Clinical and Biochemical Outcomes of High-Risk Prostate Cancer Patients treated with Third Generation Prostate Cryosurgery

Sven Wenske[1,*], Philippa Cheetham[2] and Aaron E. Katz[2]

[1]*Department of Urology, Columbia University Medical Center, College of Physicians & Surgeons, New York Presbyterian Hospital, New York, NY 10032, USA*

[2]*Department of Urology, Winthrop University Hospital, Mineola, NY 11501, USA*

Abstract: *Objectives*: To report on outcomes after modern-day primary prostate cryosurgery (CS) in D'Amico high-risk (PSA >20 ng/ml, Gleason score ≥8, or tumor stage T2c or T3) localised prostate cancer (PCa) patients treated at a large academic center.

Materials and Methods: 730 consecutive cases of total gland prostate CS were reviewed, and 80 men with high-risk disease identified. Clinical data was analyzed, with primary and secondary endpoints being overall survival, cancer-specific survival, biochemical recurrence (BCR), and clinical progression.

Results: Median age was 75.8 (55.4-88.1) years, median presenting PSA 20.0 (2.6-236.5) ng/ml, and median Gleason score 8 (6-10). Median follow-up was 49.6 (8.9-159.3) months. There were three PCa related deaths (4%); 34 (43%) and 39 (49%) men had BCR as defined by the *Phoenix*- and *Stuttgart*-criteria, respectively; 24 of the 39 (64%) men were re-biopsied. 13 of 80 (16%) had biopsy proven recurrent PCa. Nine (11%) subsequently underwent salvage CS. Six of the 39 (15%) men with BCR had metastatic disease on bone scan; 19 of 34 (49%) men with BCR received anti-androgen therapy, 18 (95%) of whom had also received neoadjuvant hormonal therapy.

Conclusions: Prostate CS is a controversial treatment for high-risk patients, and our early experience revealed low cancer-specific mortality and morbidity, with encouraging biochemical and local control rates for these high-risk patients. In our series the incidence of metastases was less than that reported by Bolla *et al.* post-EBRT and hormones, and we therefore believe that prostate CS be strongly considered for these high-risk patients, and mandate that further study of CS for high-risk disease is warranted.

Keywords: Prostate cancer, high-risk, cryosurgery, biochemical recurrence, overall survival, cancer-specific survival.

INTRODUCTION

In the last two decades, the incidence of localised low-risk prostate cancer (PCa) has increased, largely due to early detection and screening with prostate-specific antigen (PSA) [1]. Current treatment strategies for localised disease include radical prostatectomy, external beam radiotherapy (EBRT), and high-energy ablative modalities, such as prostate cryosurgery (CS). Total gland CS has been used as primary therapy for localised disease, achieving cancer control comparable to radiation and surgery [2].

Recently, focal prostate CS of small, unifocal, low-risk tumors has also been shown to offer promising efficacy in cancer control [3]. While patients with low-risk PCa can usually expect an excellent prognosis, regardless of treatment modality, beneficial outcomes for those with high-risk or high-grade disease remain unproven [4].

Published results from some studies implied that poorly differentiated cancers are only cured in a minority of cases who receive a single treatment modality, and that high-risk patients initially require more aggressive treatment [4, 5]. In their recommended treatment guidelines, the American Urological Association (AUA), European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) all suggest numerous possible management options for men with clinically localised high-risk disease. These include radical prostatectomy (RP), EBRT, or a combination of these [6-9].

Current published clinical outcome data on patients undergoing prostate CS for high-risk disease (who may not be ideal candidates for surgery or EBRT) has never been published. The aim of this study was to determine the efficacy and clinical outcomes for high-risk patients undergoing total gland prostate CS.

