Fast Neutron Radiotherapy for Locally Advanced Prostate Cancer: Final Report of an RTOG Randomized Clinical Trial [+]

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ABSTRACT

Between June 1977 and April 1983 the Radiation Therapy Oncology Group (RTOG) sponsored a phase III randomized trial investigating the use of fast neutron radiotherapy for patients with locally-advanced (stages C and D_1) adenocarcinoma of the prostate gland. Patients were randomized to receive either conventional photon radiation or fast neutron radiation used in a mixed beam (neutron/photon) treatment schedule. A total of 91 analyzable patients were entered into the study and the two patient groups were balanced with respect to the major prognostic variables. Actuarial curves are presented for local/regional control, "overall" survival, and "determinantal" or disease-specific survival. Ten year results for clinically-assessed local control are 70% for the mixed beam group vs. 58% for the photon group (p=0.03), for survival are 46% for the mixed beam group vs. 29% for the photon group (P=0.04) and for "determinantal" survival are 58% for the mixed beam group vs. 43% for the photon group (p = 0.05). This study suggests that a regional method of treatment can influence both local tumor control and survival in patients with locally-advanced adenocarcinoma of the prostate gland.

INTRODUCTION

In 1990 the American Cancer Society estimates that there will be 106,000 new cases of prostate cancer and 30,000 deaths due to this disease in the United States alone[1]. It has now become the most common cancer in the United States male (excluding non-melanoma skin cancer). The clinical course of this disease is quite variable and long term follow-up is necessary to assess the true efficacy of any new form of treatment.

Current medical management of this disease is dependent in its stage at presentation. Well-differentiated, early lesions in elderly males may require no treatment at all; somewhat more advanced lesions may be treated equally as well with either radiotherapy or surgery[2]; and patients with distant metastases are best treated with some form of hormonal manipulation. A more controversial area relates to the treatment of locally-advanced disease- - stages C and D_1 according to the American Urological Staging System[3]. Many studies seem to indicate that conventional photon radiation therapy is a reasonable treatment for this stage disease[2,4-8] while others conclude that this form of treatment does not appear to alter the natural history of this stage disease[9,10].

High linear energy transfer (LET) radiation of which neutrons are a specific type offers several theoretical advantages in the treatment of certain tumors[11]. A fast neutron typically deposits 20-100 times more energy per unit path length than does a megavoltage x-ray and this gives rise to different

radiobiological properties. Fast neutrons have a lower oxygen enhancement ratio (OER) which means they can more effectively kill hypoxic cells which may be found in large tumor masses. There is much less variability in radiosensitivity across the cell cycle than with x-rays; this could be important for slowly proliferating tumors. Cells also have much less capability for repair of both sublethal and potentially lethal damage inflicted by fast neutron radiation. Whether or not these differences result in a therapeutic gain in terms of tumor control depends on the relative biological properties of both the tumor and the normal tissues in the radiotherapy target volume. Radiobiological studies by Battermann et al[12] on human tumors metastatic to lung indicate the highest relative biological effectiveness (RBE) factors for neutrons compared with photons occur for slowly-growing, better differentiated tumors having a relatively high ability to repair photon radiation damage. To some extent, prostate cancer fits these criteria, but the efficacy of fast neutron radiotherapy for any given tumor system can only be assured in the context of a controlled clinical trial.

In the 1970's, the Radiation Therapy Oncology Group (RTOG) launched a series of randomized phase III trials comparing fast neutron radiotherapy with conventional photon radiotherapy for various tumor systems. One such trial was RTOG 77-04 for locally-advanced prostate cancer. Preliminary analyses of the data from this trial at the 5 and 8 year endpoints showed a benefit to the fast neutron form of treatment both in terms of local/regional control and survival[13,14]. In this paper we

present the final 10-year data from this study - data which is especially important given the long natural history of this disease. The data continues to show a statistically - significant improvement in both clinically-assessed local/regional tumor control and survival, and suggests that a regional form of treatment can favorably affect outcome in locally-advanced prostate tumors.

MATERIALS AND METHODS

RTOG 77-04 was open between June 1977 and April 1983 with a total of 95 patients being entered. Four patients were ultimately excluded from analysis (3 were ineligible and 1 refused the assigned treatment) leaving 91 analyzable patients. All patients had either stage C or D_1, biopsy-proven, adenocarcinoma of the prostate gland. The mandatory pretreatment included a complete history and physical examination, x-ray, complete blood count, blood chemistry studies including liver function tests, serum calcium, alkaline phosphatase, acid phosphatase, and a radionuclide bone scan. Computerized tomography (CT) scans of the pelvis were performed in about half the patients and 41 patients underwent bipedal lymphangiography and/or exploratory laparotomy.

