EIGHT YEARS EXPERIENCE WITH NEUTRON RADIOTHERAPY IN THE TREATMENT OF STAGES C AND D, PROSTATE CANCER: RESULTS OF THE RTOG 7704 RANDOMIZED CLINICAL TRIAL

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ABSTRACT

The records of 91 patients enrolled between June 1977 and April 1983 in the Radiation Therapy Oncology Group (RTOG) randomized study investigating fast neutron radiation therapy in the treatment of locally advanced prostate cancer were reviewed. Patients with stages C and D_1 adenocarcinoma were randomized to receive either combined fast neutron and photon irradiation (mixed-beam) or conventional photon irradiation alone. Survival (actuarial) at 8 years for the mixed beam cohort was 63% versus 13% for the patients receiving photons alone ($p=0.01$). Corresponding "determinental" survival rates, adjusted by exclusion of intercurrent deaths, were 82% and 54% respectively ($p=0.02$). Freedom from locally recurrent prostate cancer was 77% for mixed beam patients and 31% for patients receiving photons alone ($p<0.01$). Analyses of outcomes accounting for all major prognostic determinants confirm the greater efficacy of mixed beam treatment with $p<0.05$ for survival, determinental survival, and local control. These results suggest that a local modality (neutrons + photons) can have a favorable survival impact on locally advanced prostate cancer, and have formed the basis for the currently activated RTOG trial randomizing patients with stages B_2, C, and D_1 prostate cancer to treatment with either photons or fast neutrons alone.

INTRODUCTION

The management of loco-regionally advanced prostate cancer remains an issue of considerable controversy. While the hormonal treatment of patients presenting with metastatic disease engenders little debate, and while there is solid data to confirm the comparable efficacy of radical prostatectomy or megavoltage photon irradiation in the control of early lesions localized within the gland itself [1] the treatment of stages C and D_1 presentations is not well agreed upon by the oncologic community. A number of studies have yielded long-term survival data for patients treated with megavoltage photon irradiation for these presentations, and appear to favor this approach [2-6]. Other investigations have yielded data to support the thesis that photon irradiation does not substantially alter the natural history of the disease in this same group of patients [7-8].

This study compares conventional photon irradiation of stage C and D_1 patients to a treatment employing fast neutron irradiation as a component of the therapy. The theoretical advantage of neutrons over photons in the treatment of malignancies relates to the far greater energy deposition by neutrons in soft tissues. Considered "high LET" irradiation (LET = Linear Energy Transfer), neutrons deposit as much as 20-100 times more energy than photons per cm of tissue traversed. The biological consequences of this enhanced energy deposition are multiple, and the result is an enhanced relative biologic effectiveness (RBE) of neutrons compared with photons, as measured in both laboratory models and in human studies. Whereas conventional megavoltage photons have an

RBE = 1, neutron RBE varies from 3.3 to 8.0, depending on the specific organs and tissues being irradiated [9]. The possibility that this high RBE might be exploited in the treatment of prostate cancer is addressed in this trial.

METHODS AND MATERIALS

Ninety-five patients were accrued onto the study between June 1977 and April 1983. Four patients have been excluded from the analysis (3 ineligible by the original protocol criteria, and one refusing the assigned treatment arm). Of the remaining 91 patients, all had biopsy confirmation of adenocarcinoma and were staged as C (29 photon, 45 mixed beam) or D_1 (7 photon, 10 mixed beam) lesions. Additional eligibility criteria required patients to be less than 80 years old, have an initial Karnovsky performance score of greater than 40, and no prior history of pelvic irradiation, extensive prior surgery, or cancer (excepting non-melanoma skin cancer). Prior hormonal treatment was permitted, and 25% of the photon patients had received prior hormones versus 11% of the mixed-beam. Informed consent was obtained from all patients.

All patients underwent a pre-treatment staging evaluation including history and physical examination, complete blood counts and serum chemistries, liver function tests, alkaline and acid phosphatases, chest X-ray, and a radionuclide bone scan. Computerized tomographic scans (CT) of the pelvis were performed in approximately one half of the

patients and bipedal lymphangiography was performed on 41 patients. Three (8%) photon patients and 5 (9%) mixed beam patients underwent surgical node sampling.

