Conformal radiotherapy for detectable PSA following radical prostatectomy: efficacy and predictive factors of recurrence

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DELONGCHAMPS NB, ZERBIB M, MEJEAN A, ROUACH Y, DEBRE B, PEYROMAURE M. Conformal radiotherapy for detectable PSA following radical prostatectomy: efficacy and predictive factors of recurrence. The Canadian Journal of Urology. 2009;16(5):4813-4819.

Introduction: *Many studies have analyzed outcomes following salvage radiation therapy (RT) after biochemical recurrence--defined as the presence of detectable serum prostate-specific antigen (PSA)--following radical prostatectomy (RP). However, the management of patients with detectable PSA following RP, which is not specific for tumor recurrence, is a matter of debate. This study aimed to evaluate oncological results of three-dimensional conformal RT (3D-CRT) in patients who had biochemical recurrence.*

Materials and methods: *The study included patients who underwent RP, who had a postoperative PSA level--determined between 2 and 4 months after surgery--that was greater than 0.1 ng/ml, and who subsequently received monotherapy with 3D-CRT on the prostate bed. The patients' clinical, characteristics and the pathological characteristics of their biopsy specimens were recorded. The main endpoint was biochemical failure after 3D-CRT, defined as three consecutive elevated PSA levels.*

Results: *The tumors in the 46 patients included 4 (9%) pT2a, 7 (15%) pT2b, 14 (30%) pT2c, 10 (22%) pT3a, 10 (22%) pT3b, and 1 (2%) pT4 tumor. The Gleason score was 7 or higher in 37 patients (80%). Positive surgical margins were seen in 37 patients (80%). The patients had a median postoperative PSA level of 0.29 ng/ml (range, 0.1-5.8 ng/ml) and a median PSA doubling time (PSADT) before RT of 6 months (range, 1-53 months). The rate of biochemical recurrence free survival after 3D-RT was 66% at 30 months. Preoperative PSA, PSADT before RT, and D'Amico scores were significantly associated with biochemical failure after 3D-CRT ($p < 0.05$).*

Conclusions: *In cases of persistent PSA following RP for prostate cancer, 3D-CRT can be used as monotherapy with a significant chance of recurrence free survival. Preoperative PSA, PSADT before RT, and D'Amico score are predictive factors of recurrence following RT.*

Key Words: prostate cancer, conformal radiotherapy, PSA, radical prostatectomy

Introduction

After radical prostatectomy (RP) for prostate cancer, up to 25% of patients experience disease recurrence within 5 years.[1] In most cases, recurrence is asymptomatic and characterized by rising serum prostate-specific antigen (PSA) levels. Typically, serum PSA levels are undetectable for months or even years following surgery and then rise to 0.2 ng/ml or higher, which is a widely accepted definition of biochemical recurrence after RP. If localized residual disease is suspected after RP, radiation therapy (RT) is the usual treatment option. This treatment has been mostly evaluated in patients who have delayed biochemical recurrence, and the reported rate of 5 year survival free from biochemical recurrence in these patients ranges from 35% to 65%.[2-17] The wide discrepancy in reported oncological results may be explained by variations in the populations studied and by the heterogeneity of RT techniques. Moreover, in these studies, biochemical failure occurred

Accepted for publication July 2009

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at different times after surgery, and the patients may have had different types of prostate cancer.

Although most disease recurrence occurs after a period when serum PSA is undetectable, a few patients have detectable serum PSA levels very soon after surgical intervention. For these patients, the critical issue is to determine the likelihood of treatment failure and cancer progression. Indeed, a postoperative detectable PSA level may reflect the persistence of malignant cells that were not removed by surgery, especially in cases of positive surgical margins. But it may also reflect the presence of residual benign prostate tissue. Several parameters, such as D'Amico's preoperative score,[1] preoperative serum PSA level, PSA doubling time (PSADT) after surgery,[18] and pathological characteristics of the RP biopsy specimen,[19] may help clinicians evaluate the risk of cancer progression and choose the most appropriate treatment option.

Only scant data are available regarding patients with detectable serum PSA levels following RP. Our study aimed to evaluate the oncological results of three-dimensional conformal RT (3D-CRT) used as monotherapy in a series of patients with detectable serum PSA levels shortly after RP.

Patients and methods

Patient selection

We reviewed the medical charts of 566 patients who underwent RP for localized prostate cancer during 2001 to 2006 in Necker Hospital in Paris, France. In 82 patients (14%), postoperative serum PSA levels--determined at the first follow up visit between 2 and 4 months after surgery--were greater than 0.1 ng/ml. A total of 59 of these patients subsequently underwent 3D-CRT. Seven of these patients received concomitant hormonal therapy and six other patients were lost to follow up, leaving data from 46 patients available for analysis. Our institution does not require institutional review board approval for reporting clinical data.

