Randomized Trial of Partial Gland Ablation with Vascular Targeted Phototherapy versus Active Surveillance for Low Risk Prostate Cancer: Extended Followup and Analyses of Effectiveness

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Purpose: The prospective PCM301 trial randomized 413 men with low risk prostate cancer to partial gland ablation with vascular targeted photodynamic therapy in 207 and active surveillance in 206. Two-year outcomes were reported previously. We report 4-year rates of intervention with radical therapy and further assess efficacy with biopsy results.

Materials and Methods: Prostate biopsies were mandated at 12 and 24 months. Thereafter patients were monitored for radical therapy with periodic biopsies performed according to the standard of care at each institution. Ablation efficacy was assessed by biopsy results overall and in field in the treated lobe or the lobe with index cancer.

Results: Conversion to radical therapy was less likely in the ablation cohort than in the surveillance cohort, including 7% vs 32% at 2 years, 15% vs 44% at 3 years and 24% vs 53% at 4 years (HR 0.31, 95% CI 0.21–0.46). Radical therapy triggers were similar in the 2 arms. Cancer progression rates overall and by grade were significantly lower in the ablation cohort (HR 0.42, 95% CI 0.29–0.59). End of study biopsy results were negative throughout the prostate in 50% of patients after ablation vs 14% after surveillance (risk difference 36%, CI 28–44). Gleason 7 or higher cancer was less likely for ablation than for surveillance (16% vs 41%). Of the in field biopsies 10% contained Gleason 7 cancer after ablation vs 34% after surveillance.

Conclusions: In this randomized trial of partial ablation of low risk prostate cancer photodynamic therapy significantly reduced the subsequent finding of higher grade cancer on biopsy. Consequently fewer cases were converted to radical therapy, a clinically meaningful benefit that lowered treatment related morbidity.

Abbreviations and Acronyms

GG = Gleason Grade Group

MCCL = maximum cancer core length

MRI = magnetic resonance imaging

PGA = partial gland ablation

RP = radical prostatectomy

RT = radical therapy

VTP = vascular targeted photodynamic

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GIVEN the low probability of mortality from low risk PCa, therapeutic decisions reflect a balance between cancer control and quality of life. Current guidelines recommend AS as the preferred treatment option.[1,2] However, in practice treatment algorithms are complex and influenced by the substantial rates of reclassification or progression to higher grade or larger volume cancer with time and by patient choice.

Low risk PCa does not always remain indolent. In published cohorts of men on AS about 25% to 60% convert to RT (eg RP or radiation therapy) within 5 to 10 years, exposing them to substantial treatment related morbidity.[3–8] Thus, there remains an unmet need for more effective control of low risk cancer with treatments that pose minimal risks to urinary, sexual or bowel function. PGA with VTP is one such therapeutic approach.

The first multicenter, phase 3, prospective randomized trial evaluating PGA as treatment for localized PCa, CLIN1001 PCM301, was recently published.[9] VTP uses TOOKAD® (padeliporfin dipotassium), a stable, bacteriochlorophyll derived photosensitizer.[10] When excited by near infrared light (753 nm), TOOKAD generates superoxide and hydroxyl radicals which initiate a cascade of events leading to rapid vascular occlusion and subsequent coagulative necrosis of the targeted prostate tissue.[11] VTP is performed using anesthesia in an outpatient operating room. Intravenously injected TOOKAD is excited in the prostate by laser light delivered via transperineally placed light diffusers, targeting the lobe containing the largest cancer volume (hemigland ablation).

In PCM301 413 men with low risk PCa were randomized to VTP or AS. Patients with low risk PCa (Gleason score 6 or less, GG[12] 1), clinical stage T2a or less and PSA 10 ng/ml or less who had 2 or 3 positive cores with MCCL 5 mm or less, or 1 positive core with MCCL between 3 and 5 mm, and prostate volume 25 to 70 cc were eligible for study inclusion. The treatment arm was not blinded to participants and investigators but primary efficacy outcomes were assessed while blinded to treatment.[9] At 12 and 24 months 12-core systematic biopsies were mandated after randomization with 6 evenly spaced cores taken from each lobe. Demographics, patient characteristics and exclusion criteria are detailed in the original report.[9]

PCM301 met its co-primary and secondary end points. At 2 years in the intent to treat analysis the VTP cohort was less likely to have cancer in the biopsy at end of study ($p < 0.001$) or progression in cancer grade or volume ($p < 0.001$). Consequently the rate of conversion to RT at 2 years was lower in the VTP arm ($p < 0.001$). These positive trial results led the EMA (European Medicines Agency) to approve VTP as treatment of unilateral low risk but not very low risk localized cancer in 2017.

In PCM301 the principal benefit of PGA with VTP appeared to be a substantial delay in RT compared to AS with a consequent reduction in treatment related morbidity. Since biopsy results, which were the primary end points of PCM301, were assessed and reported at 24 months, few patients converted to RT after that time were captured in the initial report.[9] Thus, we assessed the durability of PGA in the intermediate term by analyzing the rate of conversion to RT up to 4 years after randomization by performing additional, post hoc analyses of biopsy outcomes as indicators of treatment efficacy.

MATERIALS AND METHODS

The initial PCM301 protocol (ClinicalTrials.gov NCT01310894) and extended followup with data collection up to 8 years after randomization (protocol addendum PCM301 5FU) were approved by the institutional review board centrally and at participating institutions at study initiation. All patients provided written informed consent.

To assess the intermediate results of the planned extended followup the data set was frozen on August 30, 2017. After 24 months study participants initially randomized to VTP or AS were treated by their physicians according to a local standard of care principle with management decisions, including the need for biopsy, made at the discretion of individual physicians and patients at each center. Comprehensive data, including PSA levels, biopsy results, adverse events, additional treatments and patient reported quality of life, were mandated at least annually using the approved clinical research forms submitted by the investigators.

Overall 266 patients (64%) were followed 4 or more years, including 147 (71%) in the VTP arm and 119 (58%) in the AS arm. Results at 4 years were calculated for the cumulative risk of conversion to RT and for metastasis-free, cancer specific and overall survival rates. Biopsy results were available to analyze indications for RT in 118 of the 123 patients (96%) with conversion to RT within 48 months. The types of RT included RP in 80% of cases, radiation therapy in 14% and whole gland cryotherapy or high intensity focused ultrasound in 5%. It was unknown in 1% of cases.

Additionally, post hoc analyses of annual biopsy results during the first 24 months were done to assess rates of grade progression to GG greater than 1, the location and grade of positive biopsy results in field (in the VTP treated lobe or for AS in the lobe containing the largest index