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Short Communication

Radical prostate cancer treatment in the elderly: role of cryotherapy

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Background & Aims. Data regarding efficacy and safety of radical cryotherapy for localized prostate cancer in elderly men are lacking. This study aimed to determine oncological and functional outcomes of radical cryotherapy in this setting.

Methods. From our dedicated Internal Review Board approved prospectively maintained database we selected elderly (> 75 years) patients with localized prostate cancer as assessed by a negative staging choline-PET. After cryotherapy, patients were seen at 1 month, every 3 months for the first two years, then every six months, for clinical examination, serum PSA, questionnaires for lower urinary tract symptoms (IPSS) and erectile function (IIEF-5), and assessment of pad usage for urinary continence. Biochemical recurrence was defined as a rising PSA above the Nadir of more than 2 ng/mL. Complications were scored using the Clavien-Dindo scale.

Results. From March 2012 to June 2018, 45 patients met the inclusion criteria. Mean postoperative hospital stay was for 1.06 days. At median follow-up (41 months), biochemical failure occurred in 8.8% of patients, with Kaplan-Meier plots showing an estimated 85% biochemical-free survival at 5y. Three (6.6%) patients reported urge urinary incontinence needing at least 2 pad/day; they were treated by antimuscarinic agents with complete symptoms resolution in 2 and relevant benefit in one. No patient suffered stress urinary incontinence.

Conclusions. This is the first study testing radical cryoablation in the setting of elderly patient. It showed excellent 5y biochemical recurrence-free survival not only in intermediate-risk but also in high-risk patients at the price of a reasonable/low rate of minor complications.

Key words: Elderly, Cryotherapy, Prostate cancer, Prostate biopsy

INTRODUCTION

Prostate cancer (PCa) is the most common malignancy in men. In the era of PSA screening, predictive models [1-5], novel imaging techniques [6] and biomarkers [7-10] the PCa detection rate has dramatically increased. Although many elderly men who are diagnosed with PCa will die from other causes, 70% of PCa-related deaths occur in men aged > 75 years [11 12] and PCa remains the third cause of death in male [13]. Moreover, many men who do not die from Pca will suffer significant morbidity related to this disease. Treatment of PCa in the elderly therefore represent a major clinical issue.

Though improvement of detection methods could lead to the risk of overtreating low-risk disease, evidence suggest that elderly men tend to be undertreated [14].

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Indeed, the lower cancer-specific survival (CSS) observed in elderly men may be at least partly explained by underuse of radical, therefore potentially curative, local treatments [15]. Moreover, elderly patients are more likely than younger patients to be diagnosed with aggressive cancers.

The International Society of Geriatric Oncology recommends that patients should be managed on the basis of their health status rather than on chronological age alone [16]. Similarly, the European Association of Urology (EAU) guidelines for the management of prostate cancer [14] in older men recommend that the treatment decision process should take into account the risk of dying from prostate cancer, potential adverse effects of treatment, and patient preference. Baseline health status and life expectancy should also be carefully evaluated to determine whether or not the patient is fit for treatment. Having said this, chronological age is often used as a cut-off in the screening, diagnosis and management of prostate cancer, with the 10 years life expectancy criterion remaining a standpoint in indicating radical treatment. Indeed, radical prostatectomy (RP) is usually not offered in men with a < 10 years life-expectancy due to the perceived lack of oncological benefit and the risk of debilitating side-effects.

External beam radiotherapy seems to provide similar cancer control regardless of age but a dose of > 72 Gy should be given by intensity-modulated or image-guided RT [17]. After such dose gastrointestinal (GI) and urinary side-effects are common; approximately 50% of patients reported acute urinary side effects of Grade I, 20% Grade 2, and 2% of Grade 3. Moreover, approximately 30% of patients reported acute Grade I GI toxicity, 10% Grade 2, and less than 1% Grade 3. In other words, phenomena such as dysuria, urinary frequency, urinary retention, haematuria, diarrhoea, rectal bleeding and proctitis are common [18]. Also fatigue is common.

