Original Article

Oncological outcomes of whole-gland cryoablation in patients with prostate cancer and high risk of lymph node invasion

Oscar Selvaggio[1], Ugo Giovanni Falagario[1], Marco Finati[1], Salvatore Mariano Bruno[1], Marco Recchia[1], Paola Milillo[2], Francesca Sanguedolce[3], Giovanni Silecchia[4], Luca Macarini[2], Luigi Cormio[1,4], Giuseppe Carrieri[1]

Departments of [1]Urology and Organ Transplantation, [2]Radiology and [3]Pathology, University of Foggia, Foggia, [4]Department of Urology, Bonomo Teaching Hospital, Andria (BAT), Italy

Abstract

Purpose: Prostate cryoablation has been proposed as an alternative to radical prostatectomy for men with localized prostate cancer (PCa); however, it is limited by the lack of data regarding oncological outcomes and the impossibility of performing a lymph node dissection. The aim of this study was to assess if whole-gland cryoablation is oncologically safe, especially for patients in whom pelvic lymph node dissection would be necessary.

Materials and Methods: After institutional review board approval, we identified 102 patients who underwent whole-gland prostate cryoablation between 2013 and April 2019. Lymph node invasion (LNI) probability was computed using Briganti nomogram, and a 5% cutoff probability was used to stratify the population in two groups. Biochemical recurrence after procedure was assessed using Phoenix criteria. Multiparametric magnetic resonance imaging, (CT), and bone scan or choline positron-emission tomography/CT were performed for the detection of distant metastases.

Results: Seventeen (17%) patients were treated for a low-risk PCa, 48 (47%) patients were at intermediate-risk PCa, and 37 (36%) patients were at high-risk PCa. Patients with a probability of LNI >5% ($n = 46$) exhibited higher prostate-specific antigen (PSA), PSA density, ISUP Grade Group, CT stage, and european association of urology (EAU) risk. Recurrence-free survival rates at 3 years' follow-up were 93%, 82%, and 72%, respectively for low-, intermediate-, and high-risk patients. At a median follow-up of 37 months (17–62), additional treatment and metastasis-free survival were 84% and 97%, respectively. No differences in oncological outcomes were found in patients with a probability of LNI above and below 5%.

Conclusions: Prostate whole-gland cryoablation can be considered a safe procedure with acceptable outcomes in low- and intermediate-risk patients. A high preoperative risk of nodal involvement could not be considered an exclusion criterion to perform cryoablation. Further studies are required.

Keywords: Biochemical recurrence, cryoablation, lymph node invasion, minimally invasive surgery, prostate cancer

Address for correspondence: Dr. Marco Finati, Department of Urology and Renal Transplantation, University of Foggia, Viale Pinto 1, 71122 Foggia (FG), Italy.
E-mail: m.finati@outlook.it

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INTRODUCTION

Although prostate cancer (PCa) often has an indolent course, it represents the third leading cause of cancer death in men.[1] Several treatments are available based on patient's life expectancy and cancer characteristics. EAU guidelines recommend offering active surveillance to patients with a life expectancy >10 years and low-risk disease, while radical prostatectomy (RP) is the preferred option in patients with intermediate to high risk.[2]

In patients with a risk of nodal metastases exceeding 5% computed using the Briganti nomogram,[3] MSKCC nomogram or Roach formula,[4] an extended pelvic lymph node dissection (ePLND) should be performed.[2]

In the past few years, several less invasive ablation techniques have been proposed as an alternative to RP. Among these, prostate cryoablation can be used for whole- or focal gland treatment in PCa, either as a primary or salvage treatment option.[5] To date, paucity of strong evidence and data on these treatments have confined them within a clinical trial setting or well-designed prospective cohort studies. In addition, this treatment modality does not allow performing ePLND,[2] thus possibly losing important information for staging and prognosis which cannot be matched by any other currently available procedure.

However, recent evidence does not show any survival benefit of performing ePLND during RP,[6] and to the best of our knowledge, there is no study evaluating the utility of this procedure in patients undergoing active treatment using ablation techniques.

If whole-gland cryosurgery is oncologically safe in patients with a high risk of lymph node invasion (LNI) (in whom ePLND is considered necessary) is still undetermined, and this was the aim of this study.

