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

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

Materials and Methods: A total of 431 men with pT3N0M0 prostate cancer were randomized to 60 to 64 Gy adjuvant radiotherapy or observation. The primary study end point was metastasis-free survival.

Results: Of 425 eligible men 211 were randomized to observation and 214 to adjuvant radiation. Of those men under observation 70 ultimately received radiotherapy. Metastasis-free survival was significantly greater with radiotherapy (93 of 214 events on the radiotherapy arm vs 114 of 211 events on observation; HR 0.71; 95% CI 0.54, 0.94; p = 0.016). Survival improved significantly with adjuvant radiation (88 deaths of 214 on the radiotherapy arm vs 110 deaths 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.

Key Words: prostatic neoplasms, radiotherapy, prostate-specific antigen, neoplasm metastasis

Abbreviations and Acronyms

EORTC = European Organization for the Research and Treatment of Cancer

PSA = prostate specific antigen

RT = radiotherapy

SWOG = Southwest Oncology Group

S8794 = Southwest Oncology Group Study 8794

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Of the 186,320 patients estimated to be diagnosed with prostate cancer in 2008, approximately a third will undergo radical prostatectomy, the only treatment which has been demonstrated to reduce the risk of death from the disease.[1–3] A large community based series of men in the United States undergoing radical prostatectomy would suggest that about a third will have positive surgical margins.[4] Another 9% in other surgical series would prove to have seminal vesicle invasion.[5] 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 treatment of these high risk patients and the use of adjuvant RT have 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

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and side effects of highly selected series of patients. In 1987 the SWOG initiated S8794, a randomized trial of adjuvant radiotherapy for pathological T3N0M0 prostate cancer with a primary end point 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 followup of 10.6 years, were published in November 2006, and when the data set was frozen a 25% improvement in metastastic disease-free survival was noted with RT 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 end points. 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; $p < 0.001$). Followup of subjects in this study has continued and has revealed a significant number of additional study end points (metastases and death). We report the long-term results of these 2 important study end points.

MATERIALS AND METHODS

S8794 was a randomized multi-institutional study of adjuvant RT for pathologically advanced prostate cancer after radical prostatectomy. Eligible patients with clinical T1–2 prostate cancer must have undergone radical prostatectomy within 16 weeks before randomization and must have had at least 1 criterion of pathological T3 disease such as extracapsular tumor extension, positive margins or seminal vesicle invasion. All patients had to have a negative bone scan and were initially required to have had a negative pelvic lymphadenectomy. Starting in 1995 patients were not required to undergo lymphadenectomy if they met the low risk disease criteria of 1) clinical stage T1a or T2a, Gleason 2–6 and PSA less than 10 ng/ml; 2) stage T1b-c, Gleason 2–5 and PSA less than 10 ng/ml; 3) stage T2b, Gleason 2–6 and PSA less than 6 ng/ml; or 4) stage T2c, Gleason 2–6 and PSA less than 4 ng/ml. An undetectable PSA after radical prostatectomy was not required. Additional eligibility requirements were adequate bone marrow and liver function, a performance status of 0 through 2, no evidence of total urinary incontinence, pelvic infection or urinary extravasation, and no history of intraoperative rectal injury. No prior radiotherapy or chemotherapy for prostate cancer was allowed. While central pathological review was required, a significant number of subjects either did not meet this criterion or their records were not available for evaluation. However, they were included in the study as the local institution interpreted the tumor as pathological T3 and, therefore, considered for adjuvant therapy. Nonetheless, the central pathological review concurred with the local site in 295 of 311 subjects (95%). 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 to 64 Gy to the pelvis fossa given in 30 to 32 fractions. Treatment portals included the prostatic fossa and paraprostatic tissues. Radiotherapy quality review was conducted by the Radiological 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.[7]

In terms of statistical analysis the primary end point of S8794 was metastasis-free survival, defined as the time from randomization to first evidence of metastasis 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 a third. Initial planning called for a sample of 558 patients to be accrued during 5 years with 1 year of followup. 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 followup after accrual would be required to attain the desired 80% study power. Statistical analyses used 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. An intent to treat approach was used for all analyses and all p values are 2-sided.

RESULTS

A total of 431 men were enrolled in S8794 between August 1988 and January 1997, and of these men 425 were eligible for analysis. The database for this analysis was frozen on July 24, 2008. Of the 6 ineligible subjects 2 did not undergo lymphadenectomy, 2 did not have a prostatectomy report or pathology report, 1 had residual disease at the bladder neck and 1 had pelvic lymph nodes positive for cancer. Median followup was 12.7 years for the radiation arm (25% to 75%: 11.4 to 15.1 years) and 12.5 years for the observation arm (25% to 75%: 11.1 to 14.0 years). The table displays participant characteristics.