To be eligible for randomization, patients had to be less than 80 years of age, have an initial Karnofsky status greater than or equal to 50, have not had either prior pelvic irradiation or extensive prior pelvic surgery, and could not have had a history of prior malignancy (excluding non-melanoma skin cancer). Prior hormonal therapy was allowable, but had to be adequately

documented. Informed consent was given by all patients who entered the study.

Patients were randomized through the RTOG operations office to receive either conventional photon irradiation or mixed beam (neutron/photon) irradiation. The latter treatment consists of giving a mixture of 40% neutrons and 60% photons and was deemed necessary (rather than using neutrons alone) because of the relatively low energy, unsophisticated neutron facilities available at the time of the study was carried out. The randomization was purposefully unbalanced (60% - 40%) in favor of the experimental treatment with 55 analyzable patients being assigned to the experimental arm and 36 analyzable patients being assigned to the photon control arm.

The following neutron therapy facilities participated in the study: the University of Washington (SEATTLE), the Great Lakes Neutron Treatment Association (GLANTA), the M.D. Anderson Hospital at the University of Texas (using the Texas A&M Variable Energy Cyclotron-TAMVEC), and Fermi Laboratories (FERMI). Neutron doses were scaled according to the RBE's for the various institutions: 3.3 for SEATTLE and GLANTA, 3.1 for TAMVEC, and 3.0 for FERMI. The gamma contaminant was included in the neutron dose specification.

Photon-treated patients were to receive a dose of 50 Gy to the whole pelvis (prostate and nodes) at a dose rate of 1.8 - 2.0 Gy per fraction followed by a 20 Gy boost to the prostate and any areas of proven extra-prostatic "bulk" disease. Mixed-beam treated patients received equal doses to these regions in terms of Gy equivalents (neutron dose multiplied by the institutional

RBE plus the photon dose). The dose rate was 1.8 - 2.0 Gy-equivalent per fraction. Patients on both arms were treated once-a-day for 5 days per week. The mixed-beam treated patients received 2 neutron treatments and 3 photon treatments per week. The radiation dose to the entire bladder was restricted to 60 Gy (Gy-equivalent), the dose to the posterior rectal wall was restricted to 55 Gy (Gy-equivalent), and the dose to the small bowel was limited to 55 Gy (Gy-equivalent.)

Most patients were treated either AP-PA or using a four-field "box" technique. A few patients on the photon arm received their prostate boost using rotational arc techniques. Portal films were required for each treatment field as were computer isodose calculations through the central axis plane of the pelvis and also through the prostate. Patients were evaluated in follow-up at monthly intervals for the first 3 months after treatment, at 3 month intervals for the remainder of the next 3 years, and at 6 month intervals thereafter.

Initial review of the patient records showed that 13 patients had treatments that were "in major deviation" from the protocol guidelines (5 photon and 8 mixed beam)[13]. These deviations usually involved too low a neutron dose (<25% of the total dose instead of the intended 40%) or excessively prolonged overall treatment times (>75 days). However, no statistical difference was noted in outcome for this subgroup of patients[13] and so to avoid any inadvertent bias, all patients were included in the 8-year analysis[14] and in the present analysis.

At the time of the present analysis the median time risk for the patients is 10.8 years (range 7.5 - 13). Statistical methods

used to analyze the data include the chi-square test, the Mantel-Haenszel test[15], and the Kaplan-Meier method of plotting survival curves[16]. Based on the chi-square test of independence, the two treatment groups were balanced according to the following prospectively gathered variables: age distribution, tumor grade (Mostofi schema[17]), stage (C vs. D_1), method of tumor diagnosis (transurethral prostate resection (TURP) vs. needle biopsy), percentage of patients having lymphangiograms, laparotomies, or other methods of nodal evaluation, initially elevated acid phosphatase level, degree of seminal vesicle involvement, Karnofsky performance status, race, prior hormonal therapy, cardiac disease status, and other intercurrent disease status. The presence of concomitant, benign prostatic hypertrophy was unbalanced at the marginally significant level ($p = 0.06$) and occurred more frequently in the mixed beam group. Tumor size based upon the product of the clinically-assessed major diameters was somewhat larger in the photon group ($p < 0.05$). Gleason scores[18] were retrospectively obtained on 73/91 patients for whom the biopsy material could be retrieved, were centrally reviewed, and were balanced on the two arms.

