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ORIGINAL ARTICLE

Extra-target low-risk prostate cancer: implications for focal high-intensity focused ultrasound of clinically significant prostate cancer

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Abstract

Purpose To analyse the impact of the presence of extra-target non-clinically significant cancer (NCSC) after high-intensity focused ultrasound (HIFU) hemiablation on oncological results. To analyse radical treatment free survival (RTFS) rates at 2–3 years follow-up.

Methods Retrospective single-centre study of 55 patients treated by primary HIFU hemiablation from 2010 to 2016. Inclusion criteria were unilateral MRI detected CSC, stage ≤ T2b, Gleason score (GS) ≤ 7, at least 6 mm distant from prostate apex. MRI with systematic and targeted biopsies was performed at diagnosis. Follow-up included clinical examination, PSA every 6 month, MRI and biopsies at 1 year and in case of PSA elevation. HIFU retreatment was possible. Whole-gland treatment was indicated in case of positive biopsies with GS ≥ 7 or maximum cancer core length > 5 mm, any GS.

Results Mean follow-up was 33 months (SD: 17–49 months). Presence or not of an extra-target NCSC in the untreated part of the gland had no impact on RTFS at univariate analysis ($p = 0.29$). 10 (18%) patients had a salvage whole-gland treatment after a median follow-up of 26 months (IQR 17–28). RTFS at 2 and 3 years were 92% and 80%.

Conclusion Presence or not of an extra-target NCSC in the untreated part of the gland had no impact on RTFS. NCSC lesion can be left untreated and actively monitored. RTFS was 80% at 3 years which support the concept of focal/partial treatment as a treatment option of CSC prostate cancer.

Keywords Prostate cancer · Focal therapy · Index lesion · Secondary lesion · High-intensity focused ultrasound

Introduction

Partial treatments are gaining increasing interest in the management of localized low- or intermediate-risk localized prostate cancer (PCa) [1]. These treatments are evaluated as an alternative to recommended whole-gland treatments to reduce functional morbidity while maintaining oncologic efficiency [2–4].

Partial therapy is based on the treatment of a part of the prostate, containing the index lesion. However, PCa is a multifocal disease in 60% of cases and bilateral in 65–80% [5, 6]. It is well documented that the index lesion is responsible of biochemical or metastatic progression [7–11]. The secondary non-index lesions represents 20% of total tumor volume and contains high cellular grade in only 3% of cases [12]. Last consensus reports that partial or focal therapy are indicated for low volume clinically significant cancers (CSC) visible at MRI (index tumor foci < 3 cc or < 25% of prostate volume at MRI) [4]. Non-clinically significant cancers (NCSC) take better advantage from active surveillance (AS). Results of large active surveillance cohorts, with 15 years of hindsight, show that it seems to be a safe option to leave untreated a NCSC lesion with 75% of patients showing no progression after 5 years [13]. Therefore, it is acceptable in

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partial therapy to leave untreated, a separate NCSC (Gleason = 3 + 3 one core of 5 mm length) [4]. In the light of this knowledge basis, it has been suggested that partial or focal therapy of the index tumor is sufficient. To validate this concept, we investigated the impact of the presence of NCSC on oncologic results in a series of patients treated by high-intensity focused ultrasound (HIFU) hemiablation. The main objective was to analyse the impact of the presence of contralateral NCSC on oncological results. The secondary objectives were to analyse CSC-free survival and radical treatment-free survival (RTFS) rates and at 2 years and 3 years of follow-up.

Materials and methods

Population

Retrospective cohort study enrolling men for HIFU treatment in Lille University Hospital (data base protection authorization obtained and patients consents collected). All consecutive patients between May 2010 and December 2016 were enrolled. All patients underwent Mp MRI before inclusion to determine localization contours and volume of the index lesion. Mp MRI were performed and interpreted by a uroradiologist with 15 years of experience in MRI prostate reading. Each lesion was scored by Likert scale. The PCa was determined by transrectal ultrasound 12 systematic biopsy (SB) and MRI-targeted biopsy (TB).