Study participant characteristics

	Observation	Adjuvant Radiation
No. subjects	211	214
Median age	65	64
Median yrs followup	12.5	12.7
% Preop hormonal therapy use:		
Yes	8	9
No	92	91
% Ethnicity:		
White	67	72
Black	20	19
Other	13	9
% Pathological extent of disease:		
Extracapsular extension or pos margin	68	67
Seminal vesicle invasion	11	10
Both	21	23
No. with Gleason score data	159	166
% Gleason score:		
2–6	46	57
7	38	34
8–10	16	9
No. with preop PSA data	154	148
% Preop PSA:		
Less than 10 ng/ml	52	47
10 ng/ml or Greater	48	53
No. with postop PSA data	186	190
% Postop PSA:		
Less than 0.2 ng/ml	68	65
0.2 ng/ml or Greater	32	35

Study Adherence

Of 211 men randomized to observation only 70 ultimately received radiotherapy with an initiation date available for 65 and a close approximation of the starting interval for the other 5. Radiotherapy in 5 men (7%) began within 30 days of randomization (1 also had recurrence detected before initiation of radiation), while in 39 (56%) men 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%) men but were available within 6 months before initiation of radiation therapy in 61 (87%). Median PSA immediately before radiation in all 70 patients was 1.0 ng/ml (25% to 75%: 0.3 to 1.5 ng/ml). For the 39 men with PSA only relapse median PSA at the time of radiation was 0.75 ng/ml (25% to 75%: 0.3 to 1.6 ng/ml).

Primary Outcome – Metastasis-Free Survival

Since the initial publication of the study results in 2006 when 167 total subjects had metastatic disease or had died, an additional 40 subjects reached this end point. As of this analysis of the 211 subjects randomized to observation 114 (54%) have died or have metastatic disease (median metastasis-free survival 12.9 years), and of the 214 subjects randomized to adjuvant radiotherapy 93 (43%) have reached this end point (median metastasis-free survival 14.7 years). Figure 1 displays Kaplan-Meier metastasis-free survival curves. The HR for metastasis-free survival with adjuvant radiotherapy was 0.71 (95% CI 0.54, 0.94; p = 0.016). Metastatic disease was reported in 37 subjects in the observation group vs 20 in the adjuvant radiotherapy group. These data indicate that the number of men with pathological T3 disease who must be treated with adjuvant radiotherapy to prevent 1 case of metastatic disease at a median followup of 12.6 years is 12.2.