RESULTS

The major endpoints of this study are local/regional tumor control and survival. Treatment related complication rates are a secondary endpoint. The plots in this section are calculated using the actuarial method[16] with times measured from the initiation of treatment. Statistical validity is assessed using a two-sided, Mantel-Haenzel log rank test[15].

Figure 1 shows the fraction of patients exhibiting local/regional control as a function of time. In the assessment of control, a post-treatment abnormality was assumed to be of unknown significances in the immediate post-irradiation period and was not counted as a failure until progression was noted. This method of failure determination was selected since prostate cancer is slow to respond to radiation therapy and often does not regress completely until several months after treatment is finished. Figure 1 shows the results for only clinical failures. Clinical local/regional failure was defined as either (i) product of tumor major diameters being at least 25% greater than at the time of entry onto the study, (ii) new extension of tumor beyond the prostate capsule or re-extension after becoming temporarily negative, (iii) new local extension of tumor or extension of tumor after an initial regression, (iv) pelvic nodes either becoming newly positive or again becoming positive after becoming temporarily negative, or (v) clinical evidence of tumor progression such as obstructive symptoms followed by a positive biopsy either via needle or TURP. As part of the program to evaluate tumor status in more detail, 11 patients who were treated at the SEATTLE facility and were clinically NED with normal serum acid phosphatase underwent an investigative procedure whereby two random biopsies were taken of each lobe of the prostate. The results were positive for 4 mixed beam patients and 1 photon patient. Considerable sampling error was involved since there were more than twice as many mixed beam patients surviving at the time the biopsies were performed. The significance of a positive biopsy in a patient in clinical

remission is uncertain [19,20,21]. In regards to these 5 "pathologic-only" failures, one was treated with DES, one was treated with an orchiectomy, and all 5 have been free of local disease progression for more than 5 years. One other mixed-beam patient exhibited a "biopsy-only" failure initially and 3 years later showed clinical evidence of tumor progression. At the 10-year point clinically-assessed local/regional control is 70% for the mixed beam group compared to 58% for the photon group. the difference between the curves is significant at the $p = 0.03$ level. All but one of the local/regional failures had a component in the prostate gland itself. The later patient who was treated with photons failed only in the regional nodes. If we were to include the "pathologic-only" failures in our analysis, the local control rates at 10 years would be 61% for the mixed beam patients and 52% for the photon patients.

Actuarial survival for the two patient groups is shown in Figure 2. There is a 17% survival advantage for the mixed beam form of treatment at both the 5 and 10 year endpoints - 70% vs. 53% and 46% vs. 29%. The difference between the two curves is significant at the $p = 0.04$ level.

Since prostate cancer patients are generally an older patient population, over a 10 year span many may die from non-tumor related causes. A better way to illustrate the effect of difference related to treatment alone is to construct determinantal or disease-specific survival curves. In these curves, death with active cancer present (either local/regional or distant metastases) is treated as a failure and death without tumor being present is treated as a censored observation. These

plots are shown in Figure 3. The survival advantage to the mixed beam form of treatment is 18% at 5 years and 15% at 10 years. The difference between these curves is significant at the $p = 0.05$ level.

Distant metastases have been documented in 49% (27/55) of the mixed beam-treated patients and in 55% (20/36) of the photon-treated patients. There was no significant difference noted in the time to development of these distant metastases.

Most treatment related complications were mild and consisted of the expected side effects of nausea, diarrhea, dysuria, and urinary urgency. Because of the poorly-penetrating qualities of the neutron beams, skin and subcutaneous tissue reactions were more severe for the mixed beam group. Table 1 lists the significant side effects that occurred - graded severe or greater using the joint RTOG/EORTC (European Organization for Research on Cancer Treatment) scoring scheme. A total of 5 photon-treated patients and 7 mixed beam treated patients suffered such complications (some patients had more than one such complication). As noted in the table, there was one treatment-related fatality in each arm. In each case, surgery was required for a complication and the patient died of sequelae following this. There is no statistical difference in the rate of significant complications in the two arms.