Patients were randomized to receive either photon irradiation alone or mixed beam irradiation. Mixed beam treatment involved twice weekly treatment with neutrons and three times weekly irradiation with photons. The randomization of patients was purposely unbalanced (60%-40%) to allow larger numbers of patients on the experimental mixed beam arm (55 versus 36).

The neutron treatment facilities involved included: the University of Washington, the Great Lakes Neutron Treatment Association, the M.D. Anderson Hospital and Tumor Institute at the University of Texas, and the Fermilab. Neutron doses at each facility were adjusted according to the measured RBE of the neutrons from each cyclotron. As neutron irradiation contains a small percentage of photon contamination, this photon component was included in the specified neutron dose.

The decision to make the experimental arm a neutron/photon mix arose out of concern about using neutrons alone to treat the large volumes involved in adequately encompassing the regional pelvic lymph nodes. The poor penetration of many of the neutron beams then currently available could result in an unacceptably high dose to pelvic subcutaneous tissues in the process of treating the deep-seated primary and lymph nodes to a tumoricidal dose, and possibly result in unacceptable late complications.

Patients treated with photon irradiation alone received a dose of 5,000 cGy to a field encompassing the prostate and pelvic lymph nodes at a daily rate of 180 to 200 cGy per fraction, with a subsequent boost of 2,000 cGy (same fractionation) to the prostate and areas of proven bulky extra-prostatic disease. Patients treated with mixed beam irradiation received a dose of 5,000 cGy "photon equivalent" (neutron dose multiplied by the institutional RBE, and summed with the photon dose), plus a similar 2,000 cGy photon equivalent boost, as before. A fractionation scheme of 180-200 cGy photon equivalent was given per day, and all patients were treated five days per week. Photon or photon equivalent radiation doses to the posterior rectum were limited to 5,500 cGy and to the entire bladder to 6,000 cGy.

Computer generated isodose calculations and plots were obtained in all patients, and portal films confirming the accuracy of the treatment were obtained for each treatment field.

Following completion of treatment, all patients were seen in follow-up at monthly intervals for the first three months, at three month intervals for the next 2 3/4 years, and every 6 months thereafter. At this time, the median follow-up time is 6.7 years.

Statistical analyses of data have employed the chi-square test, the Wilcoxon test [10], the Mantel-Haenzel test [11], and Kaplan-Meier actuarial tables [12].

RESULTS

Data analysis has been performed on 91 patients. Although review of patient records revealed that 13 patients were treated with major deviations from protocol (5-photon and 8-mixed beam), usually involving too low a neutron component of treatment (< to 25% of overall dose instead of 40%) or excessively long times to complete treatment (>75 days), no statistical differences in survival or local control could be confirmed for protocol violators, as reported in an earlier analysis [13]. Consequently, the results of treatment for the entire 91 patients have been included in this report.

Using chi-square analysis, the two groups proved to be balanced according to age, stage (C vs. D_1), presence of seminal vesical invasion, tumor grade (both Mostofi grade [14] and Gleason pattern score [15]), Karnofsky performance status, prior hormonal therapy, method of diagnosis (needle biopsy versus transurethral resection), percentage of patients having nodal evaluation radiographically or surgically, and percentage of patients with elevated serum acid phosphatase at presentation. Tumor size, derived from the product of the perpendicular diameters assessed on digital examination, was larger in the photon-treated group, and concomitant benign prostatic hypertrophy was more frequent in the mixed-beam group. Excepting Gleason scores, which were determined retrospectively by review of 73/91 cases for which biopsy material was available, all parameters were scored at the time of entry of each patient onto study.

Survival data is calculated according to the actuarial method of Kaplan and Meier, and is displayed in Figure 1. Sixty three percent of the mixed beam group is alive at 8 years as opposed to 13% of the photon cohort ($p = 0.01$). When one excludes intercurrent deaths from causes other than prostate cancer, the corresponding determinental survival data is summarized in Figure 2. Eighty two percent of the mixed beam group is alive at 8 years compared with 54% of the photon group ($p = 0.02$).