MATERIALS AND METHODS

The Columbia University Medical Center Institutional Review-Board (IRB) approved Cryosurgery Prostate Database was retrospectively reviewed. 730

*Address correspondence to this author at the Department of Urology, Columbia University Medical Center, College of Physicians & Surgeons, Herbert-Irving Pavilion, 161 Fort Washington Avenue, New York, NY 10032, USA; Tel: (212) 305-6408; Fax: (212) 305-6813;
E-mail: sw2510@columbia.edu

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consecutive cases of total gland prostate CS between 1994 and 2012 for the treatment of localised PCa were identified. Eligible patients for analysis included men who met the 2001 D'Amico classification for high-risk disease (PSA >20 ng/ml, Gleason score ≥8, or tumor stage T2c or T3). Prior to treatment all patients had a negative metastatic evaluation, including nodal imaging of the abdomen and pelvis, as well as a bone scan. Patients who had undergone prior surgery, EBRT, or previous prostate CS were excluded. Data on relevant pre-, intra- and post-treatment information, including patient age, pre-treatment serum PSA level, biopsy Gleason grade, biochemical failure, application of neoadjuvant (NHT) or adjuvant hormonal therapy (HT), were assessed, as well as numbers of patient that remained hormone-naïve (HN) at time of CS.

Cryosurgery of the Prostate: Technique

For all procedures the whole gland was treated by a single surgeon (AEK) using either the CryoCare® (Endocare, Austin, Texas), or SeedNet® and Presice® (Galil Medical, Yokneam, Israel) CS systems. Figure **1A** illustrates the cryoneedles inserted into the perineum through the brachytherapy-type grid. Figure **1B** depicts a typical 17-gauge cryoneedle.

The transrectal ultrasound-guided percutaneous CS procedure has been previously described [10]. The prostate was analyzed *via* transrectal ultrasound (assessing size and length of gland, location of urethra, peripheral zone, and distance to the capsule) in order to determine the optimal geometry placement of either 17-gauge cryoneedles or 2.4-mm cryoprobes and thermocouples. The cryoneedles/cryoprobes were placed approximately 10 mm apart within 5 mm of the capsule. Under transrectal ultrasound guidance two freeze-/thaw-cycles were performed according to standard protocols [10].

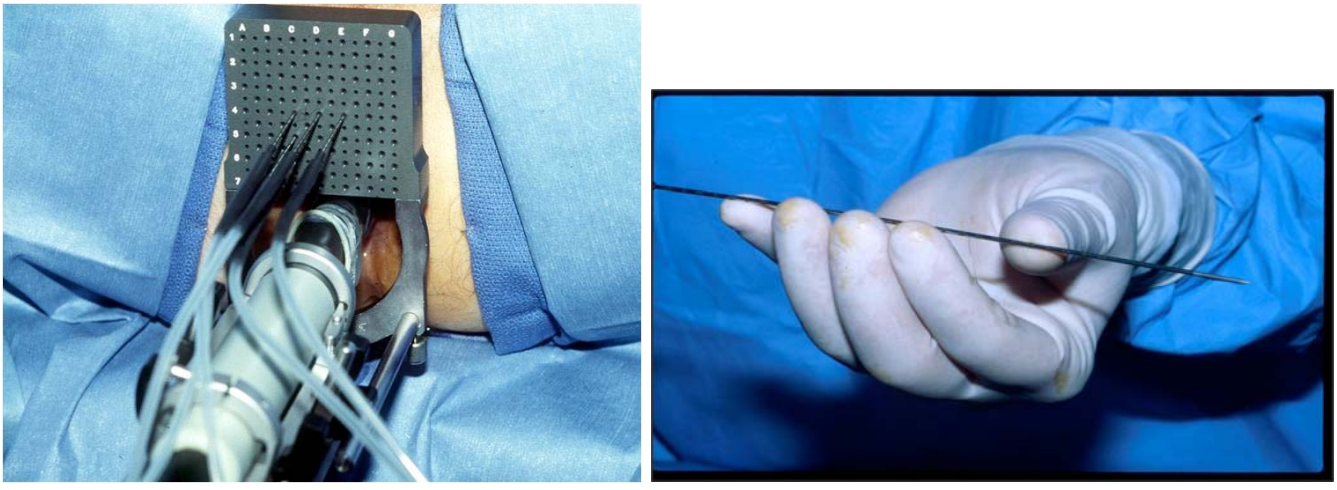
All patients were discharged on the day of the procedure with a Foley catheter for three days and then followed by serial PSA measurements (every three months for the first two years, then every six months thereafter). Additional biopsies and CT and bone scans were recommended when the PSA value increased 2 points above the nadir or if there was a change in the digital rectal examination.

