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# Predictors of biochemical recurrence after primary focal cryosurgery (hemiablation) for localized prostate cancer: A multi-institutional analytic comparison of Phoenix and Stuttgart criteria

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**Abstract**

**Background:** The Phoenix definition (PD) and Stuttgart definition (SD) designed to determine biochemical recurrence (BCR) in patients with postradiotherapy and high-intensity focused ultrasound organ-confined prostate cancer are being applied to follow patients after cryosurgery. We sought to identify predictors of BCR using the PD and SD criteria in patients who underwent primary focal cryosurgery (PFC).

**Materials and methods:** We performed a retrospective review of patients who underwent PFC (hemiablation) at 2 referral centers from 2000 to 2014. Patients were followed up with serial prostate-specific antigen (PSA). PSA levels, pre- and post-PFC biopsy, Gleason scores, number of positive cores, and BCR (PD = [PSA nadir + 2 ng/ml]; SD = [PSA nadir + 1.2 ng/ml]) were recorded. Patients who experienced BCR were biopsied, monitored carefully or treated at the discretion of the treating urologist. Cox regression and survival analyses were performed to assess time to BCR using PD and SD.

**Results:** A total of 163 patients were included with a median follow-up of 36.6 (interquartile range: 18.9–56.4) months. In all, 64 (39.5%) and 98 (60.5%) experienced BCR based on PD and SD, respectively. On multivariable Cox regression, the number of positive pre-PFC biopsy cores was an independent predictor of both PD (hazard ratio [HR] = 1.4, $P = 0.001$) and SD (HR = 1.3, $P = 0.006$) BCRs. Post-PFC PSA nadir was an independent predictor of BCR using the PD (HR = 2.2, $P = 0.024$) but not SD (HR = 1.4, $P = 0.181$). Survival analysis demonstrated a 3-year BCR-free survival rate of 56% and 36% for PD and SD, respectively. Of those biopsied after BCR, 14/26 (53.8%) using the PD and 18/35 (51.4%) using the SD were found to have residual/recurrent cancer. Of those with prostate cancer on post-PFC biopsy, 57.1% of those with BCR by the PD and 66.7% of those with BCR by the SD were found to have a Gleason score ≥7.

**Conclusion:** Both the PD and the SD may be used to determine BCR in post-PFC patients. However, the ideal definition of BCR after PFC remains to be elucidated. 

*Keywords:* Prostate cancer; Primary focal cryosurgery; Biochemical disease-free survival; Phoenix; Stuttgart

## 1. Introduction

The emergence of cryosurgery for prostate cancer (PCa) has been largely due to advances in disease diagnosis and stratification. In particular, prostate-specific antigen (PSA) screening and imaging have led to an increase in the detection of low-grade, small-volume, organ-confined tumors. Improvements in magnetic resonance imaging (MRI) have allowed assessment of the whole prostate gland with localization of relevant tumor foci to guide minimally invasive therapies [1]. These advances have led to the use of

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cryosurgery in the primary and salvage settings [2,3]. Primary focal cryosurgery (PFC) has been shown to have comparable biochemical recurrence–free survival (BCRFS) to whole-gland treatment modalities in low-risk patients with better functional outcomes [4]. Up to 33% of patients who undergo radical prostatectomy have unilateral low-grade, organ-confined disease. These cases are amenable to focal therapy that has shown promising results of good cancer control with minimal morbidity [5].

Ideal criteria to define biochemical recurrence (BCR) after PFC remain to be determined. To date, the Phoenix criteria employed to define BCR after primary radiotherapy and the Stuttgart criteria used after high-intensity focused ultrasound therapies have been applied to define BCR in post-PFC follow-up [6,7]. We sought to identify predictors of BCR using the Phoenix and Stuttgart criteria after PFC for PCa. Further, we aimed to evaluate each criterion's ability to predict biopsy-proven recurrence in those biopsied after BCR.