The success of the two treatments in controlling the local prostate cancer is depicted in Figure 3. Criteria defining local recurrence of tumor were: 1) histologic confirmation of persistent tumor by needle biopsy at 2 years post treatment, 2) increase in the product of tumor dimensions by 25% following treatment, (3) new extension of the tumor after initial regression, (4) radiographic or clinical evidence of progression in the pelvic nodes. No standardized approach to routine biopsy of the prostate was mandated in this study. A total of 11 biopsies were performed. The data in Figure 3 thus reflects recurrences scored by either clinical or pathologic criteria. Seventy seven percent of the mixed beam patients remained free of local recurrence of their tumor, as compared to 31% of the photon patients ($p < 0.01$). If one constructs curves based solely upon clinical criteria of recurrence alone, the standard upon which most of the results in the literature are based, the result is seen in Figure 4, where the differences in local control (81% and 61%) remain significant ($p<0.01$).

Complications of the two treatments are summarized in Tables 1 (photons) and 2 (mixed-beam). Scoring of complications conformed to RTOG criteria, and ranged from no measurable morbidity in the organ system involved (score of 1), to a lethal complication (score of 6). Overall, the two treatments have comparable attending side effects. The mixed-beam patients characteristically displayed greater acute and self-limited skin reactions, and a greater propensity to mild localized edema. Acute rectal complaints (usually tenesmus) were more frequent as well in the patients receiving mixed-beam therapy, without chronic or late sequelae. One patient in each treatment group suffered a fatal complication of treatment.

DISCUSSION

Neutrons and photons differ significantly in their interactions with tissues, with a far greater "intensity" (linear energy transfer or LET) of energy deposition by neutrons while traversing through tissues. As a result of this intense deposition of energy, or at least associated with it, there are a number of discreet biologic differences between neutrons and photons that would suggest a superiority of neutrons in the treatment of malignant tumors.

First, there is the decreased ability of tumors to repair neutron induced damage, assayed in laboratory systems as diminished "sublethal damage" repair, and diminished "potentially lethal" damage repair (PLDR) [16,17]. PLDR is a form of repair of radiation damage which occurs in slowly proliferating tissues with a low growth fraction and a

large quiescent (G_0) population, and might be expected to be a particularly relevant in prostate cancer.

Additionally, neutrons are less dependent than photons on the presence of cellular oxygen to achieve cell killing. Whereas there is a factor of 3 difference in the photon radiosensitivity of sensitive oxygenated tumors versus resistant hypoxic tumors, this ratio of sensitivities is 1.6 for neutron radiation [18].

Lastly, there is less variation across the cell cycle in radiosensitivity to neutrons than to photons, and there is evidence that neutrons and photons incur DNA damage by different mechanisms. Photons are thought to cause DNA strand breaks by indirect mechanisms involving the generation of free radicals. Neutron damage appears to occur by direct action on the DNA [19].

Overall, these properties of neutrons result in a greater relative biologic effectiveness (RBE) than for photons, (measured as the inverse of the ratio of neutron dose to photon dose required to achieve a given biologic endpoint). Whether this increased RBE is selective for tumors, or applies equally to normal tissues, is not fully known. In certain tissues and histologies, salivary gland adenoid cystic tumors for example, the RBE for the tumor is 8.0, whereas the RBE for the surrounding normal tissues is 3.0 [9]. Comparable data for prostate adenocarcinoma and the adjacent normal prostate, bladder, and rectum, is not as clearly known, and the tolerance of these organs to neutron irradiation has only been determined by Phase I and II clinical trials. Nonetheless, the overall differences in biologic effects between neutron and photon irradiation are compelling enough to suggest

a theoretical superiority for neutrons over photons, particularly in the treatment of slow growing, low growth fraction tumors typified by adenocarcinoma of the prostate. As the photon irradiation of locally advanced prostate cancer has been far from uniformly successful, the use of neutrons as a part of the treatment tests whether a theoretically more effective local modality can impact on overall survival of these patients.

Considerable controversy is evident in the oncologic literature regarding the most efficacious management of locally advanced prostate cancer. It is contested whether a local modality can have substantial impact at all in a clinical situation that is felt by many to imply systemic dissemination of tumor. A number of investigators have reported long-term survival data supporting the use of external beam megavoltage photon irradiation in stage C presentations [2-6]. Other investigators have presented survival data to suggest that external beam photon radiotherapy in stage C patients does not alter the natural course of the disease any more effectively than delayed androgen deprivation [8].