Design and settings

Preoperative workup before the RP consisted of determining the patient's serum PSA level and performing a digital rectal examination (DRE). Prostate biopsies included a median of 12 cores (range, 6-16 cores). The pathological determinations from the biopsy samples included percentage of cores positive for cancer, percentage of cancer involvement, and Gleason score. D'Amico preoperative score were noted for all patients.[1] Patients whose serum PSA levels were greater than 10 ng/ml underwent endorectal magnetic resonance imaging and bone scintigraphy.

All patients underwent a retropubic RP that was performed using the same technique. RP specimens were analyzed using the Stanford technique.[20]

Postoperative PSA levels were measured within 6 to 8 weeks after surgery. Further PSA measurements were performed every 3 months. As suggested in literature,[21] PSA doubling time (PSADT) was calculated based on the time interval between two PSA measurements after RP and before RT, using the formula: PSADT = Ln 2 x (t2 – t1)/[Ln (PSA t2) – Ln (PSA t1)].

The decision to irradiate was made on a case by case basis, depending on preoperative PSA, histological analysis of the biopsy specimen, and PSADT after surgery. The 3D-CRT was performed after a median of 10 months after RP (range, 3-42 months). The conformal technique enabled the operator to optimally define the clinical target volume and the organs at risk (bladder and rectum). The target volume included the prostate bed and the seminal vesicles, with a security margin to encompass subclinical disease in the periprostatic area. The planned target volume was defined by extending the clinical target volume (CTV) 0.5 cm posteriorly and 1 cm in all other directions. No elective nodal irradiation was performed. The median dose to the prostate fossa was 72 Gy (range, 68 Gy-76 Gy), delivered in 2.2 Gy daily fractions, 4 days a week.

Following 3D-CRT, the patients were seen every 6 months by a radiation oncologist and by a urologist. They had a physical examination and serum PSA levels were determined. Imaging analyses to exclude metastatic disease were performed at the physician's discretion, as was the prescription of hormonal therapy for biochemical or clinical failure after 3D-CRT. Biochemical failure after 3D-CRT was defined as an increase of the serum PSA value > 0.2 ng/ml confirmed by three successive elevations. The interval between 3D-CRT and biochemical failure was recorded. Clinical failure was defined as any clinical evidence of disease recurrence and/or disease recurrence seen in imaging procedures (CT scan or bone scintigraphy).

Measurements

The main endpoint was biochemical failure after 3D-CRT. The risk of experiencing biochemical failure was analyzed according to several variables. Preoperative variables included PSA before RP, Gleason score from biopsy samples, percentage of positive cores for cancer, percentage of cancer involvement from biopsy samples, and D'Amico score. The RP pathological parameters included Gleason score, pathological stage, and margin status. Postoperative variables included PSA after RP and PSADT before 3D-CRT.

Statistical analysis

Statistical analyses were performed using the Statistical Analysis System software (SAS Institute, Cary, NC). Survival curves were plotted using the Kaplan-Meier method. Recurrence free survival rates were calculated starting from the day after 3D-CRT. Biochemical failure was defined as occurring at the time of the third elevated PSA reading. Patients who had no biochemical evidence of disease were censured at the time of the last follow up. Because of the small sample size, the non-parametric Mann-Whitney-Wilcoxon test was used to compare quantitative variables, and Fisher's exact test was used to compare qualitative variables. For all analyses, the level of significance was set at 0.05.

TABLE 1. **Characteristics of 46 study patients and their biopsy samples**

Characteristic	**Number of patients (%)***
Age (years), mean (range)	63 (50-83)
Suspicious DRE	26 (56.5)
Preoperative PSA (ng/ml), mean (range)	9 (3.5-55.5)
D'Amico score	
Low risk	18 (39)
Intermediate risk	21 (46)
High risk	7 (15)
Biopsy Gleason score	
6 (3+3) or less	26 (57)
7 (3+4) or higher	20 (43)
Percentage of positive cores (%)	27 (8-100)
Percentage of cancer involvement (%)	11 (3-68)
Pathological stage	
pT2a	4 (9)
pT2b	7 (15)
pT2c	14 (30)
pT3a	10 (22)
pT3b	10 (22)
pT4	1 (2)
RP specimen Gleason score	
6 (3+3) or less	9 (20)
7 (3+4) or higher	37 (80)
Positive surgical margins	37 (80)

*Except where other units are indicated

Results

The characteristics of the 46 patients and their tumors are shown in Table 1. The patients had a median age of 63 years (range, 50-83 years). DRE results were suspicious of cancer in 26 patients. The tumors in the 46 patients included 4 (9%) pT2a, 7 (15%) pT2b, 14 (30%) pT2c, 10 (22%) pT3a, 10 (22%) pT3b, and 1 (2%) pT4 tumor. The Gleason score was 7 or higher in 37 patients (80%). Positive surgical margins were seen in 37 patients (80%).