DISCUSSION

This paper reports 10 year results of a prospective, randomized study comparing mixed beam (neutron/photon) radiation therapy against conventional photon irradiation for patients with

locally-advanced adenocarcinoma of the prostate gland. The mixed beam group of patients appears to fare better than the photon control group in regards to all major endpoints: local/regional control, survival, and determinantal or disease specific survival. Most of the patients entered into this study had stage C disease but 5/36 patients in the photon group and 6/55 patients in the mixed beam group had proven metastases to the pelvic lymph nodes. These patients would have been excluded from clinical trials that were restricted to patients with stage C tumors which makes comparison with other series difficult.

Table 2 summarizes our 10 year results for both local control and survival and compares these figures with other reports in the literature[8,22-26]. The mixed beam result of 70% is somewhat better than the University of Florida[8] and Patterns of Care[26] results, but is worse than the reported series from M.D. Anderson Hospital[24]; our photon results are worse than all three. In regards to actuarial survival, our mixed beam result is comparable to the M.D. Anderson results[24] and is better than the other series, while our photon result is comparable to that reported from Syracuse[23] and worse than the other series. Differences in patient population most likely account for the differences among the non-randomized photon series[8,22-26] shown in Table 2. This contention can be supported by comparing the outcome for the stage C patients entered by M.D. Anderson on the present study with the M.D. Anderson results of Zagers et el[24] for stage C patients. Ten stage C patients from M.D. Anderson were treated with the mixed beam regimen and 11 were treated with photons on our randomized trial. At 5 and 10 years,

local/regional control rates for this subset of patients were, respectively, 68% and 44% for the mixed beam groups compared to 44% and 0% for the photon group. In regards to survival, the 5 and 10 year rates were, respectively, 70% and 60% for the mixed beam group compared to 60% and 9% for the photon group. Clearly the values for the photon treated patients are markedly inferior to those reported by Zagers et al[24]. This demonstrates the role of patient selection even in reports from a single institution and further underscores the necessity of randomized trials. It is important to note that our study was randomized and the two treatment groups were balanced in regards to the major prognostic variables. Hence, our comparison of the results of the mixed beam and photon forms of treatment should be valid.

This study seems to indicate that a local regional form of treatment can favorably impact survival for locally-advanced prostate cancer. While the endpoint differences achieve statistical significance, the number of patients in the trial is relatively small. Recognizing this and also recognizing the large number of patients who present each year with locally-advanced tumors, in 1986 the Neutron Therapy Collaborative (NTCWG) Working Group elected to repeat the essence of this trial using the newly-available neutron therapy facilities that had been sponsored by the National Cancer Institute. In NTCWG 85-23 neutron radiation alone was used as the experimental arm and photon radiation in the same manner as described herein used as the control arm. Eligible patients had biopsy-proven stage B_2 (Gleason $\geq$ 7), C, or D_1 tumors. Surgical staging of lymph nodes was encouraged and used as a stratification variable. Routine

biopsy of the prostate was mandated 18 months after treatment. This study has just closed after accruing 178 patients and the data will require several years to mature. If the results confirm the prior study, then many more neutron radiotherapy facilities will be needed to optimally treat patients with locally-advanced prostate cancer.

TABLE 1: Toxicities Scored Severe or Greater According to the RTOG/EORTC Scoring Schema

Toxicity	Photon	Mixed Beam
Skin	--	2
Urinary	3	2
Rectal	1*	2
GI	1	2 (1*)

* Fatal Complications

TABLE 2: Ten Year Actuarial Local Control Rates and Survival for Various Patient Series. Except for the current study, all series are restricted to patients with stage C disease.

This Study - Stages C & D_1	Patient Number	Local Control	Survival
Mixed Beam	55	70%	46%
Photons	36	58%	29%

Photon Series - Stage C

Stanford[22]	385	---	36%
Syracuse[23]	63	---	30%
MDAH[24]	551	81%	47%
Mallinckrodt[25]	328	---	38%
University of Florida[8]	111	63%	38%
Patterns of Care[26]	296	65%	38%

