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Adjuvant Radiotherapy for Pathologic T3N0M0 Prostate Cancer Significantly Reduces Risk of Metastases and Improves Survival: Long-term Followup of a Randomized Clinical Trial

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Abstract

Purpose—Extraprostatic disease will be manifest in one third of men after radical prostatectomy. We present long-term followup of a randomized clinical trial of radiotherapy to reduce risk of subsequent metastatic disease and death.

Materials and Methods—431 men with pT3N0M0 prostate cancer were randomized to 60–64 Gy adjuvant radiotherapy or observation. The primary study endpoint was metastasis-free survival.

Results—Of 425 eligible men, 211 were randomized to observation and 214 to adjuvant radiation. Of those receiving observation, 70 ultimately received radiotherapy. Metastatic-free survival was significantly less with radiotherapy (93 events out of 214 on the RT arm, 114 events out of 211 on observation, Hazard Ratio [HR] 0.71, 95% confidence interval [CI] 0.54, 0.94; p=0.016). Survival was improved significantly with adjuvant radiation (88 deaths out of 214 on the RT arm, 110 deaths out of 211 on observation HR 0.72, 95% CI 0.55,0.96; p=0.023).

Conclusions—Adjuvant radiotherapy after radical prostatectomy for a man with pT3N0M0 prostate cancer significantly reduces the risk of metastasis and increases survival.

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Introduction

Of the 186,320 patients estimated to be diagnosed with prostate cancer in 2008, about a third will undergo radical prostatectomy, the only treatment which has been demonstrated to reduce a patient's risk of death from the disease.[1,2,3] Of men in the United States undergoing radical prostatectomy, large community-based series would suggest that about a third will have positive surgical margins.[4] Another 9% in other surgical series will prove to have seminal vesicle invasion.[5] Both positive margins and seminal vesicle invasion are associated with a significantly-increased risk of cancer recurrence, measured at the earliest time with a detectable PSA, also known as 'biochemical failure'.[6]

For decades, the management of these high-risk patients and the use of adjuvant radiotherapy has been the subject of considerable debate. Literally hundreds of case series have been published on the subject with authors advocating for and against treatment based on outcomes and side effects of highly-selected series of patients. In 1987, the Southwest Oncology Group (SWOG) initiated S8794, a randomized trial of adjuvant radiotherapy for pathologic T3N0M0 prostate cancer with a primary endpoint of metastasis-free survival. Recognizing a lower than anticipated rate of events, the SWOG Data and Safety Monitoring Committee recommended publication of study results in 2006. These results, based on a median follow-up of 10.6 years, were published in November 2006 and when the dataset was frozen, a 25% improvement in metastatic disease-free survival was noted with radiotherapy but without achieving statistical significance (p=0.06).[7] Similarly, a 20% improvement in overall survival was noted but again without achieving statistical significance (p=0.16). In that same publication we showed the positive impact of radiotherapy on shorter term endpoints. Adjuvant radiation had a highly statistically significant impact on increasing PSA relapse-free survival (HR: 0.43, 95% CI 0.31, 0.58, p<0.001) and relapse-free survival (HR 0.62, 95% CI 0.46, 0.82, p=0.001). Additionally, adjuvant radiation reduced the risk of initiation of hormonal treatment by more than half (HR=0.45, 95% CI 0.29, 0.68, p<0.001).

Follow-up of subjects in this study has continued and has witnessed a significant number of additional study endpoints (metastases and death). We herein report the long-term results of these two important study endpoints.