MATERIALS AND METHODS

Study population

Our prospectively maintained database was queried to identify patients who underwent prostate cryoablation at our institution between 2013 and April 2019. Following EAU guidelines, such treatment was offered under a prospective cohort study evaluating the efficacy of prostate cryoablation in patients with PCa, and written informed consent was given by all participants. The study protocol was carried out in agreement with the provisions of the Declaration of Helsinki after Institutional Review Board approval. Patients who previously underwent focal treatment were excluded from the analysis. In addition, to be eligible for this study, a prostate biopsy had to be performed at our institution, according to our protocol.[7] After noninfiltrative anesthesia, all patients underwent a transrectal standard biopsy using our 18-core template.[8-10] If prebiopsy multiparametric magnetic resonance imaging (mpMRI) was available, three extra cores were taken from any suspicious lesion using MRI-US fusion software guidance.[11]

Prostate cryoablation and follow-up protocol

Prostate cryoablation was performed 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. Freezing of the whole gland 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. The temperature was kept around –38°C in the mid-gland and at the neurovascular bundle using sensors positioned in the apex, external sphincter, and neurovascular bundle on both sides. A saline solution mixed with a broad-spectrum antibiotic was injected into the Denonvilliers' fascia (Onik maneuver) to separate the prostate from the rectum. A urethral catheter was placed after the procedure (to be removed 10 days after the procedure), and the patient was discharged on postoperative day 1.

Patients were followed up every 3 months after cryosurgery for the first 2 years, every six months from the 3rd to the 5th year, then once a year from the 6th to the 10th year. Every patient underwent a follow-up multiparametric MRI 1 year after surgery or earlier if deemed necessary. If mpMRI demonstrated any lesion suspicious for local relapse, a prostate biopsy was performed, and the patient was eventually retreated using cryoablation. In addition, all patients with biochemical recurrence (BCR), defined according to the Phoenix criteria as an increase in PSA level of 2 ng/mL or higher than nadir, underwent staging using abdominopelvic computed tomography (CT) and bone scan or choline positron-emission tomography/CT (PET/CT) for the detection of distant metastases. Additional treatment included re-cryoablation or androgen deprivation therapy (ADT), combined with abiraterone or enzalutamide in metastatic- or castration-resistant PCa.

Statistical analysis

The outcomes of this study were BCR, defined according to the Phoenix criteria as an increase in PSA level of 2 ng/mL or higher than nadir[12] and the need of additional treatment after prostate cryotherapy.

LNI probability was computed using the 2012 updated Briganti nomogram[3], and a 5% cutoff probability was used to stratify the population in two groups. Patients were also stratified according to EAU risk categories according to PSA, biopsy Gleason Grade Group (GGG), and clinical stage.[2]

First, descriptive statistics were performed for the overall population and stratified according to the risk of LNI. Continuous variables were reported as the median and interquartile range (IQR) and compared by the Mann–Whitney *U*-test, whereas categorical variables were reported as rates and tested by the Fisher's exact test or the Chi-square test, as appropriate.

Multivariable cox regression analyses predicting BCR and the need of additional treatment after prostate cryoablation was performed, and recurrence-free survival (RFS) was estimated using the Kaplan–Meier method. Statistical analyses were performed using Stata-SE 14 (StataCorp LP, College Station, TX, USA). All tests were two-sided with a significance level set at $P < 0.05$.

RESULTS

Descriptive characteristics of 102 patients included for analysis and stratified according to LNI probability are shown in Table 1.

Overall, 17 (17%) patients were treated for a low-risk PCa, 48 (47%) patients were at intermediate-risk PCa, and 37 (36%) patients were at high-risk PCa.

Patients with a probability of LNI >5% (n = 46, 45%) had a higher PSA, PSA density, GGG, CT stage, and EAU risk (all $P < 0.02$). Conversely, no differences were found in Age and treatment-specific variables (treatment cycles and a number of probes). The majority of patients were treated using six probes in two cycles.

Table 2 shows the oncological outcomes of the study population. The median follow-up was 37 months (IQR: 17–62). The median PSA nadir was 0.2 ng/ml with a median decrease of 5.6 ng/ml at 3 months after surgery. Overall, 17 (17%) patients had BCR, and 16 (16%) needed additional treatment, respectively. Specifically, three patients (3%) underwent re-cryoablation, while the remaining 14 (14%) ADT, three patients (3%) exhibited distant metastasis at PET/TC or bone scan during follow-up. No differences in oncological outcomes were found in patients with a probability of LNI above and below 5%.

At multivariable cox regression analysis, the probability of LNI was not associated with worse outcomes [Table 3]. Kaplan–Mayer curves showed worse outcomes in patients at intermediate to high-risk PCa when compared to those with low-risk, although no statistical significance were assessed among the three groups [Figure 1]. Specifically, RFS rates at 3 years' follow-up were 93%, 82%, and 72%, respectively, for low risk-, intermediate-, and high-risk patients (P = 0.2). Similar RFS was found in patients with a probability of LNI below and above 5% in the

Table 1: Preoperative clinical characteristics of the overall population and stratified according to lymph node invasion probability (cut off 5%)

