron therapy clinical trials than for any other tumor system. The results of seven phase III randomized trials comparing neutrons to photons for H&N squamous cell cancers have been published (5–11), and are summarized in Table 1. It should be noted that the neutrons used in these clinical studies were derived from physics laboratory-based generators, and that the trial designs varied in the proportion of neutrons delivered as part of definitive radiotherapy (i.e., neutrons alone, 'mixed-beam' on a typical 2x/week neutrons and 3x/week photons schedule, or neutrons used as a boost after moderate dose large field photon radiation). Of these early trials, the Hammersmith experience (5) provided the most compelling data suggesting the superiority of neutrons over photons in the management of advanced H&N squamous cell cancers, an observation supported in part by the M. D. Anderson (6) and RTOG 76-10A (8) randomized studies. However, the Hammersmith study has been criticized for the fact that many of the photon cases were treated at surrounding hospitals, and may have been substantially underdosed. Other investigators have reported no benefit (7, 9, 11), or in fact potentially poorer outcomes (10), with neutrons. In general, more late complications were noted in the neutron-treated patients.

A definitive phase III clinical trial using state-of-the-art equipment, including high-energy hospital-based cyclotrons with isocentric capability and optimal patient set-up features, was instituted to clarify the role of fast neutron radiation for H&N squamous cell cancers. This study, Neutron Therapy Collaborative Working Group (NTCWG) 85-22, accrued a total of 168 evaluable patients between April 1986 and March 1991. Patients with stage III or IV squamous cell cancers or lymphoepitheliomas of the oral cavity, oropharynx, hypopharyx and larynx who were not deemed suitable for surgical resection were eligible. The patients were randomized to receive 20.4 neutron Gy (nGy) in 12 fractions over 4 weeks or 70 photon Gy in 35 fractions over 7 weeks. The two treatment arms were balanced for known prognostic factors. Results of this study are summarized in Table 2. While there is a statistically significant difference in complete response rates for neutrons over photons, this is not translated into significantly improved sustained loco-regional control or survival rates. More frequent severe late toxicity was noted in the neutron-treated group.

At present time, there is no definitive evidence supporting the superiority of neutrons over photons in the treatment of advanced H&N squamous cell cancers. Potential small improvements in clinical outcome with neutrons are often offset by increased late normal tissue injury. The advantage for fast neutron therapy over conventional radiotherapy in this patient population may be limited to the logistic benefit of treatment completion in a significantly shorter period of time (4 weeks for neutrons versus 7+ weeks for photons).

Non-small cell lung cancer

Interest in the use of neutrons for treatment of non-small cell lung cancer (NSCLC) was generated by Eichhorn (12), who performed detailed autopsy evaluations on a retrospective series of patients with inoperable bronchogenic carcinomas who were irradiated with photons alone or mixed photons and neutrons to the same radiobiological dose. Sterilization of gross tumor was noted in 33% (47/149) of patients treated with telecobalt alone, compared to 48% (36/75) of patients who received 20% of their radiation dose with neutrons, and 57% (28/49) of patients in whom neutrons accounted for 35% of the total dose. The differences in tumor clearance rates were significantly different. Subsequently, a similar study was performed but with a 'randomized' design. Twenty percent (11/58) of control patients treated entirely with telecobalt radiation had complete histologic eradication of local tumor at the time of autopsy, compared to 39% (25/64) of patients who received 41% of their biologically equivalent radiation dose with neutrons, an observed difference that was statistically significant with $p = 0.016$ (12).

Two early randomized studies comparing neutrons to photons in the treatment of NSCLC have been published. The fast neutrons used in both trials were from modified physics laboratory-based equipment (13, 14). Schnabel and associates treated 115 patients, 48 of whom were randomized to receive 18 nGy with neutrons versus 54 Gy in 20 fractions for 67 patients who received photons. There was no difference in local tumor control and overall survival between the two groups (13). The RTOG performed a three-arm study (79-07) in which patients with inoperable NSCLC were randomly assigned to photons alone, neutrons alone, or a 'mixed-beam' group treated with combined photons and neutrons. All patients received 60 Gy photon-equivalent dose. There was no overall difference in local control or survival among the three groups. However, in patients who maintained objective loco-regional tumor response at 6 months from the initiation of radiotherapy, there was a slight, although non-statistically significant, trend toward increased long-term survival favoring the neutron and mixed beam arms (14). Both these studies noted a higher incidence of severe late complications with neutrons.