Materials and Methods

S8794 was a randomized multi-institutional study of adjuvant radiotherapy for pathologically-advanced prostate cancer after radical prostatectomy. Eligible patients with clinical T1–2 prostate cancer must have undergone radical prostatectomy within 16 weeks prior to randomization and must have had at least one criterion of pathologic T3 disease: extracapsular tumor extension, positive margins, or seminal vesicle invasion. All patients had to have a negative bone scan and initially were required to have had a negative pelvic lymphadenectomy. Starting in 1995, patients who met any of the following criteria of low-risk disease were not required to undergo a lymphadenectomy: (1) Clinical stage T1a or T2a, Gleason 2–6, and PSA < 10 ng/mL; (2) stage T1b-c, Gleason 2–5, and PSA < 10 ng/mL; (3) stage T2b, Gleason 2–6, and PSA < 6 ng/mL, or (3) stage T2c, Gleason 2–6, and PSA < 4 ng/mL. An undetectable PSA after radical prostatectomy was not required. Additional eligibility requirements included adequate bone marrow and liver function, a performance status of 0 through 2, no evidence of total urinary incontinence, pelvic infection or urinary extravasation, as well as no history of intraoperative rectal injury. No prior radiotherapy or chemotherapy for prostate cancer was allowed. While central pathology review was required, a significant number of subjects either did not meet this criterion or their cases were not available for evaluation but were included as their local institution interpreted the

tumor as pathologic T3 and would therefore be considered for adjuvant therapy. Nonetheless, of the 311 subjects with complete central pathology review, in 295 (95%) the central pathology review concurred with the local site. All subjects provided written informed consent and the study was approved by individual institutional review boards of the participating institutions.

Methods of randomization have been previously described.[6] Within 10 working days of randomization, subjects randomized to adjuvant radiotherapy were required to initiate radiation at a dose of 60–64 Gy to the pelvis fossa given in 30–32 fractions. Treatment portals included the prostatic fossa and paraprostatic tissues. Radiotherapy quality review was conducted both by the Radiologic Physics Center as well as by the radiotherapy study coordinator (JP).

Quality of life outcomes were monitored in a subset of subjects and have been previously reported.[8] Treatment -related complications have also been previously described.[6]

Statistical Analysis

The primary endpoint of S8794 was metastasis-free survival, defined as the time from randomization to first evidence of metastases or death due to any cause. Statistical study assumptions included a 1-sided type I error probability of 0.05 with a power of 0.8. It was assumed from data available in 1986 that median metastasis-free survival would be 6 years and that adjuvant radiation would reduce the hazard rate of metastasis-free survival by one third. Initial planning called for a sample of 558 patients to be accrued over 5 years with 1 year of follow-up. Based on a lower than expected rate of events, the independent Data and Safety Monitoring Committee recommended revision of these assumptions in April 1996 to assume a 50% prolongation of metastasis-free survival with adjuvant radiotherapy, and a median of 12 years in the observation group. The sample size goal was revised to 408 and it was anticipated that 6 years of follow-up after accrual would be required to attain the desired 80% study power. Statistical analyses employed the methods of Kaplan and Meier to develop time-to-event curves.[9] Hazard ratios, 95% confidence intervals, and p-values with an indicator for treatment were estimated using proportional hazards regression models. All analyses were conducted using SAS version 9.0 (SAS Institute, Cary, NC). An intent-to-treat approach was used for all analyses and all p-values are two-sided.

Results

A total of 431 men were enrolled in S8794 between August, 1988 and January 1997; of these, 425 were eligible for analysis. The database for this analysis was frozen on July 24, 2008. Of the six ineligible subjects, two did not undergo lymphadenectomy, two did not have a prostatectomy report or pathology report, residual disease at the bladder neck was reported in one, and one had positive pelvic lymph nodes for cancer. Median follow-up is 12.7 years for the radiation arm (25%–75%: 11.4–15.1 years) and 12.5 years for the observation arm (25% – 75%: 11.1–14.0 years).

Study adherence

Of 211 men randomized to observation only, 70 ultimately received radiotherapy with a date of initiation of radiotherapy available in 65 and a close approximation of the starting interval in the other five. Radiotherapy in five men (7%) began within 30 days of randomization (one of these also had recurrence detected prior to initiation of radiation); in 39 (56%), radiotherapy was prompted by PSA value only and in 26 (37%), for objective recurrence. PSA values within 30 days of beginning radiation were available in only 21 (30%) of men but were available within 6 months prior to initiation of radiation therapy in 61 men (87%).

Median PSA immediately prior to radiation in all 70 patients was 1.0 ng/mL (25%, 75% = 0.3, 1.5). For the 39 men with PSA only relapse, median PSA at the time of radiation was 0.75 ng/mL (25%, 75% = 0.3, 1.6 ng/mL).