Cryotherapy is emerging as an effective minimally invasive treatment option for localized PCa treatment, though current EAU guidelines recommend it within the setting of clinical trials [19]. The role of cryotherapy in the setting of elderly patients, however, has not been explored.

Therefore, the present study aimed to determine oncological and functional outcomes of elderly men with localised Pca treated by radical cryotherapy.

PATIENTS AND METHODS

From our dedicated Internal Review Board approved prospectively maintained database of Prostate Cryotherapy we selected elderly (> 75y) patients who had undergone prostate biopsy at our Institution [20-22] and were diagnosed with localized PCa as assessed by a negative staging PET-choline. Radical prostate cryotherapy was always carried out under spinal anesthesia. Depending on prostate volume, six to eight 2.4 mm cryoprobes were inserted into the prostate through the perineum under ultrasound (US) guidance. Radical ablation was obtained using an argon/helium gas-based system (Endocare, HeathTonics Inc., Austin, TX, USA); specifically, pressurized argon (300 bar of pressure and -180°C) exploited freezing, whereas both helium and room temperature were used to obtain thawing. Temperature was monitored inside and outside the prostate by sensors positioned in the apex, external sphincter, and neurovascolar bundle on both sides. Injecting saline solution mixed with a broad-spectrum antibiotic in the Denonvilliers' fascia (Onik maneuver) was used to separate the prostate from the rectum. Urethral temperature was kept at 38°C by a continuous flow system pumping saline solution at 41°C [23 24]. Cryoablation usually involved two cycles of freezing/thawing but 7 (15.5%) patients with large prostate volume required a third cycle. All procedures were carried out by one of us (OS). At the end of the procedure, a Foley urethral catheter was left in place.

Patients were scheduled for discharge on first postoperative day with the indwelling Foley catheter to be kept in place for ten days and prescribed pain killers as needed [25].

Patients were seen at 1 month postoperatively, every 3 months for the first two years, then every six months. Follow-up consisted in clinical examination, serum PSA, validated questionnaires for lower urinary tract symptoms (IPSS) and erectile function (IIEF-5), and assessment of pad usage for urinary continence. Biochemical recurrence was assessed using Phoenix criteria and defined as a rising PSA above the Nadir of more than 2 ng/mL [26]. Complications were scored using the Clavien-Dindo scale.

RESULTS

From March 2012 to June 2018, a total of 45 patients met the inclusion criteria. Their descriptive characteristics are summarized in Table I. Median age was 79 years, median preoperative PSA was 5.8 ng/dL, median total percentage of cancer (TPC%) was 16.5 and median prostate volume was 44 cc. Clinical stage was cT1c in 23 patients. cT2b in 1, cT2c in 20,and cT3a in 1. Finally, Gleason Group (GG) was 1 in 17.8% of patients, 2 in 24.4%, 3 in 17.8%, 4 in 33.3%, and 5 in 6.7%.

Mean postoperative hospital stay was for 1.06 days as 3 patients were discharged on second postoperative

Table I. Patients descriptive characteristics.

	Number of patients = 45
Age at surgery (IQ)	79 (77, 79)
Preoperative PSA ng/ml (IQ)	5.8 (4.8, 9.0)
Biopsy Gleason group (%)	
1	8 (17.8%)
2	11 (24.4%)
3	8 (17.8%)
4	15 (33.3%)
5	3 (6.7%)
Clinical stage (%)	
cT1c	23 (51%)
cT2b	1 (2%)
cT2c	20 (44%)
cT3a	1 (2%)
TPC % (IQ)	16.50 (6.00, 36.00)
Prostate volume cm3 (IQ)	44.00 (32.20, 56.00)
Follow up month (IQ)	40.93 (18.47, 54.20)

PSA: prostatic specific antigen; TPC: Total percentage cance.

day due to hematuria. Postoperative complications are reported in Table II.