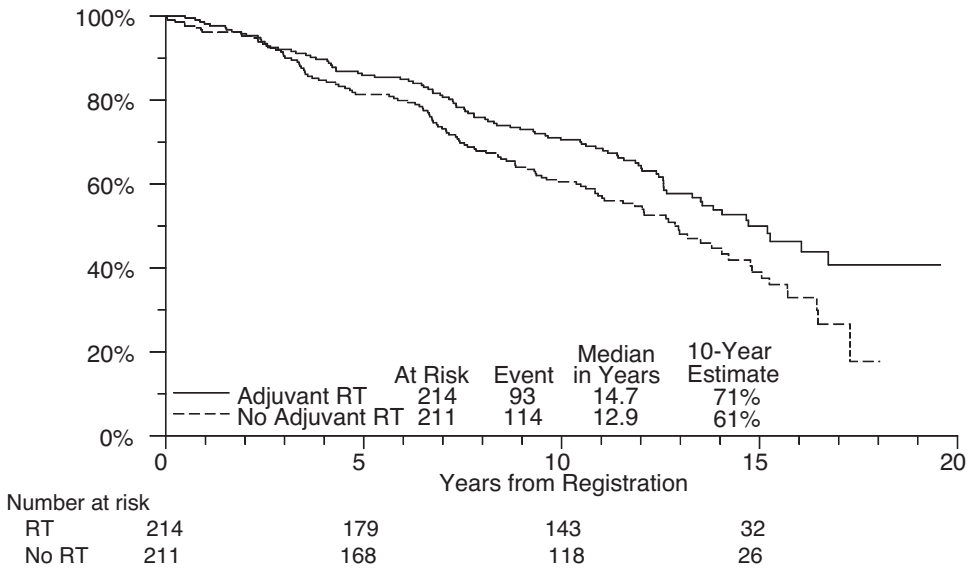

Figure 1. Metastasis-free survival by treatment arm

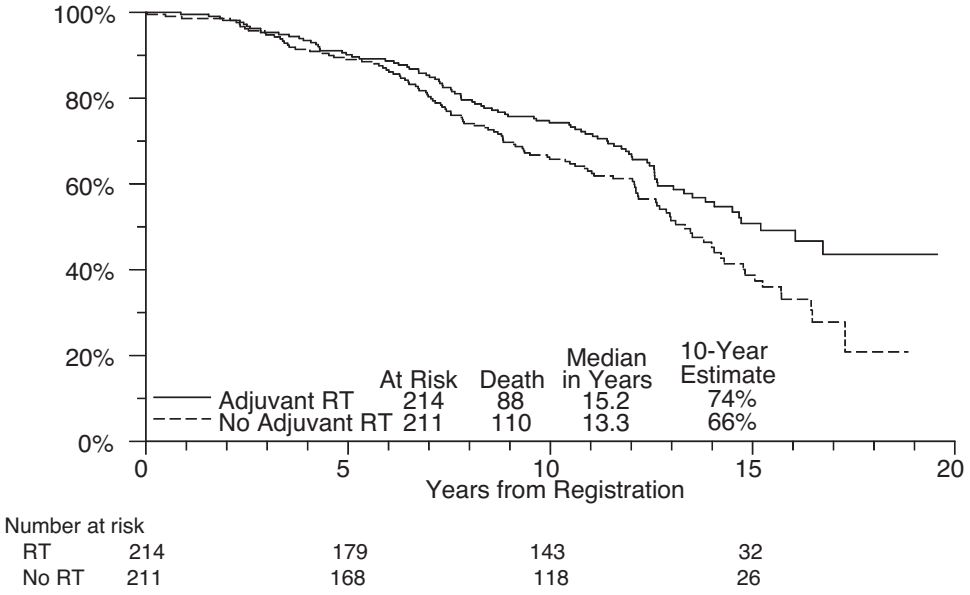

Figure 2. Survival by treatment arm

Overall Survival

Of the 211 subjects in the observation only group 110 (52%) have died and of the 214 in the adjuvant radiotherapy group 88 (41%) have died. Median overall survival in the observation and adjuvant radiotherapy groups was 13.3 and 15.2 years, respectively. Figure 2 displays Kaplan-Meier survival curves. The HR for overall survival with adjuvant radiotherapy is 0.72 (95% CI 0.55, 0.96; p = 0.023). The number of men with pathological T3 disease who must be treated with adjuvant radiotherapy to prevent 1 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

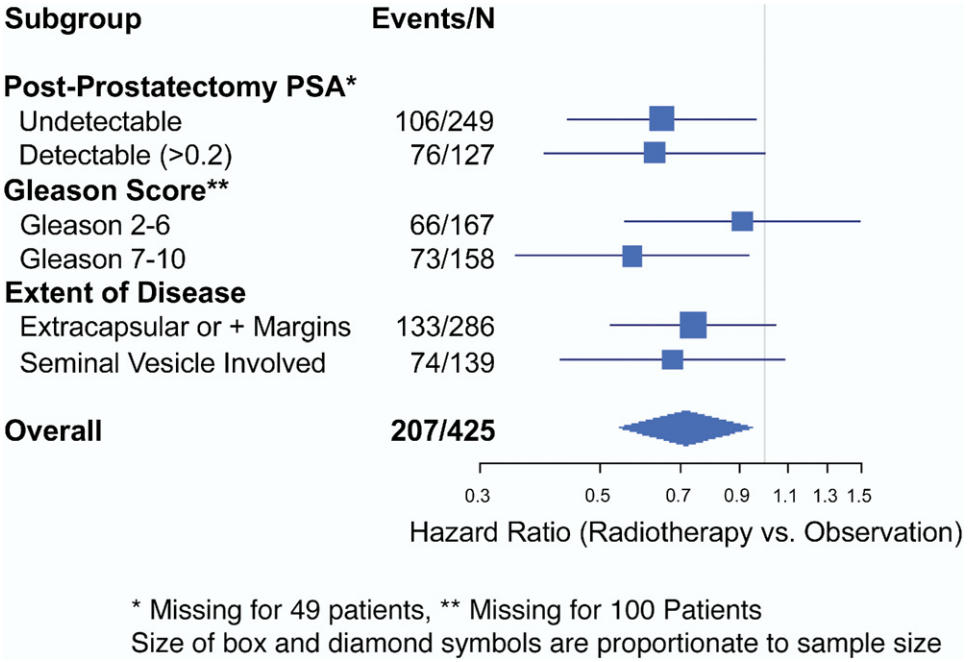

Figure 3. Metastasis-free survival HR estimates and corresponding 95% CI for subsets of patients based on baseline risk factors

for a number of subsets defined by baseline prognostic factors. These factors include post-prostatectomy PSA (0.2 ng/ml or less and greater than 0.2 ng/ml), seminal vesicle involvement (yes and no) and Gleason grade (less than 7 and 7 or greater). 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 1, suggesting a benefit from radiotherapy. The test of the interaction of each prognostic factor with radiotherapy was nonsignificant (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 in those men 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 (log rank $p = 0.03$).