Primary Outcome - Metastasis-free survival

Since the initial publication of the study's results in 2006 when 167 total subjects had developed metastatic disease or died, an additional 40 subjects have reached this endpoint. As of this analysis, of 211 subjects randomized to observation, 114 (54%) have either died or developed metastatic disease (median metastasis-free survival 12.9 years); of 214 subjects randomized to adjuvant radiotherapy, 93 (43%) have reached this endpoint (median metastasis-free survival 14.7 years). Figure I displays the Kaplan-Meier metastasis-free survival curves. The Hazard Ratio (HR) for metastasis free survival with adjuvant radiotherapy is 0.71 (95% confidence interval 0.54, 0.94; p=0.016). Metastatic disease was reported in 37 subjects in the observation group compared to 20 in the adjuvant radiotherapy group. These data indicate that the number of men with pathologic T3 disease who must be treated with adjuvant radiotherapy to prevent one case of metastatic disease at a median followup of 12.6 years is 12.2.

Overall survival

Of the 211 subjects in the observation only group, 110 (52%) have died; of the 214 subjects in the adjuvant radiotherapy group, 88 (41%) have died. Median overall survival in the observation and adjuvant radiotherapy groups were 13.3 and 15.2 years, respectively. Figure 2 displays the Kaplan-Meier survival curves. The HR for overall survival with adjuvant radiotherapy is 0.72 (95% confidence interval 0.55, 0.96; p=0.023). The number of men with pathologic T3 disease who must be treated with adjuvant radiotherapy to prevent one death at a median followup of 12.6 years is 9.1.

Subset Analyses

Figure 3 provides point estimates and 95% confidence intervals for the metastasis-free survival hazard ratios of radiotherapy compared to observation for a number of subsets defined by baseline prognostic factors. These factors include (1) post-prostatectomy PSA (≤0.2 ng/ml and > 0.2), (2) seminal vesicle involvement (yes and no), and (3) Gleason grade (<7 and ≥ 7). The size of the symbol identifying the point estimate is proportional to the sample size for that subset. In each case, the treatment hazard ratio estimate is less than one, suggesting benefit of radiotherapy. The test of the interaction of each prognostic factor with radiotherapy was non-significant (interaction p-values: p=1.0 for PSA group, p=0.20 for Gleason category, p=0.61 for seminal vesicle factor), providing no evidence to suggest that any particular subset should not receive radiotherapy.

Despite the fact that there is a significant benefit of radiotherapy among those with a detectable PSA after surgery, the risk of metastasis or death is greater for those with a detectable PSA who receive radiotherapy compared to those with an undetectable PSA who receive radiotherapy as illustrated in Figure 4 (logrank p=0.03).

Discussion

This report, over 20 years after initiation of S8794, demonstrates that adjuvant radiotherapy at the relatively modest dose used in the late 1980's significantly reduces the risk of metastases in a man with pathologic evidence of extraprostatic disease after radical prostatectomy. This significant reduction was realized despite the application of salvage radiotherapy, perhaps the most commonly-used approach to these patients today, in a third of the patients in the observation group. Additionally, this reduction in metastases and

improvement in survival was despite an almost doubled use of hormonal therapy in the observation group. It is important to place this outcome in perspective. The median 1.7 year survival benefit may apply to over 30,000 men per year in the US.[10,11] In the realm of advanced prostate cancer, the only treatment proven to improve survival - docetaxel - improves survival by only 1.9 – 2.3 months.[12,13]

In addition to the most important outcomes of prostate cancer (metastases and survival), all other measures of disease recurrence were improved with adjuvant radiotherapy. For those men with an undetectable PSA postoperatively, the median delay in time to PSA recurrence was substantial: over 7 years.[7]