Biochemical Recurrence

Biochemical recurrence (BCR) was defined using two definitions. The definition as formulated at the second RTOG-ASTRO Consensus Conference in Phoenix 2005 for patients after EBRT for PCa: A serum PSA level of 2 ng/ml or more above the nadir PSA (*Phoenix* definition) was considered BCR [11].

We also applied the recently published Stuttgart definition of BCR after high-intensity focused ultrasonography (HIFU) of the prostate, which is defined by a serum PSA level of 1.2 ng/ml above the nadir PSA [12].

Biochemical progression free survival (BPFS) was calculated using *Stuttgart* criteria and follow-up TRUS biopsy results, as the *Stuttgart* criteria are considered more stringent based on a lower PSA cut-off above the



A **B**

Figure 1: A. Illustration of six cryoprobe needles being inserted through the brachytherapy-type grid into the perineum, with the transrectal ultrasound probe in the rectum.
B. 17-gauge cryoneedle.

Table 1A: Preoperative Patient Characteristics: Entire Cohort

Characteristic		Value	(Range)
Patients (n)		80	
Age (years; median)		75.8	(55.4-88.1)
PSA (ng/ml; median)		20.0	(2.6-236.5)
Gleason score (n)	6	4 (5%)	
	7	16 (21%)	
	8	25 (32%)	
	9	25 (32%)	
	10 Unknown	4 (5%) 6 (8%)	
Clinical stage (n)	T1	6 (7.7%)	
	T2	10 (12.8%)	
	T3 Unknown	19 (25.6%) 45 (56.3%)	
Follow-up (months; median)		49.6	(8.9-159.3)

Table 1B: Preoperative Patient Characteristics: Hormone-Naïve Patients

Characteristic		Value	(Range)
Patients (n)		24	
Age (years; median)		73.0	(61.6-88.1)
PSA (ng/ml; median)		10.6	(2.6-236.5)
Gleason score (n)	6	2 (9%)	
	7	3 (13%)	
	8	12 (52%)	
	9	5 (22%)	
	10 Unknown	1 (4%) 1 (4%)	
Clinical stage (n)	T1	3 (13%)	
	T2	3 (13%)	
	T3 Unknown	7 (29%) 11 (46%)	
Follow-up (months; median)		42.8	(16.1-128.5)

Table 1C: Preoperative Patient Characteristics: Patients Receiving Neoadjuvant or Adjuvant Hormone Therapy

Characteristic		Value	(Range)
Patients (n)		56	
Age (years; median)		76.3	(55.4-87.9)
PSA (ng/ml; median)		22.8	(2.7-97.2)
Gleason score (n)	6	2 (4%)	
	7	13 (23%)	
	8	13 (23%)	
	9	20 (35%)	
	10 Unknown	3 (5%) 5 (9%)	
Clinical stage (n)	T1	3 (5%)	
	T2	7 (13%)	
	T3 Unknown	12 (21%) 34 (61%)	
Follow-up (months; median)		57.3	(8.9-159.3)

nadir after treatment, as compared to the *Phoenix* definition.

Primary and Secondary Endpoints

Primary endpoints for analysis included overall survival (OS) and cancer-specific survival (CSS). Secondary endpoints were BPFS, BCR, and clinical progression.

Statistical Analyses

Data were summarized as the medians and ranges for continuous variables, and in frequency tables for categorical variables. Kaplan-Meier analyses were applied to determine OS and CSS rates. The statistical software package SPSS 12.0 for Windows (SPSS Incorporated, Chicago, IL) was used for all statistical analyses.

