



## Prostate cancer radiotherapy

## Poorer outcome in Polynesian patients with prostate cancer treated with definitive conformational radiation therapy

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## ABSTRACT

**Purpose:** To compare freedom from biochemical failure (FFBF) of French Polynesian (FP) and Native European (NE) prostate cancer patients after definitive conformal radiotherapy (RT).

**Patients and methods:** Data were reviewed from medical records of 152 consecutive patients (46 FP and 106 NE) with clinically localised prostate cancer treated with definitive RT. Neoadjuvant androgen deprivation therapy (ADT) was used in 22% of cases. Definition for biochemical failure was a rise by 2 ng/mL or more above the nadir prostate-specific antigen (PSA) level. The median follow-up was 34 months.

**Results:** In comparison to NE patients, FP patients were younger ( $p = 0.002$ ) with a higher low-risk proportion ( $p = 0.06$ ). Probability of 5-year FFBF was 77% in the NE cohort and 58.0% in the FP cohort ( $p = 0.017$ ). Univariate analysis showed that FP ethnicity was associated with worse prognosis in high-risk tumours ( $p = 0.004$ ). Cox multivariate analysis showed that factors associated with FFBF were risk category ( $p < 0.017$ ), and FP origin ( $p = 0.03$ ), independently of ADT and radiation dose.

**Conclusion:** FP ethnicity was an independent prognostic factor for biochemical relapse after definitive conformal RT for prostate cancer.

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French Polynesia is a set of 48 islands spread over five archipelagos, about 6000 km east of Australia. The population of French Polynesia was 256,000 in 2007, with three ethnic groups: Polynesians (78%), Europeans (12%), and Asians (10%). Medical coverage is good on the largest islands but there is no Radiation Oncology Department in French Polynesia, and patients requiring radiotherapy (RT) are transferred to France.

The French Polynesian health care system is similar to that in France, with complete public health coverage, managed by the Social Welfare Fund. Treatment of cancer is free of charge, and that includes diagnostic tests, surgery, RT, drug treatments, follow-up, and transportation from place of residence to place of treatment.

Poorer outcome and advanced disease at diagnosis have already been described for the Māori male population, part of the Pacific Islands population [1,2]. It is still not clear whether prostate cancers are biologically more virulent in indigenous men or whether the mortality rates simply reflect differential access to early diagnosis (including screening) and treatment. Classical prognostic factors

such as clinical and/or pathological stage, Gleason score and prostate-specific antigen (PSA) levels have been clearly identified for the survival of prostate cancer [3,4]; however, there is scant outcome data for the FP population.

The purpose of this study was to compare freedom from biochemical failure (FFBF) of French Polynesian (FP) and Native European (NE) prostate cancer patients after definitive conformal RT.

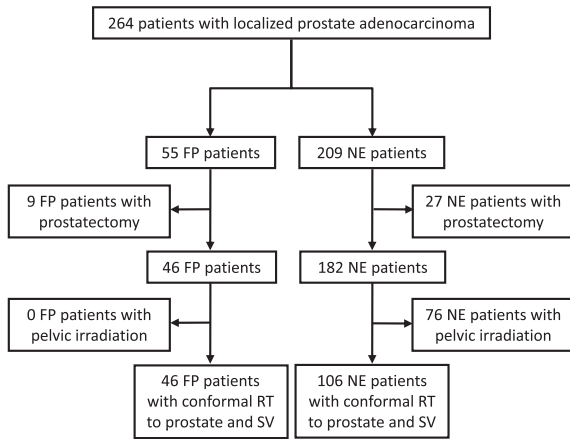
## Material and methods

## Study design and patient populations

We conducted a retrospective study of 264 consecutive patients with localised prostate adenocarcinoma, treated in our institution with conformal RT between April 1999 and July 2007. Thirty-six patients (9 FP and 27 NE) were excluded because they received irradiation after radical prostatectomy, and 76 patients (0 FP and 76 NE) were excluded because they received pelvic irradiation (Fig. 1). Therefore, 152 patients were included: 46 were FP and 106 were NE, 14 of whom were living in French Polynesia. All patient medical records were discussed at our institution's Multidisciplinary Meeting for the Management of Urologic Malignancies, after which, patients were transferred from French

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**Fig. 1.** Flowchart. Abbreviations: FP, French Polynesian; NE, Native European; RT, Radiotherapy; SV, seminal vesicles.

Polynesia to Paris. After treatment, FP patients returned to Polynesia and were followed by their urologists (GD and SL).