## 2. Methods

### 2.1. Patients, data collection, and tumor assessment

We performed a retrospective medical record review from an International Review Board–approved database on patients who underwent PFC for clinically localized PCa at Columbia University Medical Center and Winthrop University Medical Center from August 2000 to February 2014. Patients were excluded from analysis if they had received radiotherapy or hormonal therapy before PFC. The cryosurgery technique has been previously described by Cheetham et al. [8]. Patients who underwent PFC received a full ablation of one lobe of the prostate (i.e., hemiablation; 50% of the total prostate tissue ablated). Patient demographics, preprocedure biopsy data and postprocedure follow-up information, including laboratory tests, imaging, and prostate biopsies were recorded.

Patients were stratified by D'Amico risk criteria for low-risk, intermediate-risk, and high-risk disease [9]. Standard post-PFC follow-up included PSA checks every 3 months for a year and every 6 months thereafter. BCR was defined using the Phoenix definition (PD) (PSA nadir + 2.0 ng/ml) and Stuttgart definition (SD) (PSA nadir + 1.2 ng/ml) [10]. After BCR, patients were managed in one of a few options. Patients were observed, further assessed with either repeat prostate biopsy or MRI, or primarily treated, at the discretion of the attending physician. There was no standardized postrecurrence management.

### 2.2. Statistics

Continuous variables were presented as median (interquartile range [IQR]) and categorical variables as percentages. Survival estimates and cumulative event rates of overall BCR were computed and depicted using Kaplan-Meier methods. Unadjusted Cox proportional hazards regression model was developed using time-dependent BCR by PD and SD method. All variables that were evaluated in the unadjusted models were included in the multivariable Cox proportional hazards model. Unadjusted and adjusted hazard ratios with 95% CIs were reported.

All calculations were performed using SAS 9.4 (SAS/STAT 13.1; SAS Institute, Cary, NC) for windows. Hazard ratios were considered significant if the 95% CI did not include one, and all other results were considered significant if $P < 0.05$.

## 3. Results

A total of 163 (122 from Columbia University Medical Center and 41 from Winthrop University Hospital) patients who underwent PFC between August 2000 and February 2014 were identified. Median follow-up time was 36.6 (IQR: 18.9–56.4] months. Baseline demographics and pathological data are presented in Table 1. Median age and pre-PFC PSA were 72 (67–78) years and 6.2 (4.3–7.8) ng/ml, respectively. Most (128/163, 78.5%) patients had a Gleason score of $\leq 3 + 4$, and 152/163 (93.3%) were in D'Amico low-risk or intermediate-risk categories.

A total of 149 (91.4%) patients had a PSA nadir at least 50% lower than the pre-PFC PSA. Based on PD and SD, 64 (39.5%) and 98 (60.5%) patients experienced BCR at a median time to BCR of 21.6 (10.4–39.1) and 15.9 (8.8–30.4) months, respectively.

On univariate analysis, higher pre-PFC PSA, higher post-PFC PSA nadir, percentage decrease in PSA and pre-PFC biopsy number of positive cores were predictors of BCR by PD and SD (Tables 2 and 3). When controlling for potential confounders, higher number of positive pre-PFC cores remained an independent predictor of BCR by PD (hazard ratio [HR] = 1.4; 95% CI: 1.2–1.7; $P = 0.001$) and

Table 1
Baseline patient demographics/pathology

| Variable | *N* (%) |
|---|---|
| Median age (IQR), y | 72 (67–78) |
| Median pre-PFC PSA (IQR), ng/ml | 6.2 (4.3–7.8) |
| Gleason score, no. (%) | |
| ≤6 | 75 (46) |
| 3 + 4 | 43 (26) |
| 4 + 3 | 13 (8) |
| ≥8 | 8 (50) |
| Missing | 24 (15) |
| Median no. of cores (range) | 12 (6–32) |
| Median no. of positives cores (range) | 2 (1–8) |
| Median percentage core involvement (range) | 20 (2–100) |
| Risk categories, no. (%) | |
| Low-risk | 85 (52) |
| Intermediate-risk | 67 (41) |
| High-risk | 11 (7) |