RESULTS

Between January 1994 and February 2012, 730 consecutive cases of total gland prostate CS were conducted. 80 patients were identified as high-risk as defined by the D'Amico classification. Of these, 56 patients (70%) received NHT or HT, 24 (30%) were identified as remaining HN at CS.

Baseline pre-operative patient characteristics are summarized in Tables **1A-C**. There were no intra- or post-operative complications. No new urinary incontinence was reported during follow-up. Three patients were lost to follow-up (two in the NHT group, one in the HN group; Table **1A**). Clinical data was also substratified by HN or NHT/HT patients, and depicted in Tables **1B** and **1C**.

Men in the HT/ NHT group received either LH-RH agonists alone, or in combination with an anti-androgen, for either NHT (N=37) or HT (N=5), or in a combination of both (N=14). For those who received NHT, median time of treatment was three (0.4-147.3) months before CS; for those treated adjuvantly with HT, median time of duration was 26.8 (0.9-61.2) months.

During the four-year follow-up period, the OS rate was 78%, and CSS rate for the whole group was 96%. When substratified by men that received CS without NHT (i.e. remained HN), we found a CSS of 100% and OS of 83%, vs. 95% and 75% in the NHT group. Kaplan Meier analyses of OS and CSS for the entire cohort and for the subsets are depicted in Figures **2** and **3** respectively. Table **2** illustrates the numbers of patients in each group that were still alive and those that had died, whether or not they had died of PCa.

There were 27 patients in the NHT arm that received at least a three-month course of NHT before CS, a recommended minimum duration of treatment length in a neoadjuvant setting [13]. CSS in this group was 94%, OS 75%. In the subgroup of patients with HT, there were ten patients with at least 24 months of HT after CS, in which CSS was 90%, and OS 80%.

According to the *Phoenix* definition, 34/80 (43%) had BCR. Ten of these men (30%) were HN at time of

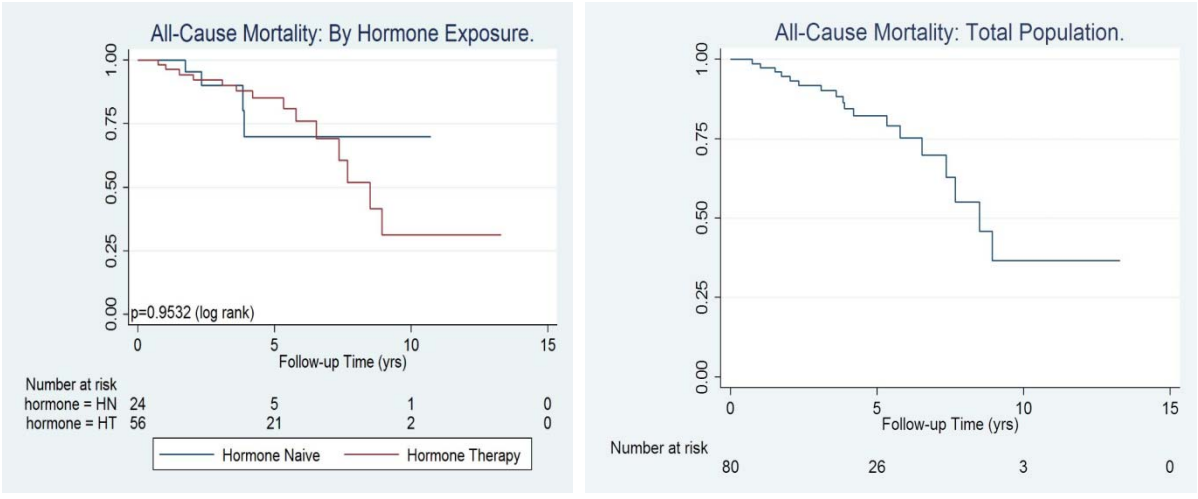


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Figure 2: A. Kaplan Meier analyses of overall survival – entire cohort.
B. Graph for men substratified by hormonal treatment: men that remained hormone-naïve (HN), and men that received anti-androgen therapy (HT).