Similar debate surrounds the treatment of patients with histologically proven pelvic lymph node metastases. While pelvic irradiation has been advocated by some, with long term survivals reported in patients with surgically documented lymph node involvement [20], the efficacy of this treatment is discounted by others, who find equivalent survivals in groups treated without pelvic irradiation [7], by palliative surgery, or by hormonal deprivation [21].

This study cannot provide data to either prove or disprove the efficacy of photon irradiation in these clinical settings. It appears, however, with a median follow-up of 6.7 years, that there is evidence to suggest that the treatment involving neutrons is superior to that employing solely photons, both by criteria of survival and local control. A stepwise Cox analysis, applied to identify patient parameters determining overall survival yielded the finding that treatment modalitiy (mixed beam vs. photons) was the most important predictor of outcome ($p < 0.01$), even over stage (C vs D), elevation of serum acid phosphatase, and age. This has been discussed in detail in a prior report [13].

It is evident that the photon results in this study (5 year survival and local control rate of 51% and 61%) are inferior to that reported from other institutions, where external beam photon irradiation was used to treat stage C patients. Perez et al. have described a tumor-free 5 year actuarial survival of 56% for a similar cohort of patients, with a local failure rate of 12% for patients receiving at least 7,000 rad to the prostate [3]. The results of Rangala et al. are a 5 year actuarial disease-free survival of 69% in stage C patients, with a "local recurrence-free survival" of 76% [5]. Bagshaw has reported a 5 year actuarial survival of 61% in 219 patients with extracapsular extension of tumor outside the prostatic capsule [1], and the Patterns of Care study, reviewing national practice standards and results in prostate cancer, revealed a 19% 5 year local recurrence rate in stage C tumors treated with at least 6500 rad [22]. Neglia et al. found a 5 year survival of 58.5% for their patients with advanced stage C disease

(invading bladder or rectum, or fixed to pelvic sidewalls), and a local control rate of 71.7% for these patients, who are similar in their advanced stage to those in this study. Less advanced stage C patients in that series had a local control of 93.8% and 5 year survival of 72.2% [3]. As these investigators correlated photon control rates and survival outcomes with tumor size, and as there is a similar correlation found in the post-irradiation biopsies performed in the Stanford series [23], this may account for some of the differences in outcome, as most of our patients had locally extensive tumors. Additionally, the inclusion of stage D_1 patients in our results may bias the outcomes unfavorably.

In an effort to better understand these results, survival analysis was performed on the current patient groups, excluding the patients with documented D_1 presentations. Figure 5 compares the survival of stage C mixed-beam treated patients with stage C photon treated patients from both this study as well as from a prior RTOG study (#75-06) [24] involving similarly treated stage C patients. With the stage D_1 patients so excluded, the 5 year survival data for the two photon groups, 58% (current study) and 65% (#75-06) are more comparable with other published series using photon irradiation. Nonetheless, the mixed-beam therapy group exhibits a superior result when compared to both photon-treated groups.

One issue as yet unresolved is whether the mixed-beam treatment is superior to photons in achieving complete <u>histologic</u> clearance of tumor. Post treatment biopsy was not mandatory in this study, and as only 11 patients have been biopsied (on a somewhat <u>ad hoc</u> basis), no conclusions can be drawn from the study in this regard. Much disagreement surrounds

the significance of a post-treatment biopsy uncovered in the clinical context of a normal prostate exam, with published data which suggests either no prognostic significance for this finding [25,26], or conversely, a signficantly adverse outcome [27]. As a majority of Stage C patients may prove to have a positive biopsy 18 months or more following treatment [23], this is another parameter by which the efficacy of mixed beam treatment will need to be judged.

With the advent of a new generation of hospital based, high-energy cyclotrons, designed solely for medical applications, and capable of delivering doses at depth comparable to the dose distributions of a megavoltage linear accelerator, the opportunity has emerged to use neutrons alone in the treatment of prostate cancer.