During surgery, an ilio-obturator lymphadenectomy was performed in 21 patients, and it did not show any evidence of nodal metastases.

The median time between RP and the first postoperative follow up was 3 months (range, 2-4 months). The mean and median value of postoperative PSA was of 0.65 ng/ml and 0.29 ng/ml, respectively. The patients had a median PSADT after RP and before 3D-CRT of 6 months and a mean PSADT of 10 months (range, 1-53 months).

Three patients (7%) experienced persistently rising PSA despite 3D-CRT. After a median follow up of 23 months (range, 9-81 months) following 3D-CRT, six other patients (13%) experienced biochemical failure. Of the nine patients who experienced treatment failure, one showed evidence of symptomatic bone metastases. Three patients were treated by hormonal therapy. The other six patients were treated by watchful waiting. Overall, the rate of biochemical recurrence-free survival was 66% at 30 months, Figure 1.

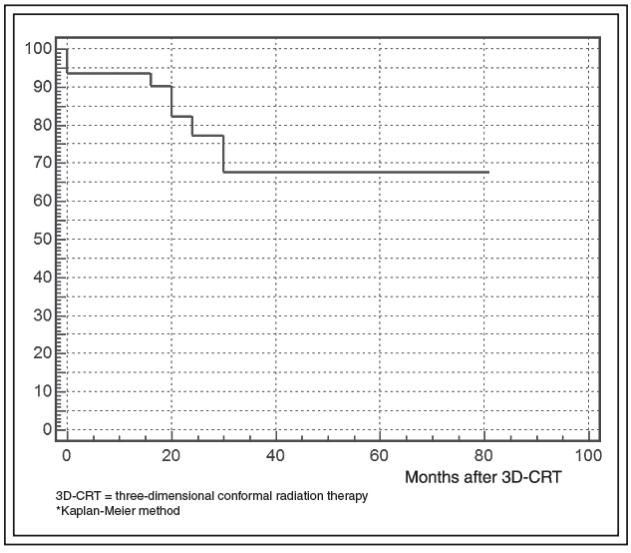

Figure 1. Estimation of recurrence free survival after 3D-CRT in 46 patients.*

TABLE 2. **Prognostic factors of recurrence free survival at 30 months after 3D-CRT***

	Biochemical recurrence after 3D-CRT	No biochemical recurrence after 3D-CRT	p value
Preoperative variables			
Median age (years)	67	63	0.9
Median PSA (ng/ml)	14	8	0.05
Median % of positive cores	40	25	0.1
Median % of cancer involvement on biopsies	18	9	0.1
Biopsy Gleason score			0.1
≤ 6 (3+3)	1	25	
≥ 7 (3+4)	8	12	
D'Amico score			0.02
Low risk	0	18	
Intermediate risk	6	15	
High risk	3	4	
RP specimen variables			
Pathological stage			0.1
pT2	3	22	
pT3a	4	6	
pT3b	2	8	
Gleason score			0.1
≤ (3+3)	0	9	
≥ (3+4)	9	28	
Positive surgical margins	8 (89%)	29 (78%)	0.9
Postoperative variables			
Median PSA (ng/ml)	0.6	0.29	0.9
Median PSADT (months)	5	8	0.007

*univariate analysis

Among the clinical, biological, and pathological variables examined, only preoperative PSA, D'Amico score, and PSADT before 3D-CRT were statistically associated with biochemical recurrence free survival, Table 2. A comparison of patients according to their D'Amico scores showed that biochemical recurrence free survival at 30 months was 100%, 54% and 41%, in patients with low, intermediate, and high risk of recurrence, respectively, Figure 2, p = 0.02. At 30 months, biochemical recurrence free survival was 66% among patients who had a PSADT before RT greater than 6 months, but it was only 32% in patients whose PSADT before RT was 6 months or less, Figure 3, p = 0.07.