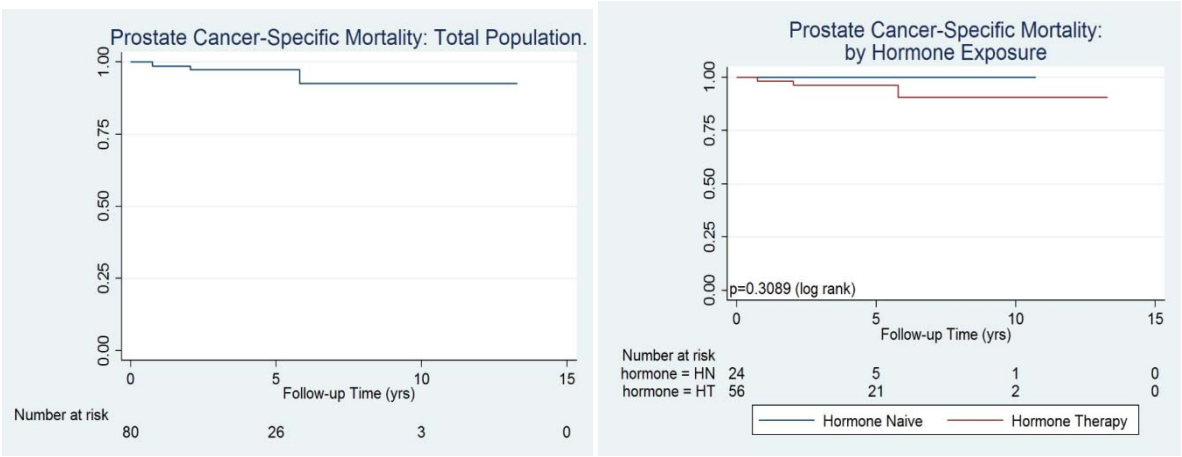

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Figure 3: A. Kaplan Meier analyses of cancer-specific survival – entire cohort.
B. Kaplan Meier analyses of cancer-specific survival – graph for men substratified by hormonal treatment: men that remained hormone-naïve (HN), and men that received anti-androgen therapy (HT).

Table 2: Survival Statistics Stratified According to Whether Patients Undergoing Cryosurgery Remained Hormone-Naïve (HN), or Received Neoadjuvant Hormone Therapy (NHT)

	HN	NHT	Total
Alive	20	42	62 (78%)
Dead, not related to prostate cancer	4	11	15 (19%)
Dead, related to prostate cancer	0	3	3 (4%)
Total	24	56	80 (100%)

CS (i.e. the subgroup analysis of the 24 HN men revealed ten men [44%] with BCR at a median follow-up of 42.8 [16.1-128.5 months]). 24/34 (70.6%) received NHT. When applying the more recently published *Stuttgart* criteria, overall 39 men (49%) met the criteria for BCR.

Of 39 men with BCR, 21 (54%) underwent a repeat transrectal prostate biopsy, to histologically determine if recurrent disease was present. In addition, one other patient was re-biopsied because of a high PSA velocity. However, this patient strictly did only fit the criteria for BCR according to the *Stuttgart* criteria (as the PSA was less than nadir plus 2 ng/ml at the time of re-biopsy). Twelve of 39 patients with BCR (31%) were confirmed to have recurrent cancer histologically. Prostate histology was benign in 9 patients (23%). The

Table 3: Number of Patients with Biochemical Recurrence (BCR), Stratified According to Whether Patients Undergoing Cryosurgery Remained Hormone-Naïve (HN), or Received Neoadjuvant Hormone Therapy (NHT)

	HN	NHT	Total
Malignant pathology on prostate biopsy	4	9	13 (37%)
Benign pathology on prostate biopsy	3	6	9 (26%)
Patient unfit for biopsy due to co-morbidity	1	1	2 (6%)
Patient received hormones based on rising PSA	1	3	4 (11%)
Evidence of metastases on bone scan	0	3	3 (9%)
PSA <5 ng/ml, physician deemed biopsy not warranted in view of patient age	2	0	2 (6%)
Patient declined biopsy / lost to follow-up	0	2	2 (6%)
			35

one patient with a high PSA velocity, who had not strictly failed, also had biopsy proven recurrent cancer.