	Overall population (n=102), n (%)	Probability of LNI ≤5 (n=56), n (%)	Probability of LNI >5 (n=46), n (%)	P
Age (years)	76 (72–79)	76 (71–78)	77 (72–79)	0.2
PSA (ng/ml)	6.1 (4.6–9.7)	5.2 (4.2–7.7)	7.6 (5.2–11.3)	0.007
PSA density	0.16 (0.10–0.25)	0.14 (0.09–0.22)	0.19 (0.12–0.32)	0.018
Prostate volume (cc)	45 (30–56)	45 (33–58)	43 (30–55)	0.4
GGG				
1	22 (22)	22 (39)	0	<0.0001
2	29 (28)	18 (32)	11 (24)	
3	21 (21)	5 (9)	16 (35)	
4	26 (25)	9 (16)	17 (37)	
5	4 (4)	2 (4)	2 (4)	
cT stage				
1	45 (44)	42 (75)	3 (7)	<0.0001
2	52 (51)	14 (25)	38 (83)	
3	5 (5)	0	5 (11)	
EAU risk				
Low	17 (17)	17 (30)	0	<0.0001
Intermediate	48 (47)	26 (46)	22 (48)	
High	37 (36)	13 (23)	24 (52)	
Treatment cycles				
1	1 (1)	1 (2)	0	0.5
2	95 (93)	51 (91)	44 (96)	
3	6 (6)	4 (7)	2 (4)	
Number of probes	6 (6–6)	6 (6–6)	6 (6–6)	0.7

GGG: Gleason Grade Group, EAU: European Association of Urology, PSA: Prostate-specific antigen, LNI: Lymph node invasion, cT: Clinical extent of prostate tumour

Table 2: Oncological outcomes of the overall population and stratified according to lymph node invasion probability (cut off 5%)

	Overall population (*n*=102), *n* (%)	Probability of LNI ≤5 (*n*=56), *n* (%)	Probability of LNI >5 (*n*=46), *n* (%)	*P*
PSA nadir (ng/ml) (IQR)	0.2 (0.1–0.6)	0.2 (0.1–0.4)	0.3 (0.1–1.2)	0.070
PSA drop (ng/ml) (IQR)	5.6 (4.4–8.3)	5.1 (4.2–7.2)	6.1 (4.7–10.1)	0.14
Time to PSA nadir (months) (IQR)	3 (3–3)	3 (3–6)	3 (3–3)	0.053
Follow-up	37 (17–62)	43 (28–67)	26 (15–48)	0.011
BCR	17 (17)	10 (18)	7 (15)	0.7
Additional treatment	16 (16)	9 (16)	7 (15)	0.9
Metastasis during follow-up	3 (3)	2 (4)	1 (2)	0.7
Follow-up biopsies (*n*=15)				
Negative	9 (60)	6 (67)	3 (50)	0.11
GGG 1	2 (13)	1 (11)	1 (16)	
GGG≥2	4 (27)	2 (22)	2 (33)	

LNI: Lymph node invasion, PSA: Prostate-specific antigen, IQR: Interquartile range, BCR: Biochemical recurrence, GGG: Gleason Grade Group

Table 3: Multivariable cox regression analysis predicting biochemical recurrence after prostate cryoablation

Covariate	BCR			Additional treatment		
	HR	95% CI	*P*>|*Z*|	HR	95% CI	*P*>|*Z*|
Age (per years)	1.01	0.91–1.11	0.923	1.02	0.92–1.12	0.738
PSA (per unit)	0.95	0.72.1.25	0.730	1.03	0.97–1.09	0.309
EAU						
Low	Reference			Reference		
Intermediate	1.48	0.29–7.44	0.635	1.36	0.28–6.54	0.703
High	2.64	0.50–14.00	0.254	2.34	0.50–11.01	0.284
LNI probability (%)						
≤5	Reference			Reference		
>5	0.79	0.28–2.27	0.668	1.06	0.53–17.91	0.213

EAU: European Association of Urology, PSA: Prostate-specific antigen, LNI: Lymph node invasion, BCR: Biochemical recurrence, HR: Hazard ratio, CI: Confidence interval

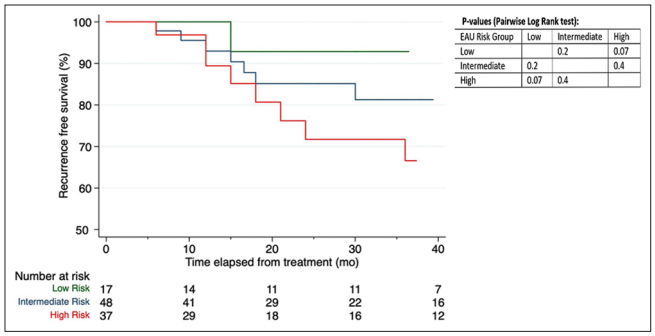

Figure 1: Kaplan–Mayer curve showing recurrence-free survival in patients at low-, intermediate-, and high-risk prostate cancer according to EAU risk stratification

overall population and in a subanalysis including only the intermediate-risk group [Figure 2].