A definitive phase III trial, NTCWG 85-24, comparing neutrons versus photons for inoperable (mostly stage III) NSCLC using state-of-the-art neutron generators, was undertaken from September 1986 to March 1991. After

Table 1

Summary of published randomized trials comparing neutron to photon radiotherapy for loco-regionally advanced (stages III and IV) head and neck squamous cell cancer

Trial (Reference)	Treatment arms	Evaluable patients	Complete response (CR)	Loco-regional control (LRC)	Actuarial 2-year survival	Severe late complications	Comments
Hammersmith (5)	Neutrons 15.6 nGy in 12 fx over 4 wks	70	77%	76%	28%	10/70	Statistically significant improvement in CR and LRC with neutrons. Survival trend favoring neutrons, but not statistically significant.
	Photons 45.4–68.4 Gy over 4–6 wks	63	43%	19%	15%	2/63	
MD Anderson (6)	Mixed-beam 2x neutrons and 3x photons/wk to 70 photon Gy equivalent	54	80%	44%	37%	7%	Actuarial analysis showed improved LRC and survival at 2 years favoring neutrons, which is lost at later times.
	Photons 70 Gy in 35 fx over 7 wks	41	68%	41%	20%	10%	
European collaborative trial (7)	Neutrons 15.6–18 nGy in 20 fx over 4 wks	100	70%	34%	33%	Increased late skin injury with neutrons, but overall complication rate similar.	No differences in CR and LRC. No overall difference in survival, but larynx patients have better survival with photons.
	Photons 54–70 Gy in 20–35 fx over 4–7 wks	95	66%	39%	39%		
RTOG 76-10A (8)	Neutrons 20.4–25 nGy over 7–8 wks	23	52%	42%	25%	18%	Statistically significant CR rate favoring neutrons, but lost with surgical salvage (*42% with surgery). Survival and complication differences not significant.
	Photons 66–74 Gy over 7–8 wks	12	17%*	13%	0%	33%	
RTOG 76-10B (9)	Mixed-beam 2x neutrons and 3x photons/wk 7.5–10 neutron Gy + 40–44 photon Gy over 7–8 wks	163	56%	27%	30%	18%	No overall differences in CR, LRC or survival. Difference in complication rate is statistically significant. There is significantly better nodal control in the mixed-beam arm, but primary tumor control and survival favors photons in node-negative patients. Reasons for potential geographic miss of tumor by neutrons are given to explain the apparent inconsistencies.
	Photons 66–74 Gy over 7–8 wks	134	58%	34%	33%	10%	
Edinburgh (10)	Neutrons 15.6–16.7 nGy in 20 fx over 4 wks	85	71%	45%	29%	24%	Non-significant trend to improved survival for photon patients, especially for oropharynx and larynx primaries. More severe late toxicity with neutrons.
	Photons 54–56 Gy in 20 fx over 4 wks	80	78%	45%	41%	13%	
RTOG 78-08 (11)	Neutron boost 25–30 Gy photon equivalent over 2–3 wks	57	60%	20%	32%	16%	No statistically significant differences in CR, LRC and survival. Increased severe complications with neutrons.
All patients: 45–50 Gy photons in 25 fx to wide fields	Photon boost 25–30 Gy over 2–3 wks	58	64%	31%	41%	7%	

Table 2

Results of NTCWG 85-22: neutrons versus photons for loco-regionally advanced head and neck squamous cell cancer

	Neutrons	Photons
Number of evaluable patients	83	85
Complete response rate	71%	51% ($p = 0.002$)*
Sustained LRC rate	39%	31% ($p = 0.2$)*
Actuarial 2-year overall survival rate	36%	36%
Major late complication rate	19%	9% ($p = 0.13$)*

* Statistical analysis by χ^2 or log-rank test.
LRC = loco-regional control

Table 3

Results of NTCWG 85-24: neutrons versus photons for inoperable non-small cell lung cancer

	Neutrons	Photons
All patients		
Number of evaluable patients	99	94
Local control*	85 (86%)	82 (87%)
Median survival	9.7 m	8.9 m
Overall actuarial survival		
1 year	40%	36%
2 year	14%	10% (p = n.s.)**
Squamous cell subset		
Number of evaluable patients	48	45
Overall actuarial survival		
1 year	36%	25%
2 year	16%	3% ($p = 0.02$)**
'Favorable prognostic' subset***		
Number of evaluable patients	45	28
Overall actuarial survival		
1 year	46%	35%
2 year	19%	6% ($p = 0.15$)**