A total of 18/39 men (46%) did not have a prostate biopsy to assess for recurrent disease despite meeting criteria for BCR. The reason a prostate biopsy was not performed in these patients is detailed in Table **3**.

Altogether, 13/80 men (16%) had biopsy-proven recurrent PCa (Table **3**); nine out of these (11% of the entire cohort) underwent a salvage CS. No patient underwent adjuvant radiation or salvage prostatectomy. One patient required a transurethral resection of the prostate (TUR-P) 58 months post CS for gross hematuria secondary to prostate regrowth at the bladder neck and prostatic urethra. Six of 39 men (18%) with BCR had a bone scan suggestive of metastatic disease. Eighteen men (46%) with a negative bone scan also underwent CT-imaging of the abdomen and pelvis, which did not reveal nodal disease. Ten patients (26%) with confirmed BCR had no further documented imaging. There were 19/39 men (49%) with BCR that received salvage HT, 18 (95%) of whom had also received NHT.

There was no significant difference in OS (74% NHT vs. 80% HN), CSS (87% NHT vs. 100% HN), or BDFS for NHT treated and HN men, as depicted in the Kaplan Meier analyses Figure **2-4**.

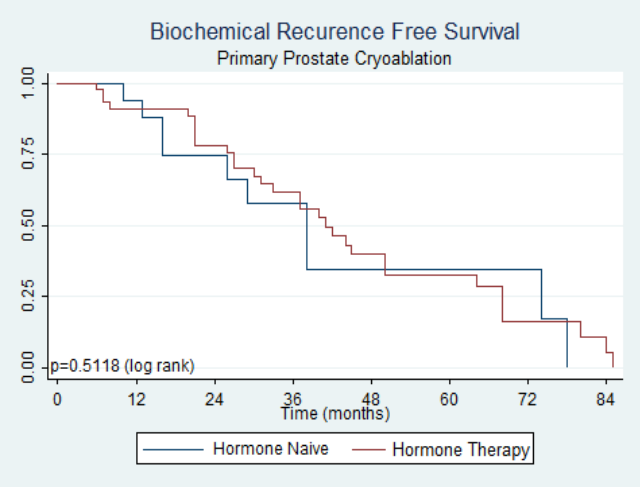

Figure 4: Kaplan-Meier analyses for biochemical recurrence. Data stratified according to men who remained hormone-naïve (HN) and those who received anti-androgen therapy (HT).

DISCUSSION

CS is a controversial treatment option for high-risk PCa patients, with features of their disease that put them at high-risk for clinical and/or BCR. To date, the application of total gland ablative cryosurgery for these patients has been very limited.

Primary prostate CS as a treatment option for men with localised PCa with low-risk features has been described, with clinical and biochemical outcomes comparable to that of surgery or radiation [2]. Several studies have assessed the safety and efficacy of salvage CS (i.e. after EBRT) once BCR has been confirmed [14, 15]. However, few studies have assessed clinical outcomes after primary prostate CS for high-risk disease, as defined by the 2001 D'Amico criteria [16].

In a series of 44 high-risk patients undergoing prostate CS El Hayek *et al.* reported BDFS rates of 61%, 53% and 43% for 12, 24 and 48 months respectively [17]. This is comparable with our own BDFS rate of 59% at a mean follow up of 53 months. However, in the El Hayek study, the authors' definition of high-risk disease (and subsequent stratification of risk groups) differ from the one used in our series. Median follow-up for the two groups was comparable. Similar BDFS rates were found by Long *et al.* [18]. However, risk stratification was again based on different definitions, and a different definition of BCR was used.