Discussion

Many studies have evaluated patient outcomes after salvage RT for prostate cancer.[2-17] However, treatment failure after RP can occur in different clinical situations, and salvage therapy can consist of different RT techniques. Studies evaluating salvage RT have looked at very heterogeneous patient populations who received different treatments, as suggested by the variability of reported oncological outcomes in these studies [2-17] To our knowledge, the largest published series of patients treated with salvage RT for biochemical recurrence after RP included 501 patients.[12] In this study, fewer than one third of the patients had

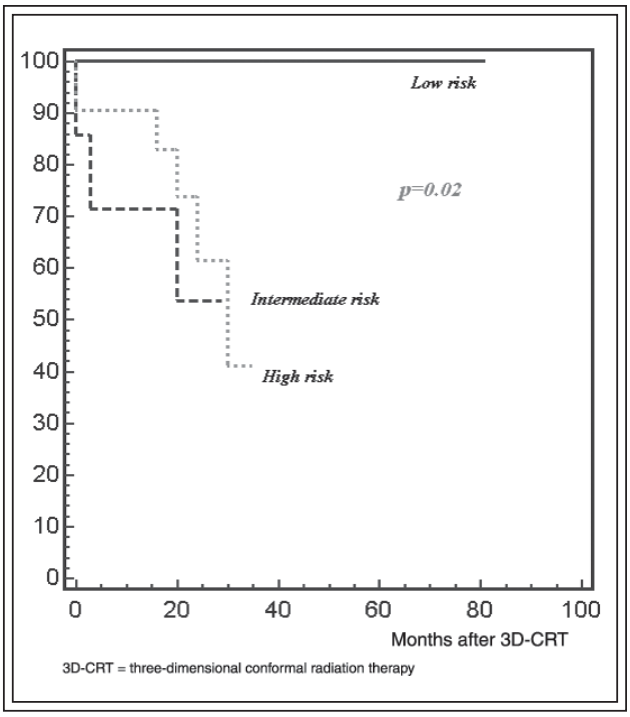

Figure 2. Estimation of recurrence free survival (%) after 3D-CRT based on D'Amico score.

a detectable PSA within weeks after surgery, and the remaining patients experienced delayed biochemical recurrence. Ten percent of the patients had received hormonal therapy before surgery, and another 20% of the patients had received hormonal therapy during salvage RT. The patients had a median PSA of 9.8 ng/ml prior to RP, and before RT, they had a median PSA of 0.72 ng/ml, and a median PSADT of 7.4 months. After a median follow up of 45 months after RT, 50% of the patients experienced biochemical failure, and the 4 year recurrence free survival rate was 45%.

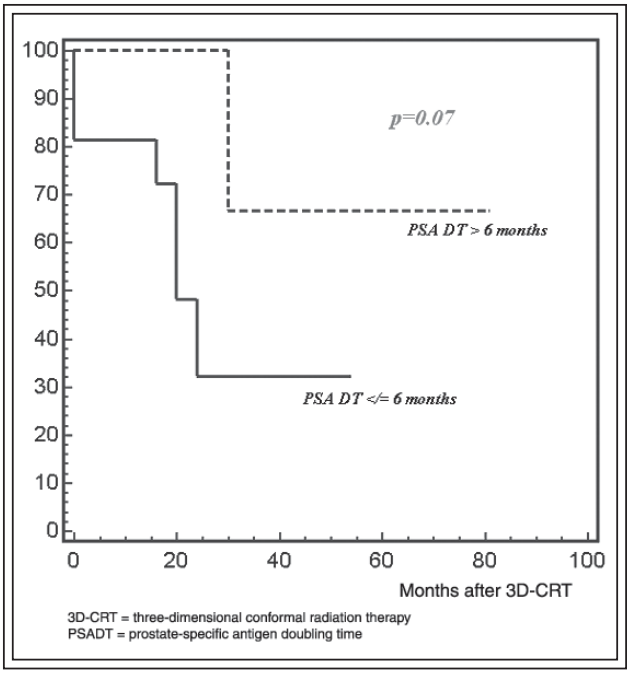

Figure 3. Estimation of recurrence free survival (%) after 3D-CRT based on PSADT before radiotherapy.

Results from other series suggest, however, that there is a great discrepancy in recurrence free survival rates, Table 2. In the two largest recently published studies, patients inclusion into the studies began in the late 1980s, when RT techniques and delivered radiation doses differed from current practice.[12,15] A significant number of patients were treated with nonconformal techniques, and the median delivered radiation dose was less than 65 Gy. As recently suggested, recurrence free survival may be significantly improved with a higher radiation dose.[22] Also, the absence of strict inclusion criteria may have introduced some significant bias. It is likely that the interval between surgery and PSA relapse is an important oncological parameter. A longer remission period may be linked with a higher probability of localized recurrence.[23] This parameter may therefore have a major impact on the results of RT.