DISCUSSION

More than 20 years after the initiation of S8794 this report demonstrates that adjuvant radiotherapy at the relatively modest dose used in the late 1980s significantly reduces the risk of metastasis in a man with pathological 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 occurred 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 more than 30,000 men per year in the United States.[1,10] In the realm of advanced prostate cancer docetaxel, the only treatment proven to improve survival, improves survival by only 1.9 to 2.3 months.[11,12]

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 at more than 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 2 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 5 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 point (47% vs 5%) in the radiotherapy group but by 2 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) be-

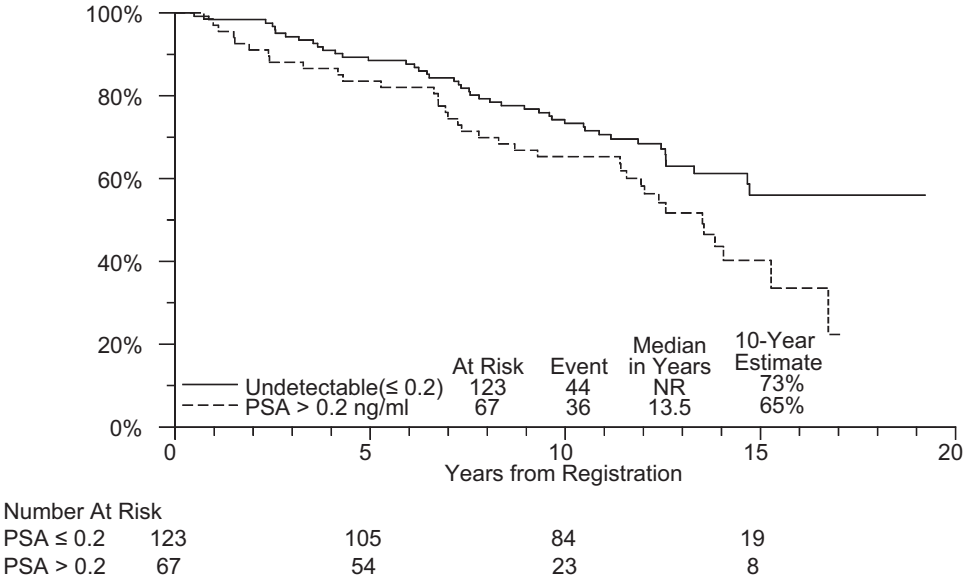

Figure 4. Metastasis-free survival for radiotherapy arm stratified by PSA status after prostatectomy

tween 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 during the following 3 years. This gradual switch toward a superior quality of life in 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, all of which have negative impacts on quality of life.[13,14]

A limitation of this study is the incomplete central pathological review with only 311 of 425 (73%) men having a complete central pathological review. Nevertheless, of those with a 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 a central review was only conducted at high volume institutions and for 566 of 1,005 patients. Similar to our study 552 of 566 men were deemed eligible after review. However, a review of the EORTC trial demonstrated that with central review only patients with positive margins benefitted from adjuvant radiation.[15] Additionally, it must be acknowledged that Gleason grades assigned during this trial are probably lower than would be assigned with a contemporary review, as would be the case for any study with 20-year outcomes.[16] It is also important to acknowledge that the extent of disease in patients from the late 1980s and early 1990s may have been of a greater volume than in 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 postoperative PSA is undetectable, a common strategy is simply to follow the PSA and initiate radiotherapy when PSA becomes detectable or before the achievement of some PSA threshold (eg 1.5 ng/ml).[17,18] These data indicate 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. Approximately a third of subjects assigned to observation ultimately received radiotherapy at the time of a PSA or local relapse. Thus, the study 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 to radiotherapy for the subset of patients with a detectable PSA after prostatectomy (fig. 3), that group's metastasis-free survival is inferior to that of those who received radiotherapy when PSA was still undetectable (fig. 4). Although these 2 observations are based on subsets of the data, they do indicate 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 the increased burden of therapies as well as an increased risk of metastasis and death.

This study points out 2 challenges for the academic and clinical trials community. Important therapeutic advances in the management of localized prostate cancer require large numbers of patients and just as importantly prolonged followup. 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 as well as 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 on the observations of this study. One suggestion would be to randomize patients with T3N0M0 prostate cancer to adjuvant radiotherapy or to salvage radiotherapy as soon as an ultrasensitive PSA is positive.[19] We examined possible study designs such as this and 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 or less) and using rates of failure as seen in this study, a 2-sided alpha of 0.05 and a power of 90%, and an accrual during 8 years with 9 additional years of followup would require a sample size of 8,300 men. With the poor track record of accrual of patients with localized prostate cancer to clinical trials in the United States, 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 similar designs across the studies we anticipate that meta-analyses will be conducted.

CONCLUSIONS

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

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