### Staging

All patients had a physical examination, including digital rectal examination, PSA determination, and ultrasound-guided transrectal prostate biopsy with Gleason score histological grading. All FP pathological samples were analysed at the Polynesian medical centre by an experienced pathologist trained for 15 years in France. All patients underwent pelvic computed tomography; those with PSA levels >10 ng/mL underwent a bone scan. Other staging modalities such as magnetic resonance imaging of the prostate or pelvis were performed at the discretion of the attending physician. Diagnostic lymphadenectomy was performed for patients with risk >10% of nodal involvement according to the Partin tables [5]. All patients with histologically proven positive lymph nodes were excluded from our study. Staging was performed in accordance with the 2002 American Joint Committee on Cancer Staging System [6].

### Treatment characteristics

All patients were treated with three-dimensional conformal external-beam RT. Radiation was delivered in 2.0-Gy daily fractions, using 18-MV photons. Conformal RT delivered 46 Gy with a four-field technique to a planning target volume 1 (PTV1) of a 1-cm margin around the prostate and seminal vesicles in three dimensions, except for the rectal-prostate interface, where a 0.5-cm margin was used. Then an additional irradiation of 20 Gy to 34 Gy was delivered to PTV2 that included only the prostate with the same margins as PTV1. No patients received pelvic node irradiation. Twenty-five percent of patients received 70 Gy, 25% received 74 Gy, and 33% received 76 Gy. All patients were given specific instructions before each fraction, i.e., empty the rectum and bladder one hour before CT planning, and before each irradiation session. Positioning quality control was carried out with portal imaging during the three days before the first irradiation session and then weekly thereafter.

Thirty-three patients in the intermediate and high-risk categories (22%: 3 FP and 22 NE) received neoadjuvant and/or concurrent androgen deprivation therapy (ADT) (gonadotropin-releasing hormone agonist) for 6–24 months.

### Toxicity assessment

Toxicity was recorded using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0

guidelines [7]. Acute toxicity and late toxicity were defined as reported toxicity that occurred within, or after 90 days after RT completion, respectively.

### Response assessment

The primary end point was freedom from biochemical failure (FFBF) defined using the RTOG-ASTRO Phoenix Consensus Conference criteria, i.e., a rise by 2 ng/mL or more above the nadir PSA level [8]. Other end points included biochemical progression free survival (BPFS), which included biochemical failure, distant metastasis, salvage ADT, and death from any cause (dates of death were obtained from the city of birth). Because of insufficient data, outcome in terms of distant metastases or overall survival could not be analysed.

PSA assays were repeated 6–8 weeks after the completion of RT, and patients returned for follow-up visits, which included a clinical examination and a PSA test every four months the first year and every six months thereafter, until end point (September 2010). All PSA tests were performed in the same laboratory (either in France or in French Polynesia) for any given patient. The median follow-up time was 34 months from the first day of RT to the last measured PSA.

### Statistical analysis

The association between ethnic origin and clinicopathological parameters was analysed using the Chi-square test for categorical variables (Yates' correction was used when a count was smaller than 5); the independent *t* test was used for continuous variables. Univariate analyses of FFBF and BPFS were performed using the Kaplan–Meier method and log-rank test. Univariate analysis was performed on ethnic origin, tumour stage, Gleason score, pre-treatment PSA levels, radiation dose, and use of ADT. Patients were also grouped according to prognostic risk categories: low-risk patients had PSA levels ≤10 ng/mL, Gleason score ≤6, and AJCC category T1c or T2a disease; intermediate-risk patients had PSA levels of between 10 ng/mL and 20 ng/mL, Gleason score of 7, and/or AJCC category T2b disease; high-risk patients had PSA levels of more than 20 ng/mL, Gleason score of 8–10, and/or AJCC category T2c to T3a disease [3]. The Cox proportional hazards model was used for multivariate analysis to determine prognostic factors for FFBF and BPFS. Multivariate analysis was performed according to risk categories, ethnic origin, and ADT. The year of radiotherapy was included as a covariate to adjust for the possible effect of a learning curve. Statistical analyses were performed using SAS software, version 8.2 (SAS Institute Inc, Cary, NC, USA). For all tests, a two-sided *p* < 0.05 was considered statistically significant.

The review board at our institution approved this study. The study was conducted in accordance with the Helsinki Declaration of 1975, revised in 2000. Written consent was not obtained from the participants because this was a retrospective review of existing patient data.

## Results

### Patient characteristics

FP men were younger than NE men: median age was 65 (51–73) and 69 (52–82) years, respectively (*p* < 0.002). FP patients tended to have more favourable tumours than NE men: proportion of patients with a low-risk prognosis disease was 30% and 14%, respectively (*p* = 0.06). No statistically significant differences in mean PSA values at presentation or Gleason score were observed between the FP and NE cohorts. The most frequent comorbidities were cardiovascular diseases and diabetes, with a similar proportion in the

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