The persistence of a detectable PSA level after RP is uncommon. To our knowledge, having a persistent, detectable PSA after RP has not been part of inclusion criteria in any studies evaluating salvage RT, and therefore our study constitutes the first evaluation of salvage RT in such patients. In this situation, clinicians are confronted with the difficult dilemma of deciding whether or not to irradiate the patient. Indeed, some patients may not have residual cancer, but may only have benign prostate cells left within the prostate bed. In patients with a rising PSA level in the months following surgery, this hypothesis may be rejected. The next question is then to distinguish occult metastasis from localized disease. Unfortunately, imaging studies have a low sensitivity in detecting either localized or systemic disease.[24] In our retrospective analysis, the decision to irradiate was taken on a case by case basis, and it relied on PSADT and the presence of surgical positive margins on the RP biopsy specimen, as suggested in the literature.[23] Nevertheless, in these patients with residual PSA, the value of postoperative RT has not been clarified. On the other hand, it is now acknowledged that post-RP RT should be delivered early, before PSA levels reach 1 ng/ml.[12,15] Early and delayed RTs have similar morbidity, but treatment is more efficient at the early signs of biochemical recurrence.[12,15] Our results

showed that 3D-CRT was efficient in 80% of patients after a median follow up of 23 months.

Statistical analysis showed that preoperative PSA, D'Amico score, and PSADT before 3D-CRT were significantly associated with recurrence free survival after 3D-CRT. These findings are consistent with earlier reports suggesting that a preoperative PSA < 10 ng/ml is associated with better oncological outcome after salvage RT.[12,15] On the other hand, our results concerning D'Amico score may be criticized. Because of the small sample size, multivariate analysis was not possible, suggesting that D'Amico score might not be associated with oncological outcomes independent from PSA levels.

In our study, the median PSA level before radiotherapy was low. Only two patients had a PSA level above 1 ng/ml. For patients with a PSA below 1 ng/ml, calculating PSADT may be of great value, by adding a substantial parameter at the very earliest signs of disease recurrence. According to Freedland et al,[25] patients with a PSADT shorter than 9 months have a greater probability of dying from their prostate cancers. Additionally, as previously suggested and confirmed by our results, PSADT may also predict post-RP RT efficacy.

The identification of histological predictive factors of RT efficacy is controversial. Buskirk et al[15] evaluated the results of RT in 368 patients with biochemical failure after RP. They found that Gleason score and seminal vesicle involvement on a RP specimen were the only pathological variables associated with recurrence free survival after RT. Stephenson et al[12] reported that positive surgical margins were also independently associated with recurrence free survival after RT. However, other authors suggested that only PSA and PSADT before RT were significantly associated with oncological outcomes. In our study, we did not find any association between the pathological characteristics of RP biopsy specimens and recurrence free patient survival after 3D-CRT, but these negative results could be due to our small sample size.

Our study has several limitations, including the small number of patients and the short follow up time. During the study period, only 82 patients had a detectable PSA after RP, and 46 of these patients were included in our analyses. Multivariate statistical analysis could not be performed.

On the other hand, we intentionally used very strict inclusion criteria regarding patient characteristics and RT techniques. While most previous studies evaluated RT in all patients who experienced a rising PSA level after RP, our work aimed to evaluate 3D-CRT--the current gold standard method for treating patients who have detectable serum PSA very shortly after surgery. We also excluded the patients who received hormonal therapy before or during RT to eliminate these confounding factors.

The European Organization for Research and Treatment of Cancer (EORTC) 22911 randomized study recently demonstrated significant improvement with adjuvant RT versus salvage RT in terms of biochemical recurrence free survival and clinical local control at 5 years, but not for overall survival.[26] Similarly, adjuvant RT significantly increased biochemical recurrence free survival versus observation in the Southwest Oncology Group (SWOG) 8794 study.[27] The authors concluded that oncological control was better with adjuvant RT than with watchful waiting followed by salvage RT. However, a significant number of patients included in these studies had a detectable PSA level, and one may argue that some patients randomized for adjuvant RT were in fact randomized for early salvage RT. To make a definite conclusion, we would need to compare adjuvant RT versus early salvage RT.

Conclusion

Our study suggests that patients with detectable serum PSA levels following RP for prostate cancer who subsequently receive monotherapy with 3D-CRT confined to the prostate bed can have a high chance of recurrence free survival. Preoperative PSA, PSADT before 3D-CRT, and D'Amico score predicted biochemical relapse following 3D-CRT. □

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