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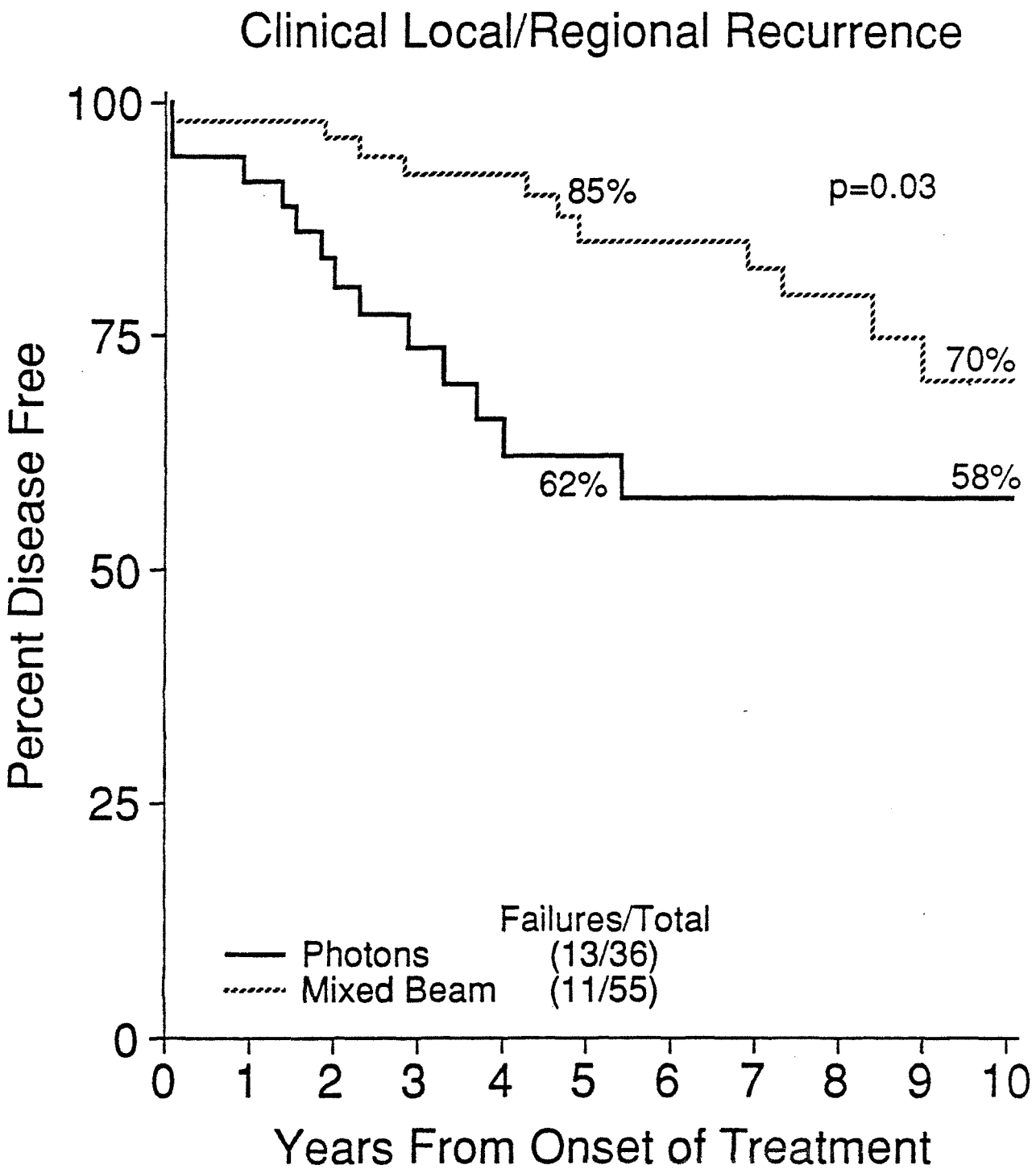
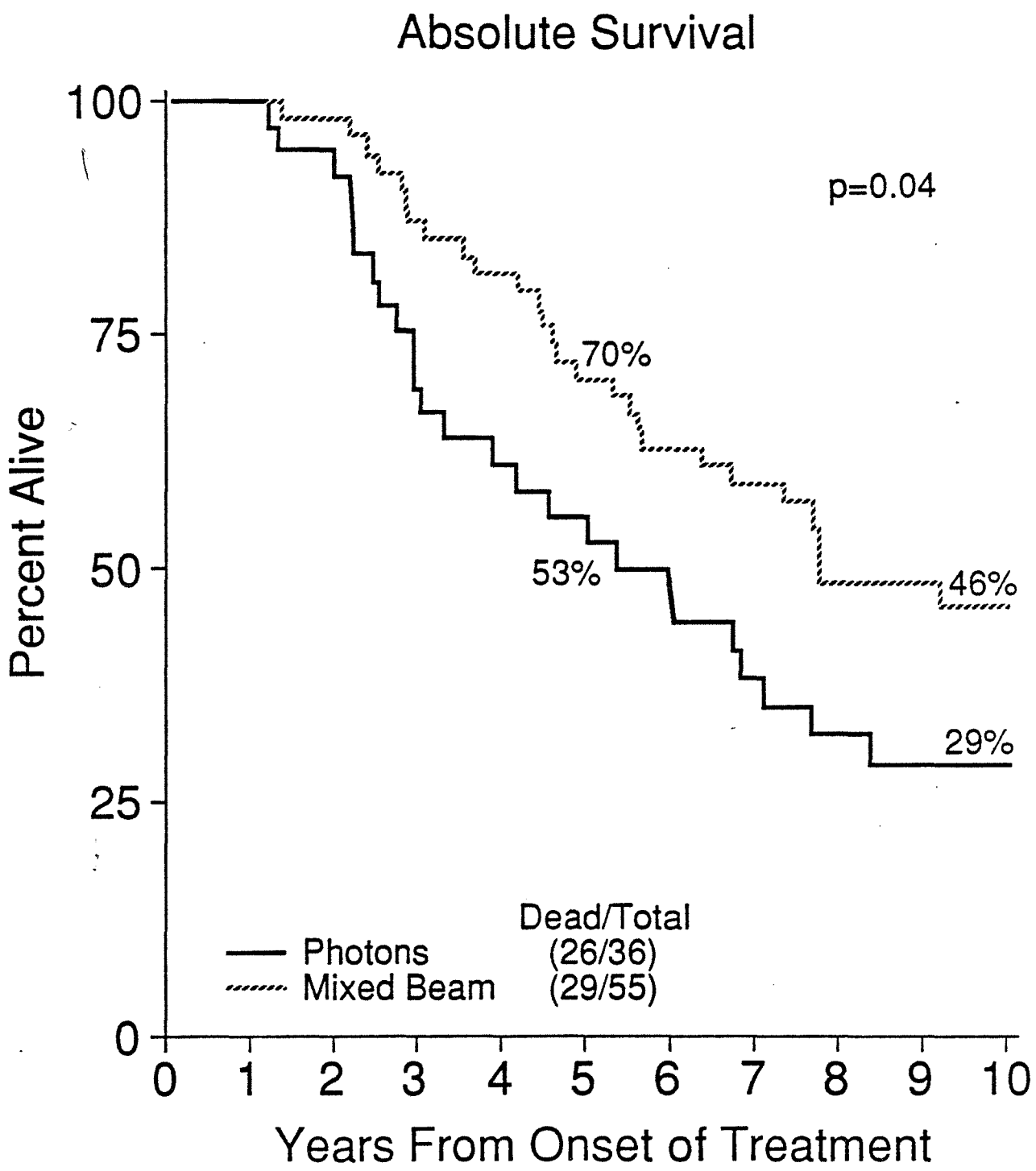
FIGURE CAPTIONS