At median follow-up of 41 months, biochemical failure occurred in 4 (8.8%) patients, with Kaplan-Meier plots showing an estimated 85% biochemical-free survival at 5y (Fig. 1). Patients with biochemical failure were offered multiparametric MRI and prostate re-biopsy. One refused them as well as further treatment and follow-up; the other 3 underwent prostate biopsy and were diagnosed with prostate cancer. Two underwent second radical cryotherapy while the third elected to undergo

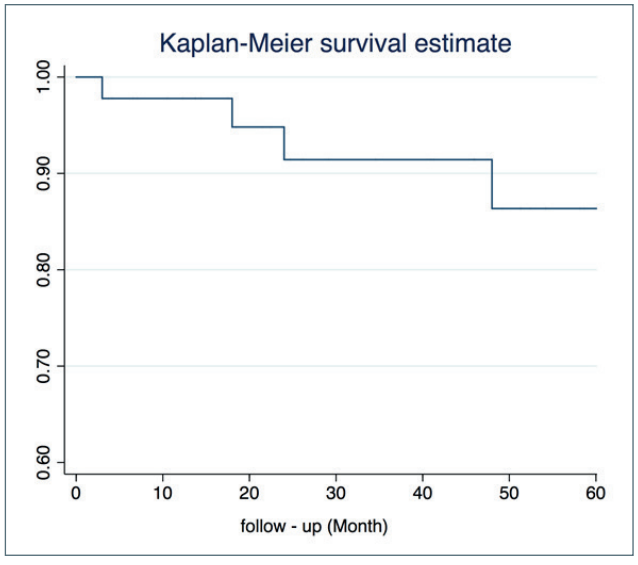

Figure 1. Biochemical recurrence of prostate cancer.

Table II. Overall complications after radical prostate cancer treatment.

Complications post-operative	% patients
Perineal Hematoma	6.6 (3/45)
Scrotal Hematoma	6.6 (3/45)
Urinary tract infection	4.4 (2/45)
Perineal pain	13.3 (6/45)
Scrotal/penil swelling	6.6 (3/45)
Hematuria	6.6 (3/45)
Rectal discomfort	8.8 (4/45)
Retention	4.4 (2/45)

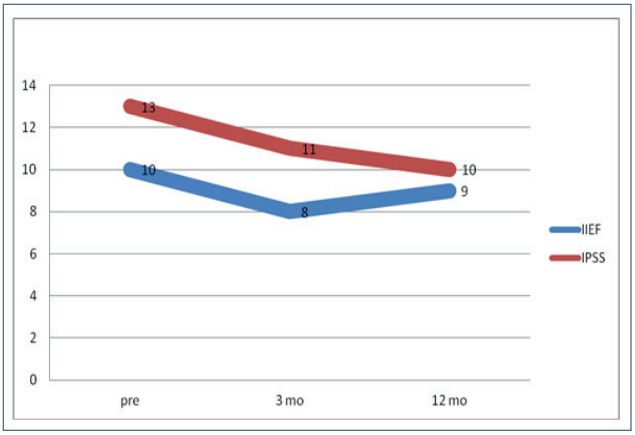

Figure 2. IPSS and IIEF-5 score at follow-up.

androgen deprivation treatment.

Changes in median IPSS and IIEF-5 score are reported in (Fig. 2). Pre-operatively, 9 patients reported mild Erectile Dysfunction (ED) and 2 no ED; at 12-month follow-up, only 1 reported mild ED and none no ED. Three (6.6%) patients reported urge urinary incontinence needing at least 2 pad/day; they were treated by antimuscarinic agents with complete symptoms resolution in 2 and relevant benefit in one. No patient suffered stress urinary incontinence.