Despite significant reductions in adverse outcomes related to prostate cancer progression with adjuvant radiotherapy, we have previously reported on side effects and quality of life in the two groups in this study. We conducted a companion quality of life study in 217 men randomized to S8794 with assessments at baseline, 6 weeks, 6 months, and annually for five years.[8] A strength of this analysis was the inclusion of a 6-week assessment, designed to capture the side effects of radiotherapy at their peak. Tenderness and urgency of bowel movements were significantly more common at the 6 week time point (47% versus 5%) in the radiotherapy group but by two years, there was little difference between the groups. Urinary frequency was more commonly seen in the radiation group but there was no difference in the rate of erectile dysfunction (common in both groups) between groups. Global assessment of quality of life, while initially worse in the adjuvant radiotherapy group became similar by year 2 and was increasingly superior in the radiotherapy group over the following 3 years. This gradual switch toward a superior quality of life with the adjuvant radiotherapy group should be examined in the context of the increased rates of PSA recurrence, salvage radiotherapy, and hormonal therapy in the observation group and which all have negative impacts on quality of life.[14,15]

A limitation of this study is the incomplete central pathologic review with only 311/425 (73%) having complete central pathology review; nevertheless, of those with full review, there was a 95% concordance between central and institutional pathology reviews. This was also a limitation of the EORTC 22911 adjuvant radiotherapy trial in which central review was only conducted in high volume institutions and for 566 of 1005 patients. Similar to our study, 552/566 were deemed eligible after review. A review of the EORTC trial, however, found that with central review, only positive margin patients benefitted from adjuvant radiation.[16] Additionally, it must be acknowledged that Gleason grades assigned during this trial are probably lower than would be assigned with a contemporary review; such would be the case for any study with 20-year outcomes.[17] It is also important to acknowledge that the extent of disease in patients from the late 1980's and early 1990's may have been of a greater volume than contemporary patients, potentially increasing the differences in outcomes between treatment arms. Balancing against this bias may be the radiation dose used. Higher contemporary doses of radiotherapy may have increased differences in outcomes.

For many if not most clinicians who face the patient with evidence of extraprostatic disease and in whom the postoperative PSA is undetectable, a common strategy is simply to follow the PSA and initiate radiotherapy at the time PSA becomes detectable or prior to the achievement of some PSA threshold (e.g., 1.5 ng/mL).[18,19] These data argue that the salvage radiotherapy approach may place the patient at a higher risk of metastasis and death. The first evidence of this comes from the study group crossovers in this trial: about one third of subjects assigned to observation ultimately received radiotherapy at the time of a PSA or local relapse. The study thus compared immediate (adjuvant) radiotherapy to treatment at the time of disease recurrence (salvage radiotherapy). The second observation is that,

although there is a significant benefit of radiotherapy for the subset of patients with detectable PSA post-prostatectomy (see Figure 3), that group's metastasis-free survival is inferior to those who received radiotherapy when the PSA was still undetectable (Figure 4). Although these two observations are based on observations from subsets of the data, they do argue that the practice of waiting until PSA is detectable, while associated with a superior initial quality of life and fewer patients receiving radiotherapy, risks later decrements in health-related quality of life due to increased burden of therapies as well as an increased risk of metastasis and death.

This study points out two challenges for the academic and clinical trials community. The first is that important therapeutic advances in the management of localized prostate cancer require large numbers of patients and just as importantly prolonged follow-up. The hundreds of publications involving case series of patients treated with and without radiotherapy could not accurately compare outcomes of treatment due to inherent selection biases and unmeasured disease and patient-related variables. In the absence of initiating and completing these randomized studies, optimal patient care cannot be attained. To that end, the second challenge will be to build upon the observations of this study. One suggestion would be to randomize patients with T3N0M0 prostate cancer to either adjuvant radiotherapy or to salvage radiotherapy as soon as an ultrasensitive PSA is positive.[20] We have examined possible study designs such as this and have found that to test whether delayed radiotherapy is not inferior to immediate radiotherapy (defined as a metastasis-free survival hazard ratio of delayed/immediate of ≤ 1.10) and using rates of failure as seen in this study, a two-sided alpha of 0.05 and a power of 90%, and an accrual over 8 years with 9 additional years of follow-up would require a sample size of 8300. With the poor track record of accrual of patients with localized prostate cancer to clinical trials in the US, unless there is a fundamental change in the structure of clinical trials, it is unlikely that such a trial will be started or completed.