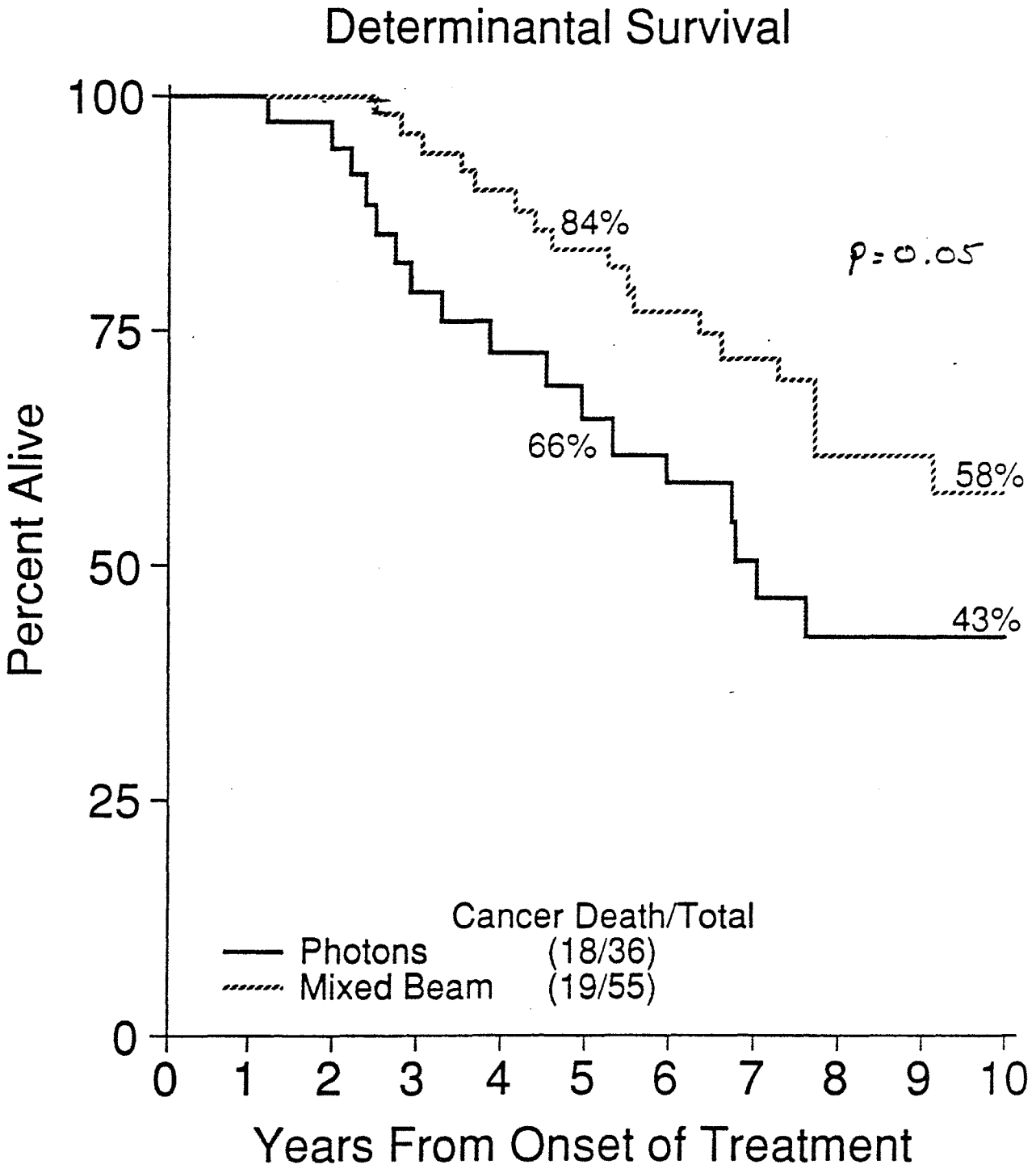
Figure 1: Time to local/regional tumor progression using only clinical criteria. The mixed beam group is shown as the dotted line and the photon group is shown as the solid line. The difference between the two curves is statistically significant at the $p = 0.03$ level. The numbers in parentheses indicate the fraction of patients exhibiting a "failure" at the time of analysis.