In April of 1986, the RTOG initiated a randomized trial comparing neutrons versus photons in the treatment of stages B_2 (Gleason score > 6), C, and D_1 adenocarcinomas of the prostate. Surgical staging of pelvic lymph nodes has been encouraged, and routine biopsy of the prostate 18 months post-treatment is mandatory. Patients with radiographic or histologic evidence of pelvic nodal involvement receive large fields covering the pelvic lymph nodes followed by boost fields to the prostate. Those without evidence of nodal spread receive small treatment fields covering the prostate alone, as results from a prior RTOG trial (#77-06) fail to show an advantage for prophylactic pelvic nodal irradiation for node negative patients [28].

To date, acute reactions among the patients treated with neutrons have been reasonable and self-limited, and the neutron fractionation

schema, given as 12 treatments over a period of 4 weeks, has been well received by the patients.

Should this study prove as successful as the current study, it will add further evidence that a local modality can successfully impact on the survival of patients with locally advanced prostate cancer.

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FIGURE LEGENDS

Figure 1: RTOG 7704: SURVIVAL

Figure 2: RTOG 7704: DETERMINENTAL SURVIVAL
Intercurrent non-cancer deaths excluded

Figure 3: RTOG 7704: LOCAL CONTROL OF PROSTATE CANCER
Clinical and biopsy criteria combined

Figure 4: RTOG 7704: LOCAL CONTROL OF PROSTATE CANCER
Clinical criteria alone

Figure 5: COMPARISON OF RTOG 7704 AND RTOG 7506
Stage C (No Positive Nodes) -- Survival

Table I

RTOG 7704 - COMPLICATIONS OF PHOTON TREATMENT

36 Patients

Complication	Grade* 1	2	3	4	5	6	Total 2-6	(%)
Local Edema	33	3	0	0	0	0	3	(8%)
Skin	31	5	0	0	0	0	5	(14%)
Urinary	24	5	4	3	0	0	12	(33%)
Rectal	24	9	2	0	0	1	12	(33%)
Gast Int	26	8	1	1	0	0	10	(28%)
Hematologic	36	0	0	0	0	0	0	(0%)
TOTAL		30	7	4	0	1	42	

Total Patients with a complication = 23 (64%)

*1=None
2=Mild
3=Moderate
4=Severe
5=Life Threatening
6=Lethal

Table II

RTOG 7704 - COMPLICATIONS OF MIXED-BEAM TREATMENT

55 Patients

Complication	Grade* 1	2	3	4	5	6	Total 2-6	(%)
Local Edema	41	12	2	0	0	0	14	(25%)
Skin	31	18	4	2	0	0	24	(44%)
Urinary	34	18	2	1	0	0	21	(38%)
Rectal	23	25	6	1	0	0	32	(58%)
Gast Int	33	16	4	1	0	1	22	(40%)
Hematologic	53	1	1	0	0	0	2	(4%)
TOTAL		90	19	5	0	1	115	

Total Patients with a complication = 42 (76%)