We look forward to updates of the EORTC randomized trial as well as the German ARO 96-02/AUO AP 09/95 study that randomized 385 patients after prostatectomy to radiotherapy with 60 Gy or observation alone. Ultimately, because of very similar designs across the studies, we anticipate that meta-analyses will be conducted.

Conclusions

Adjuvant radiotherapy within 18 weeks after radical prostatectomy for a man with pT3N0M0 prostate cancer significantly reduces risk of PSA recurrence, metastasis, and need for hormonal therapy as well as significantly increases survival.

Acknowledgments

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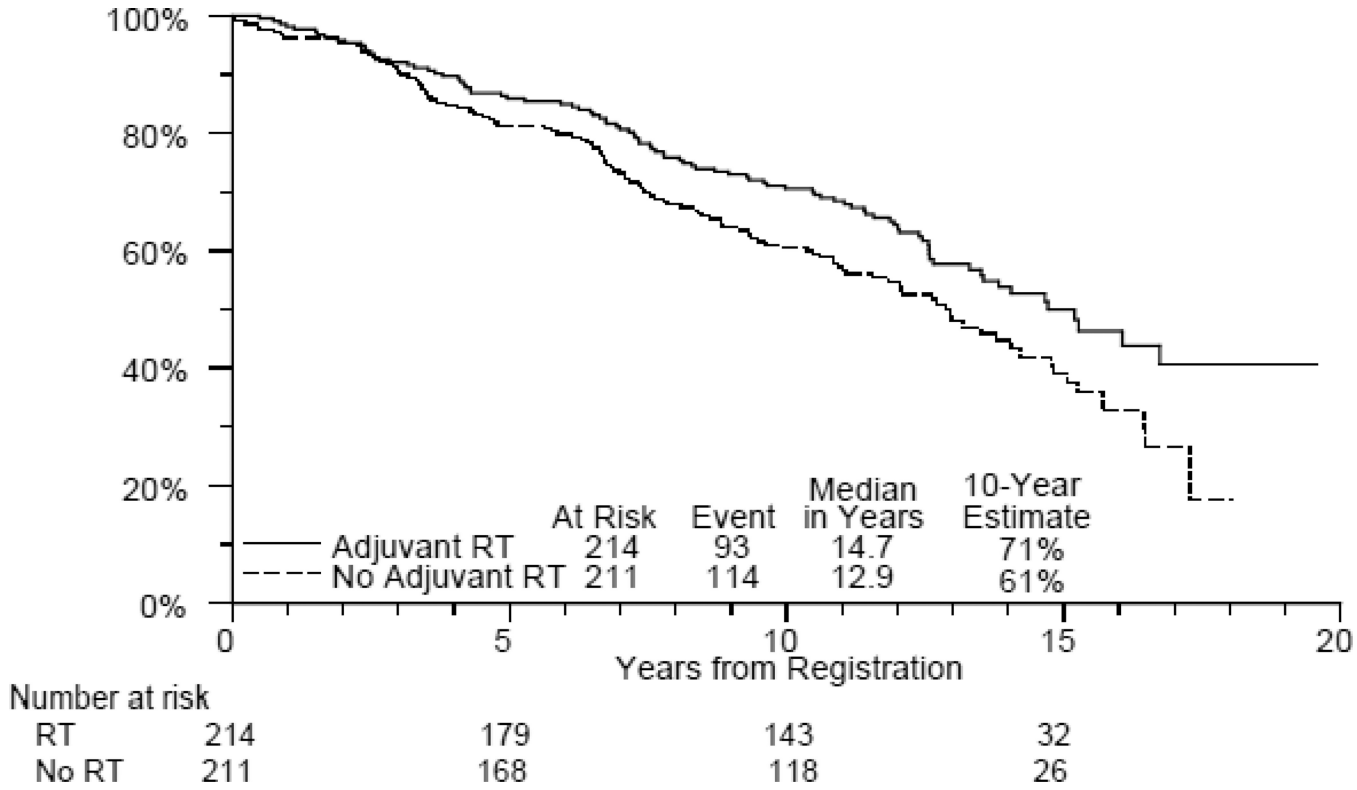