Figure 2: Overall patient survival as a function of time. The mixed beam group is shown as the dotted line and the photon group is shown as the solid line. The difference between the curves is statistically significant at the $p = 0.04$ level. The numbers in parentheses indicate the fraction of deceased patients at the time of analysis.

Figure 3: Determinantal or disease-specific patient survival using active cancer present at the time of death as the endpoint. Deaths due to intercurrent disease with cancer controlled are treated as "censored" observations. The mixed beam group is shown as the dotted line and the photon groups is shown as the solid line. The difference between the two curves is statistically significant at the $p = 0.05$ level. The numbers in parenthesis indicate the fraction of patients exhibiting a faliure at the time of analysis.


Clinical Local/Regional Recurrence
100
75
50
25
0
Percent Disease Free
85%
p=0.03
70%
62%
58%
Failures/Total
Photons (13/36)
Mixed Beam (11/55)
0 1 2 3 4 5 6 7 8 9 10
Years From Onset of Treatment


Absolute Survival
100
75
50
25
0
Percent Alive
p=0.04
70%
53%
46%
29%
Dead/Total
Photons (26/36)
Mixed Beam (29/55)
0 1 2 3 4 5 6 7 8 9 10
Years From Onset of Treatment


Determinantal Survival
100
75
50
25
0
Percent Alive
84%
66%
58%
43%
p = 0.05
Cancer Death/Total
Photons (18/36)
Mixed Beam (19/55)
0 1 2 3 4 5 6 7 8 9 10
Years From Onset of Treatment