DISCUSSION

In the present study, we reported mid-term outcomes of patients treated at our institution within a prospective cohort study. Our cohort showed comparable oncological results with previous literature. According to the COLD Registry, a multicenter pooled database including outcomes of 1,198 patients treated with primary whole-gland cryoablation, the 5-year biochemical disease-free survival was 91%, 79%, and 62% for low-, medium-, and high-risk groups, respectively.

To the best of our knowledge, this is the first study reporting outcomes of patients undergoing prostate whole-gland cryoablation according to their risk of node invasion.

While whole-gland cryoablation has all the benefits of minimally invasive treatment and good local control of the disease,[13] it cannot be delivered to pelvic lymph nodes and does not offer the opportunity of histological analysis of the whole prostate, periprostatic tissue, and nodes to assess the final pathology T and N stage. The lack of accurate staging might compromise adjuvant therapies selection and consequent prognosis, although recent evidence suggests performing ePLND does not provide a survival benefit. In this perspective, we tried to evaluate if an LNI probability risk calculator should be an adequate criterion to better select patients for cryoablation, thus excluding those who would need an ePLND.

Our preliminary results showed similar survival rates in the two groups of patients with a preoperative probability of LNI above and below 5%. However, the presence of locally advanced disease (pT3a-pT3b) as well as a subclinical involvement of lymph nodes may jeopardize the safety of this procedure in unfavorable intermediate-risk and high-risk patients.[14] Latest advancements in imaging modalities for PCa may overcome this limitation.[15] Prostate

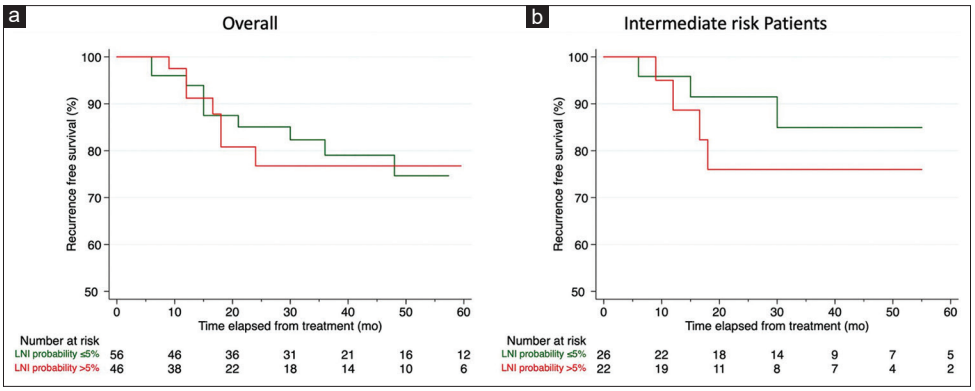

Figure 2: Kaplan–Mayer curve showing recurrence-free survival according to risk of LNI (a) in the overall population and (b) in the intermediate-risk group. LNI: Lymph node invasion

MRI may help to rule out the presence of extracapsular disease in patients at high-risk PCa.[16-18] Even if we did not routinely use prebiopsy MRI to enroll patients in the present study, none of the patients who underwent MRI during the follow-up showed extraprostatic disease. In addition, all patients at intermediate to high risk underwent preoperative staging imaging using either abdominal CT scans and bone scans or choline PET/CT.[2] Patients with cM1 disease were not enrolled and were treated with multimodal therapies after a discussion of each case in a multidisciplinary meeting. Finally, PSMA PET/CT or choline PET/CT were used during follow-up in patients with BCR, and only two patients showed evidence of distant metastasis after primary treatment.

This study is limited by its retrospective nature and by the relatively short follow-up. MRI was used during the follow-up to identify clinical recurrences and guide follow-up biopsies if deemed appropriate. Finally, not every patient underwent prostate biopsy during the follow-up; thus, we cannot draw conclusions on the real rate of patients with clinical recurrence. Even if mpMRI target biopsy GGG has shown higher concordance with the final pathology results,[19,20] sampling errors are unavoidable, and prostate biopsy will always underestimate or overestimate disease grade and volume.

However, our partial results could lead to multicentric series, which together with imaging diagnostics improvement, may establish prostate cryoablation as an acknowledged alternative among other radical treatments.

CONCLUSIONS

Whole gland cryoablation provided minimally invasive treatment with good oncological outcomes in patients with low to intermediate-risk PCa, Outcomes of such procedure for high-risk PCa are suboptimal, with up to 30% of patients developing BCR at 3 years of follow-up. A high preoperative risk of LNI should not be an exclusion criterion for patients treated with radical cryoablation, although it could not provide adequate cancer staging and consequent adjuvant therapies' selection.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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