* Local control defined as freedom from radiological evidence of disease progression within the irradiated volume.
** Statistical analysis by log-rank test
*** 'Favorable prognostic' group excludes patients with T4 or N3 disease, pleural effusions, or weight loss > 5% from baseline.

stratification for prognostic factors and treating institutions, a total of 200 patients were randomized to receive either 66 photon Gy in 33 fractions over 7 weeks or 20.4 nGy in 12 fractions over 4 weeks. Eligibility criteria included histologic proof of NSCLC without distant metastases or cytologically positive pleural effusion, surgical unresectability and/or medical inoperability, and patient Karnofsky performance score ≥ 70. A total of 193 patients, 99 on the neutron arm and 94 on the photon arm, were analyzable. The two treatment groups were balanced for all known prognostic factors. Results of the study are summarized in Table 3 (15). As a consequence of obscuring radiation pneumonitis and fibrosis, local tumor control within the irradiated fields, was difficult to assess, and the loco-regional control rates reported are unquestionably overestimated, especially in light of the autopsy-based data of Eichhorn described previously (12). While there was no overall difference in survival between the two treatment arms, there was a statistically significant survival advantage favoring neutrons in subgroup analysis for patients with squamous cell histology. Additionally, there was a possible trend, although non-statistically significant, towards increased survival for the neutron-treated patients when analysis was limited to those with 'favorable prognostic' factors (i.e., excluding patients with T4 or N3 tumors, pleural effusion, or weight loss > 5% from baseline). With the exception of some increased mild to moderate asymptomatic late skin and subcutaneous changes seen with neutrons, toxicity was equivalent in both treatment arms.

Any potential advantage for neutrons over photons in treatment outcome for NSCLC would have to be explainable in terms of loco-regional control of tumor, despite the difficulties in assessing this clinically in irradiated patients. Due to radiation-induced radiographic changes, loco-regional tumor control is a suboptimal measure of therapeutic efficiency in NSCLC patients. Survival, which includes the impact of loco-regional control, represents a better study endpoint. Furthermore, improved loco-regional tumor control would only lead to improved survival in clinical situations where distant metastases do not completely dominate the natural history. These considerations may explain the observed benefit of fast neutron radiotherapy in selected patients with inoperable but otherwise 'prognostically' favorable NSCLC.

Prostate adenocarcinoma

Numerous laboratory investigations have demonstrated that neutron-irradiated cells are less susceptible to hypoxia-induced radioresistance, have decreased sublethal and potentially lethal damage repair, and show less variation of cell cycle radiosensitivity as compared to conventional low linear energy transfer (LET) radiation (16). These observations have suggested that neutrons may provide a therapeutic benefit in the treatment of slow-growing, low-growth fraction, and often bulky tumors such as prostate adenocarcinomas.

Only two randomized clinical trials comparing neutron to photon radiotherapy for prostate cancer have been completed. From 1977 to 1983, 91 evaluable patients with stage C or D1 disease were randomized to mixed-beam versus photon radiation in a Radiation Therapy Oncology Group study (RTOG 77-04). The mixed-beam (2x/week neutrons, 3x/week photons) design was incorporated because of concerns regarding poor depth-dose characteristics with the neutron beams obtained from physics-based generators. The randomization was purposely unbalanced such that 60% of the patients were assigned to the mixed-beam arm. All patients received 50 Gy photon equivalent

dose to the pelvis at 1.8–2.0 Gy daily fraction (neutron dose was adjusted according to institutional RBE and expressed as photon dose equivalent), followed by a boost of 20 Gy photon equivalent to the prostate and areas of known bulky periprostatic extension (17). The updated results from this study have been recently published (18). Statistically significant differences favoring mixed-beam over photons have persisted to the 10-year analysis time-point, in terms of clinical loco-regional tumor control (70% versus 58%, $p = 0.03$) and overall survival (46% versus 29%, $p = 0.04$). Late severe normal tissue toxicity appeared similar in both treatment arms.