Our overall BDFS rate of 59% was slightly lower than that recently reported for a series of patients in a long-term follow-up after radical prostatectomy, but metastases-free survival and CSS were comparable [1]. Our results were also comparable to those of Saliken *et al*. who reported a BDFS rate of 48% in their subgroup analysis of men with high-risk features at 60 months after prostate CS [2]. However, Saliken *et al.* defined BCR as a serum PSA level of greater than 0.3 ng/ml. Substratifying patients according to whether or not they received NHT did not result in any difference in biochemical outcome in that analysis, similar to our own results.

The rationale for using NHT in high-risk patients is based on the premise that these men will eventually fail, because they already have local or distant micrometastases at the time of diagnosis. The higher the D'Amico risk category, the more likely the patient will receive NHT or adjuvant hormone therapy [19]. Differences in survival outcomes between HN and NHT patients may be explained by differences in baseline clinical features (significantly lower PSA serum level [10.6 ng/ml in the HN group vs. 28.8 ng/ml in the NHT group], and a significantly higher number of patients

with Gleason 8 in the HN subgroup, and more patients with Gleason 9 or 10 disease in the NHT group). These features may explain why NHT was initiated in these patients.

In our series, a retrospective analysis of non-randomized but consecutive patients, NHT did not appear to confer any survival advantage, and BDFS rates were similar in both, HN and NHT groups. However, the follow-up period was shorter in the HN group (42.8 vs. 55.5 months), and differences in BCR may only become evident after prolonged follow-up.

Bolla *et al*. have previously demonstrated that immediate concurrent hormone-therapy for patients undergoing EBRT as primary treatment for high-risk disease results in significant improvement in survival. The 5-year OS in the Bolla series was 62% and 78% for EBRT alone and EBRT with concurrent hormone-therapy, respectively. The 5-year CSS in the Bolla series was 79% and 94% for EBRT alone and EBRT with concurrent hormone-therapy, respectively [19]. In our analysis, we found a 4-year OS of 78% and CSS of 96% for the whole group. When substratified into those that received CS with and without NHT, we computed a 100% CSS and 83% OS in the HN group, and 95% CSS and 75% OS in the group that received NHT plus CS.

Bolla *et al.* also reported on the cumulative incidence of distant metastases during the 66 months follow-up period; 35% in the group treated with EBRT alone, versus only 12% in the group treated with the combination of EBRT and androgen deprivation. In our series with only a slightly shorter median follow-up of 49.6 months (although early BCR is considered to be caused by lymphogenic or hematogenic metastases in most cases, and delayed BCR more likely to indicate local recurrence, we still consider the length of our follow-up period sufficient; further analyses with longer follow-up data are to follow), we report an 8% (6/80) incidence of metastases for the overall group. However, when substratified into those that did and did not receive NHT the incidence of metastases was 12% (6/56) and 0% (0/24) respectively. There was no significant survival advantage between the two groups in our analysis when salvage HT was initiated. Clearly, our results are very different to the Bolla series in that those who received NHT and CS did worse than those who were HN. This is most likely explained by the fact those that received NHT were already a worse prognostic group of patients, and thus more likely to develop metastases in the first place than those in the HN group.

We used the *Phoenix* and *Stuttgart* criteria to define BCR after CS. To date, there is no specific definition for BCR following prostate CS. Thus, drawing comparisons of different outcome analyses is difficult and also emphasizes the need for a definition of BCR specific to CS (both total and focal gland CS) [20]. However, we applied the recently published *Stuttgart* criteria for BCR for patients after HIFU therapy to our patient cohort, not demonstrating any significant change in number of patients with BCR.

CONCLUSIONS

In conclusion, we report CSS and OS rates of 96% and 78% respectively, with a BCR rate of 43% in patients with high-risk localised PCa undergoing prostate CS. Our findings suggest that prostate CS is a valid treatment option in a subset of patients with high-risk disease. Furthermore, our results suggest that NHT does not confer any survival advantage or improved BCR rates for men with high-risk features, compared to those who are HN. Longer follow-up data is required to confirm these findings in a larger cohort of men with high-risk disease.

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