*1=None
2=Mild
3=Moderate
4=Severe
5=Life Threatening
6=Lethal

Figure 1

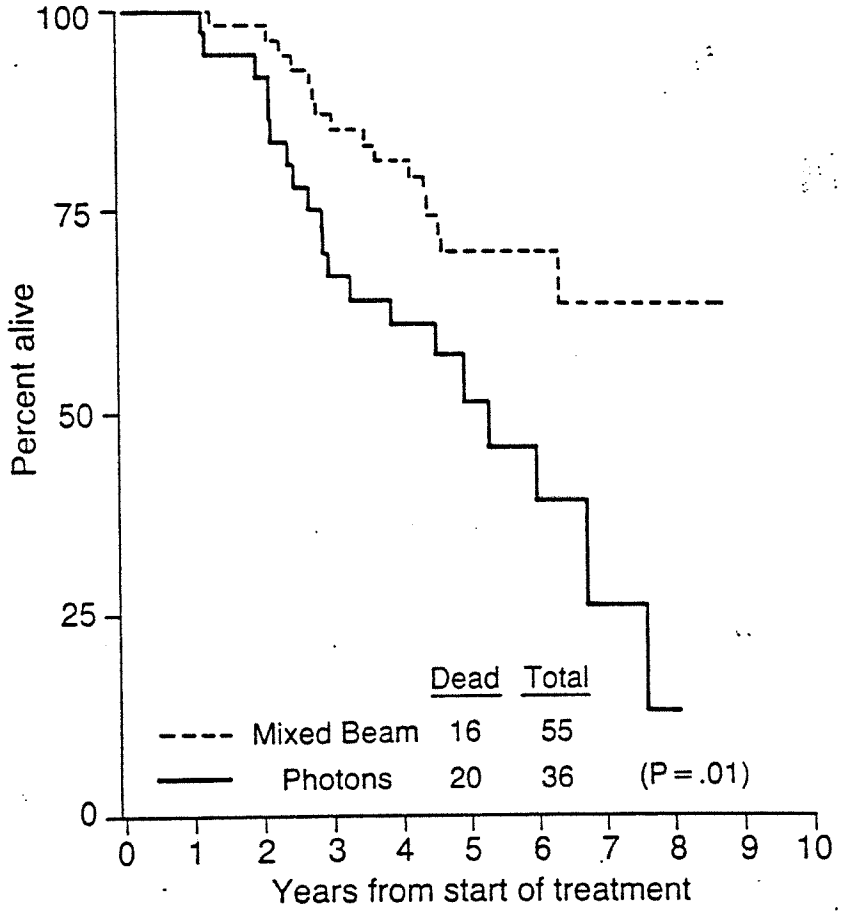

100
75
50
25
0
Percent alive
Dead Total
Mixed Beam 16 55
Photons 20 36 (P = .01)
0 1 2 3 4 5 6 7 8 9 10
Years from start of treatment

Figure 2

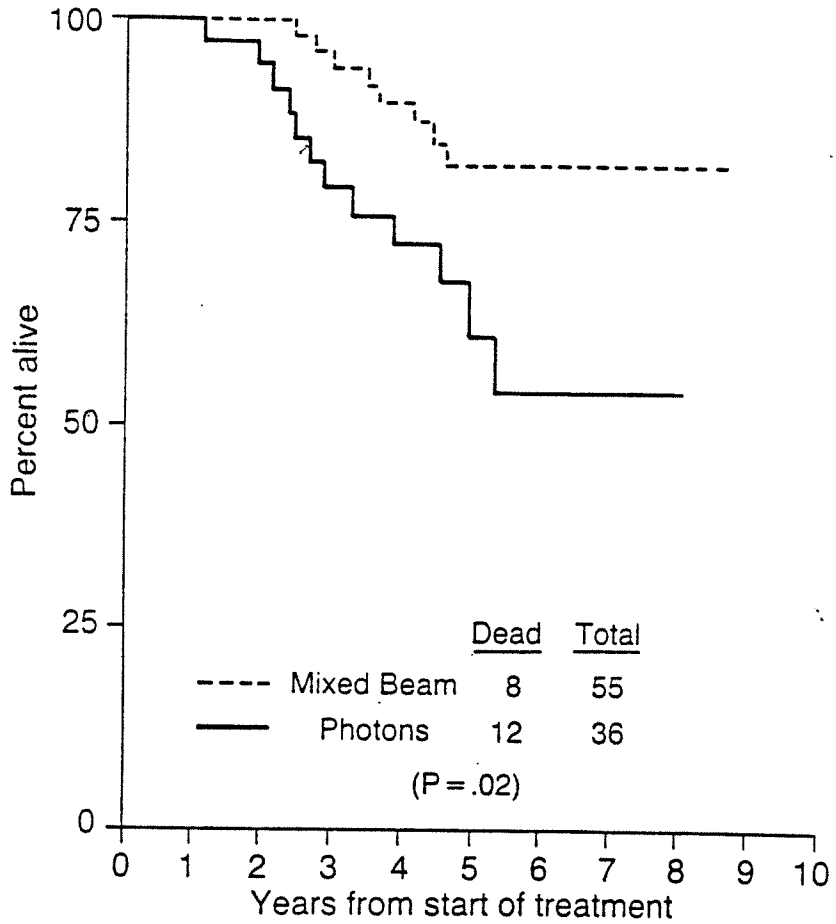

100
75
50
25
0
Percent alive
Dead
Total
Mixed Beam
8
55
Photons
12
36
(P = .02)
0
1
2
3
4
5
6
7
8
9
10
Years from start of treatment