Fig. 1.
Metastasis Free Survival by Treatment Arm

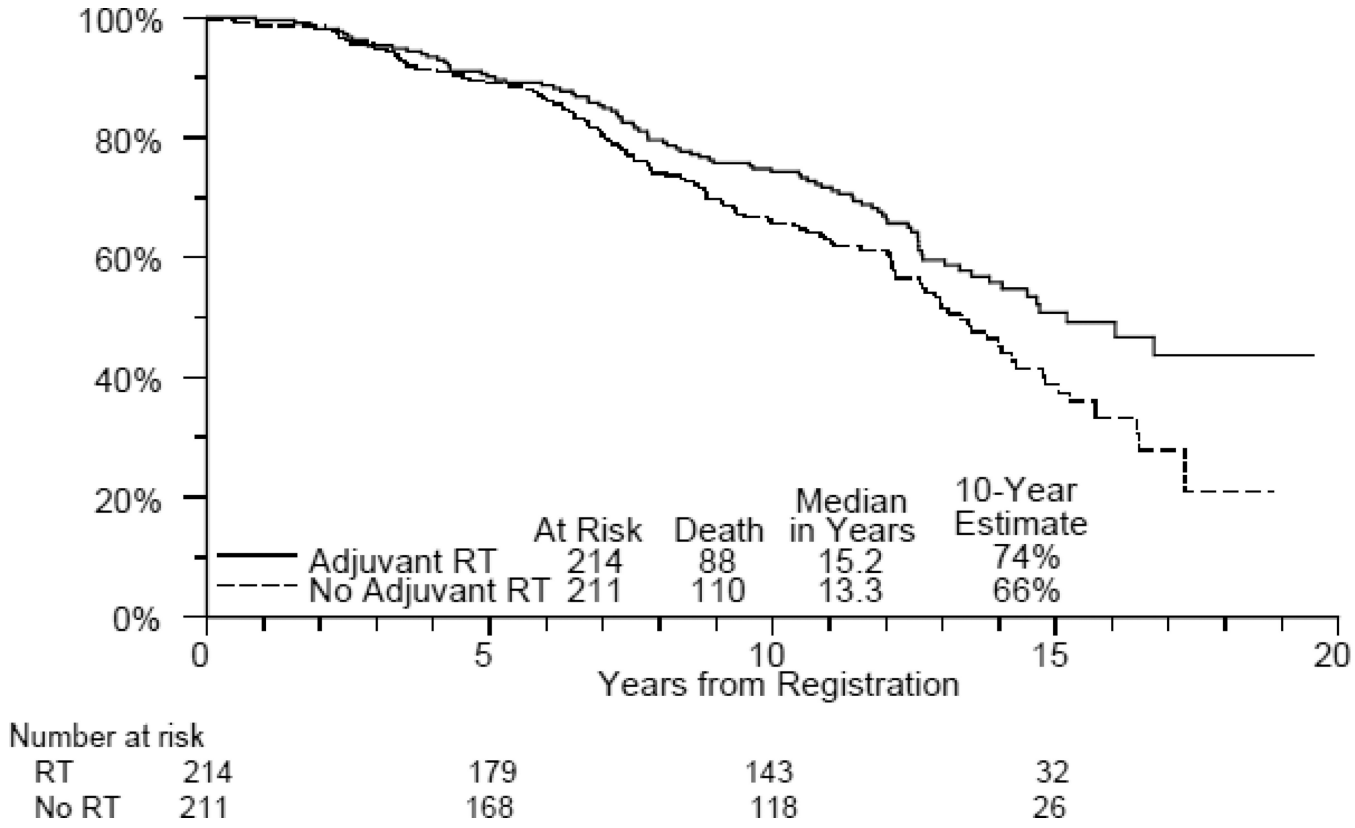
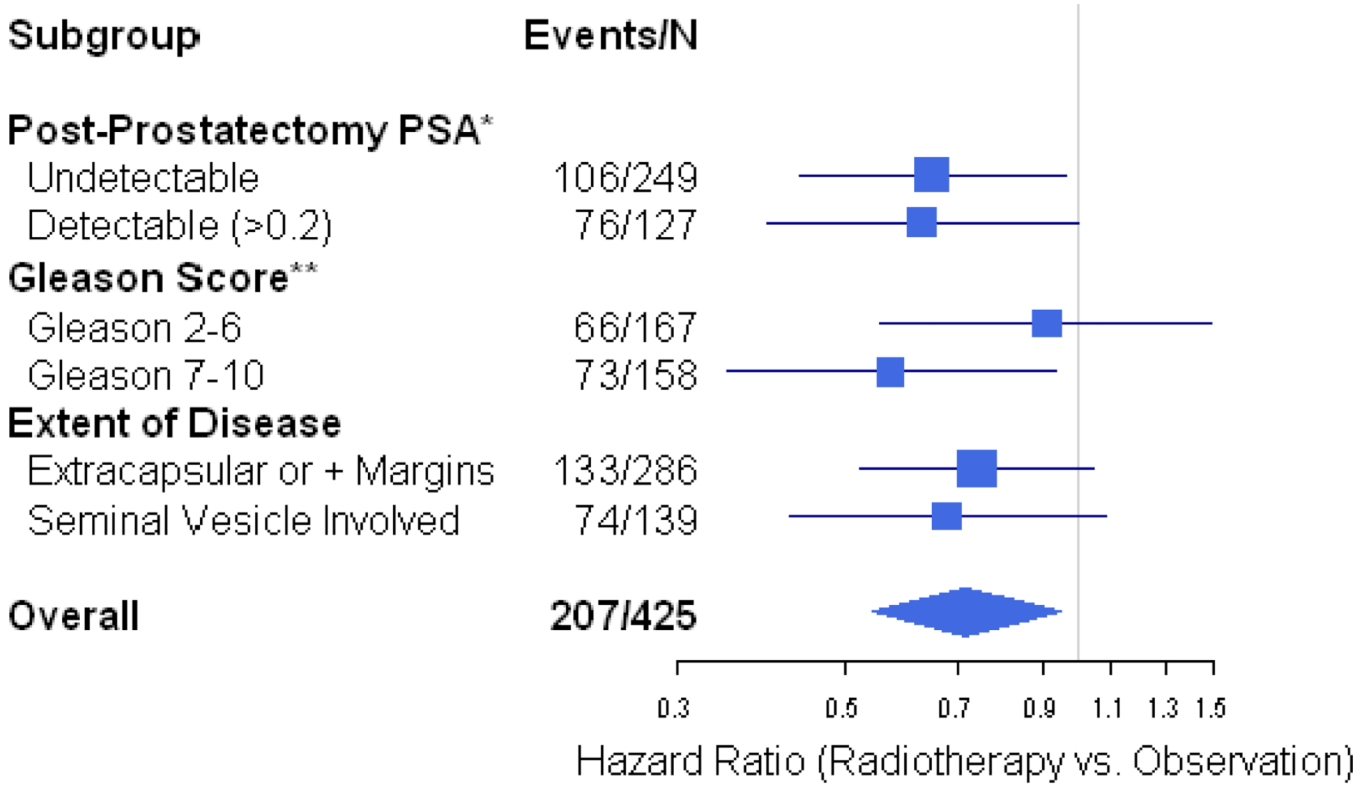