A confirmatory phase III study (NTCWG 85-23) employing modern, hospital-based cyclotrons was implemented. From April 1986 to October 1990, a total of 172 evaluable patients were randomized to definitive neutron versus photon radiotherapy. With the improved treatment beam characteristics of the new neutron generators, it was decided that the investigational arm would consist solely of neutron rather than mixed-beam radiation. Patients with stages C, D1, and high grade (Gleason grade $\geqslant 7/10$) B2 tumors, no common iliac adenopathy, and no prior curative surgery were eligible. Patients were stratified by stage, Gleason grade, and surgical nodal staging. Photon-treated patients received 50 Gy in the pelvis, with a boost of 20 Gy for a total gross tumor dose of 70 Gy, at 1.8–2.0 Gy per fraction over 7–8 weeks. Neutron patients received 13.6 nGy in the pelvis, with a boost of 6.8 nGy, for a total dose of 20.4 nGy in 12 fractions over 4 weeks (1.7 nGy per fraction). The two treatment groups were balanced for all known prognostic factors. Results of NTCWG 85–23 are summarized in Table 4 (19). Significantly improved outcomes for neutrons over photons have been observed with respect to clinical and histological loco-regional control rates. Likewise, a significantly lower proportion of neutron-treated patients alive at 5 years have elevated prostate specific antigen levels, as compared to photon patients. However, in this slow-growing tumor system for which secondary therapies, such as hormones, are widely used and effective, these observed advantages for neutron radiation have not yet translated to improved overall or cancer-specific survival.

While neutrons were associated with significantly increased severe late toxicity, further analysis revealed this to be dependent on the amount of beam collimation available at each of the neutron treatment facilities (19). Colostomies for bowel injury constituted a significant proportion of the severe late complications seen, with a total of six in 87 neutron-treated study patients. However, of 51 patients treated with neutrons on NTCWG 85-23 at the University of Washington using a cyclotron equipped with a continuously variable multileaf collimator, none have required a colostomy. To date, over 250 patients have received fast neutron radiotherapy for prostate cancer at the University of Washington Medical Center hospital-based cyclotron, with no resultant colostomies, emphasizing the importance of beam energy, collimation and detailed treatment planning.

Conclusions

- Fast neutron radiotherapy can be delivered safely and effectively with modern high-energy, hospital-based, isocentric-capable neutron generators. The increased severe late toxicity seen in many of the earlier trials were due in great part to the use of lower-energy physics laboratory-based machines with poor patient set-up capabilities. However, even with state-of-the-art equipment currently available, the therapeutic margin for neutrons is smaller than with low LET radiation, and

Table 4

Results of NTCWG 85-23: neutrons versus photons for loco-regionally advanced prostate adenocarcinoma

	Neutrons	Photons
Number of evaluable patients	87	85
Clinical complete response	94%	96% (p = n.s.)
Actuarial 5-year clinical LRC rate*	89%	68% (p < 0.01)***
Actuarial 5-year histological LRC rate**	87%	68% (p = 0.01)***
Abnormal PSA at 5 years	17%	45% (p < 0.001)***
Cancer-specific survival rate	68%	59% (p = n.s.)***
Actuarial 5-year severe complication rate	11%	3% (p = 0.03)***

* Clinical LRC was assessed by digital rectal examination, serum acid phosphatase, and when available, prostate specific antigen.

** Histological LRC incorporated clinical LRC data as well as the results of routine post-treatment biopsies in selected patients, irregardless of their clinical status.

*** Statistical analysis by χ^2- or log-rank test

LRC = local-regional control;

PSA = prostate specific antigen

attention to careful beam collimation and treatment planning is crucial.

- There is no definitive evidence supporting the superiority of neutrons over photons in the treatment of locally advanced head and neck squamous cell cancers. The advantage for fast neutron therapy in this patient population may be limited to the logistic benefit of treatment completion in 4 weeks versus 7+ weeks for conventional photon radiotherapy.
- Fast neutron radiotherapy appears to provide a survival advantage for carefully selected patients with inoperable non-small cell lung cancer, namely those with squamous cell histologies and/or 'favorable prognostic' factors, for whom the risk of occult distant metastases may be relatively lower.
- Fast neutron radiotherapy provides superior clinical and histologic loco-regional tumor control over conventional photons for patients with locally advanced prostate adenocarcinomas. While previous experience has indicated an improvement in survival favoring neutrons as well, additional follow-up is required for the most recent randomized study (NTCWG 85-23) to determine if increased loco-regional tumor control with neutrons eventually leads to a survival advantage.

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