DISCUSSION

Radical treatment of localized prostate cancer in men over 75 years is a controversial issue. Several factors such as treatment efficacy and safety, life expectancy, and the postulated marginal cancer-specific survival benefit need to be taken in due account.

The present study pointed out that radical cryotherapy provided, in elderly patients with localized PCa, a 5y biochemical recurrence-free survival of 85%. This result is particularly encouraging considering that 40% of

patients had a high-risk disease, given their GG 4 and 5. Indeed, all 4 biochemical failures occurred in patients with high-risk disease, specifically 2 in patients with GG4 and 2 with GG5. These data suggest that elderly men with localized high-risk prostate cancer may benefit from this local treatment. Our 77.8% 5y biochemical recurrence-free survival in high-risk patients compares well with the biochemical recurrence-free survival reported after radical prostatectomy for high-risk prostate cancer, which ranges from 58.4 [27] to 85% [28]. This is of great clinical relevance in view of the fact that, as mentioned above, radical prostatectomy is usually not offered to elderly patients due to the perceived lack of oncological benefit and the risk of procedure-related complications [29], though their occurrence, like for most surgical procedures, is much linked to case volume [30].
Indeed, elderly patients with high-grade localized PCa are usually offered radiotherapy or androgen deprivation treatment (ADT) or both. Radiotherapy may be an attractive treatment option for patients who cannot tolerate surgery. The reported 5y biochemical recurrence-free survival for radiotherapy in high-risk PCa, however, is 52.7% [31], quite lower than the one we obtained. Apart from efficacy in high-risk PCa, counseling regarding radiotherapy should take into account its common GU and GI side-effects as well as the unpleasant sense of fatigue. Though the incidence of radiotherapy associated adverse effects do not seem to increase with age [12], patients with peripheral vascular disorders seem to be at higher risk of complications following this treatment.
The scenario is not that different for ADT that may involve metabolic disturbances and even severe cardiovascular events [32-34]. These harmful effects of ADT are cumulative, with the most significant survival disadvantage seen in those with comorbidity-adjusted life expectancy of > 10 years. Nevertheless, a significant proportion of older men with localized prostate cancer are treated with ADT, which denies them the opportunity to receive radical treatment while exposing them to the devastating side-effects of such treatment. Of course, the combination of radiotherapy and ADT, which is recommended in high-risk disease, may expose to all such adverse events. Not to mention treatment duration, which is obviously much longer for both radiotherapy and ADT when compared with cryotherapy. Taken together, these considerations would strongly support a role for cryotherapy in elderly patients with high-risk localized PCa.
More complex is the issue of radical treatment in elderly males with low or intermediate risk localized PCa. While active surveillance (AS) seems to be a reasonable options in patients with GG1, even when not all standard criteria [35 36] for AS are meet, counseling becomes a bit more difficult in patients with intermediate risk disease. On one hand, elderly men, especially those with chronic comorbid conditions, are likely to die from other causes rather than their PCa. On the other hand, however, increase life expectancy and the risk of biopsy having downgraded the tumor question AS. In this scenario, the possibility of offering a minimally-invasive approach having a 100% 5y biochemical recurrence free rate, as we had no failure in patients at intermediate risk, is definitely appealing. Not to mention that most patients are happy to receive a minimally-invasive yet potentially curative treatment for their cancer rather than live with it untreated. Finally, side-effects were not common and, in any case, minor. Of course, clinical factors predicting treatment outcome [37] and wise clinical judgement remain essential like in other common urological procedures [38-40].
This study is not without limitations. First, it is a single centre study with a relatively small number of patients; however, this allowed stringent inclusion criteria. Second, it is retrospective but data were prospectively collected.
In conclusion, this is to our knowledge the first study testing radical cryoablation in the setting of elderly patient. Cryotherapy provided an excellent 5y biochemical recurrence-free survival not only in intermediate-risk but also in high-risk patients at the price of a reasonable if not low rate of minor complications.

Conflict of Interest

The authors declare no conflict of interest.

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