Figure 3

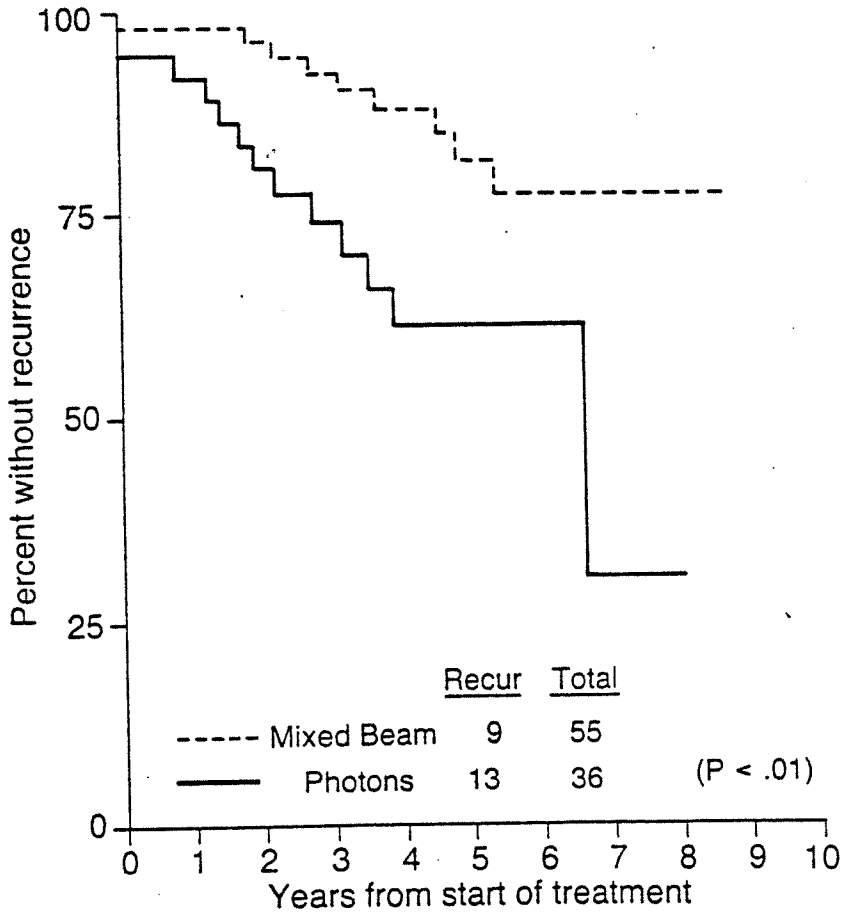

100
75
50
25
0
Percent without recurrence
0 1 2 3 4 5 6 7 8 9 10
Years from start of treatment
Recur Total
Mixed Beam 9 55
Photons 13 36
(P < .01)