Fig. 2.
Survival by Treatment Arm



* Missing for 49 patients, ** Missing for 100 Patients
Size of box and diamond symbols are proportionate to sample size

Fig. 3.
Metastasis-Free Survival Hazard Ratio Estimates and Corresponding 95% Confidence Intervals for Subsets of Patients Based on Baseline Risk Factors

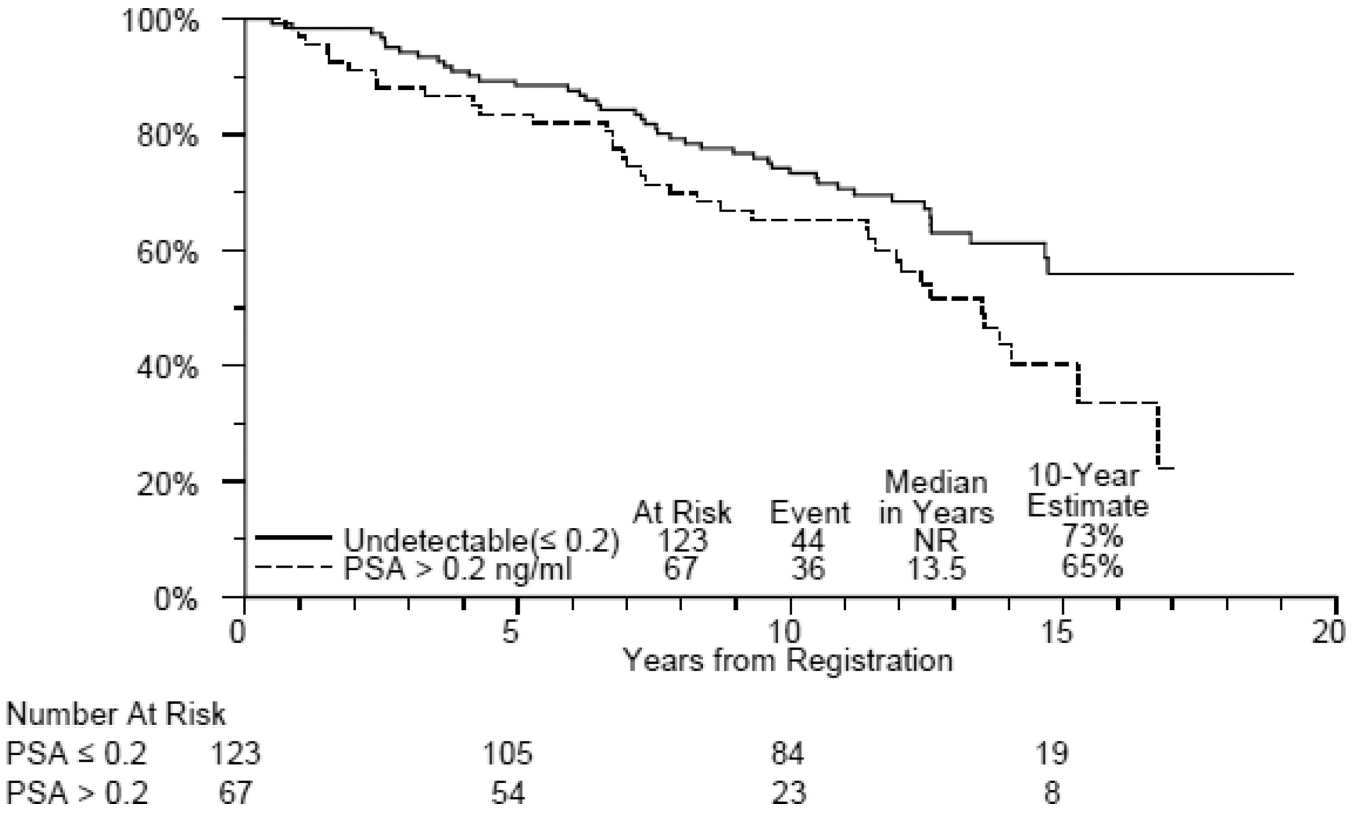


Fig. 4.
Metastasis Free Survival For Radiotherapy Arm Stratified by PSA Status After Prostatectomy

Table I

Study Participant Characteristics

	Observation	Adjuvant Radiation
Number of subjects	211	214
Median age (years)	65	64
Median follow-up (years)	12.5	12.7
Preoperative hormonal therapy use		
Yes	8%	9%
No	92%	91%
Ethnicity		
White	67%	72%
African American	20%	19%
Other	13%	9%
Pathologic Extent		
Extracapsular extension or positive margin	68%	67%
Seminal vesicle invasion	11%	10%
Both	21%	23%
Gleason Score (n=325 with data)	N=159	N=166
2–6	46%	57%
7	38%	34%
8–10	16%	9%
Preoperative PSA (n=302 with data)	N=154	N=148
< 10 ng/mL	52%	47%
≥ 10 ng/mL	48%	53%
Postoperative PSA (n=376 with data)	N=186	N=190
< 0.2 ng/mL	68%	65%
≥ 0.2 ng/mL	32%	35%