Figure 4

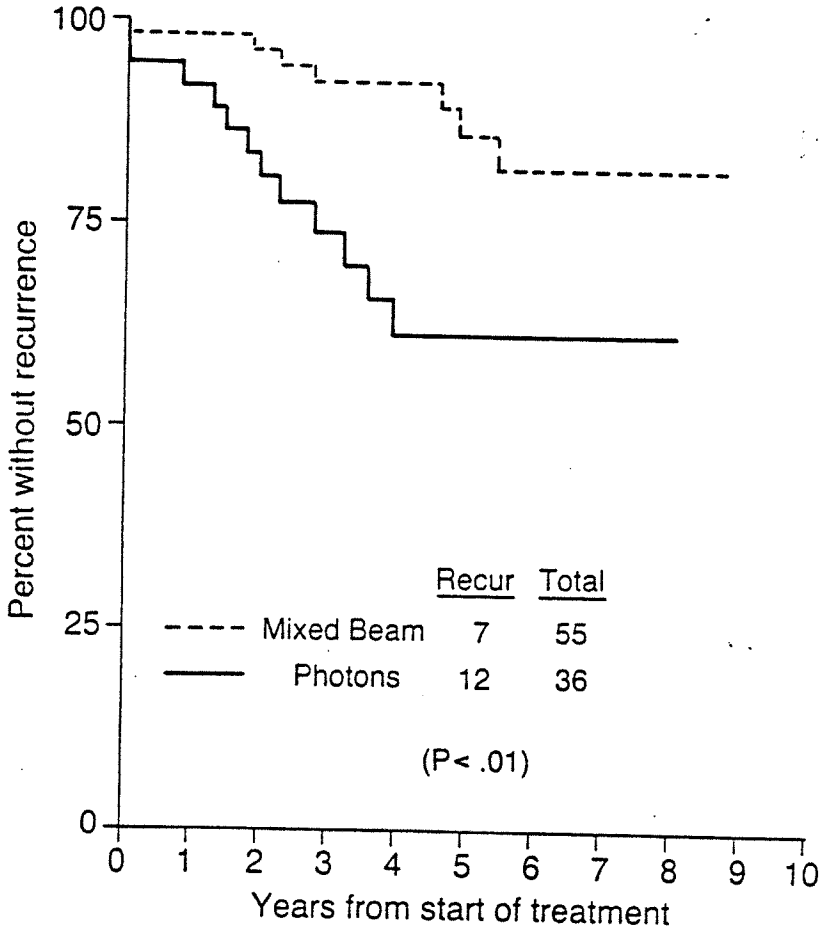
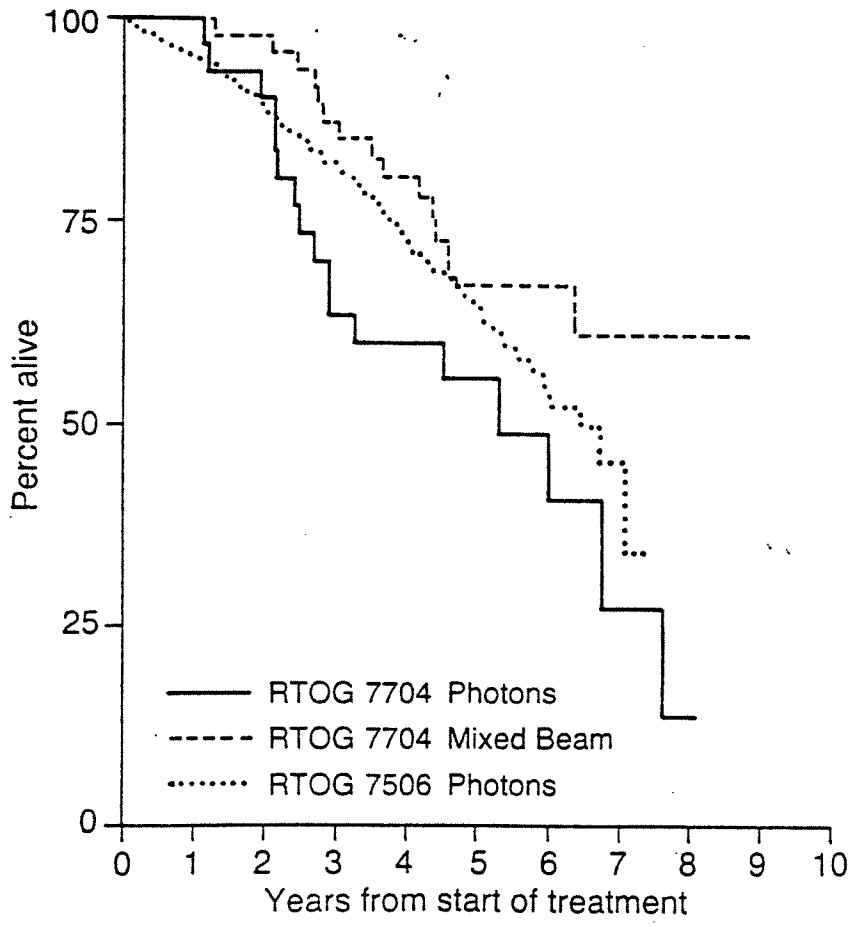

100
75
50
25
0
Percent without recurrence
Recur Total
Mixed Beam 7 55
Photons 12 36
(P< .01)
0 1 2 3 4 5 6 7 8 9 10
Years from start of treatment

Figure 5


100
75
50
25
0
Percent alive
0 1 2 3 4 5 6 7 8 9 10
Years from start of treatment
RTOG 7704 Photons
RTOG 7704 Mixed Beam
RTOG 7506 Photons