Inclusion criteria Clinically significant cancer (CSC) was defined as follows: before 2013: presence of any amount of Gleason grade 4, or maximum cancer core length (MCCL) ≥ 6 mm at 12 SB or MRI-TB or more than two sextants positive for cancer. After 2013, same definition but excluding cases with only one single core invaded as SB with < 3 mm of Gleason score ≤ 3 + 4 (accepted as NCSC). Treatment-naïve patients with T1/T2 clinical stage and unilateral CSC located ≤ 6 mm from the apex and < 5 mm from the sagittal midline were included as previously described [14]. Only in the contralateral lobe was non-CSC accepted, defined as cancer with no Gleason grade 4, maximum cancer core length (MCCL) < 6 mm at 12 SB with < 2 sextants positive for cancer and negative MRI-TB in case of lesion Likert score ≥ 3. A total of 62 patients who underwent HIFU hemiablation were included. Seven patients were excluded because of loss of follow-up or follow-up of less than 1 year.

Data collection

Clinical data including age, PSA at baseline, 1 month, 3 months and every 6 months, clinical T stage, pathological data including number of positive SB, MCCL at baseline and for follow-up biopsies, Gleason score of index lesion and any separate contralateral lobe NCSC and prostate volume at ultrasound.

Treatment procedure

Patients were treated by hemiablation of the prostate with ablatherm HIFU® and focal one® devices (EDAP TMS). A 6-mm security margin from the apex was respected to preserve sphincter functionality. A pre-ablation TURP was performed in patients at risk of urinary retention (pre-treatment obstructive symptoms). A urethral catheter was placed before ablation and removed on day 1 or 2 postoperatively.

Follow-up

MRI-TB and SB were performed as per-protocol at 1 year and as for cause in case of PSA elevation (PSA velocity ≥ 0.5 ng/ml/year).

Salvage treatment

A salvage treatment was indicated in case of CSC at biopsy, whether in target or extra-target area. It was either by a second hemiablation, if recurrent/de novo CSC (depending on the side of the recurrence) present in treated or untreated area with location and contours fulfilling inclusion criteria or by whole-gland treatment (radiotherapy or radical prostatectomy). A third-line salvage treatment was performed in case of recurrent/de novo CSC recurrence after two hemiablation treatments.

Statistical analysis

Statistical analyses were done on SAS® software v9.3 (SAS institute Inc., Cary, NC, USA) by the biostatistics department of the University of Lille. The Kaplan–Meyer method was used to analyse the radical treatment free survival (RTFS) and the recurrence-free survival. The log rank test and the Cox model were used for comparisons of survival estimates. Statistical significance was considered at $p < 0.05$.

Results

A total of 55 patients were included and treated by hemiablation between 2010 and 2016. Mean follow-up was 33 months (SD: 17–49 months). The clinical, pathological, biological and imaging data at inclusion are shown in Table 1. Of the 55 patients with a mean age of 63 and mean PSA of 6.18 ng/ml (SD 3.72–8.64), 24 (44%) had a Gleason score 3 + 3 = 6 and 31 (56%) had a Gleason score 7 (one patient had a Gleason score = 4 + 4 = 8). Most patients had a non-palpable tumor (T1c) ($n = 42$, 77%) but visible at MRI.

Table 1 Histological and imaging characteristics

Histological characteristics of treated lesion	All cases ($n=55$)	Cases without untreated NCSC controlateral lesion ($n=45$)	Cases with untreated NCSC controlateral lesion ($n=10$)	p
Mean number of positive biopsies (− 1 SD/+ 1 SD)	2.7 (1.2–4.2)	2.44 (0.95–3.93)	3.80 (2.77–4.83)	**0.00547**
Mean percentage of positive biopsies (− 1 SD/+ 1 SD)	20.4 (9.6–31.2)	18.4 (8.08–28.78)	29.40 (21.29–37.51)	**0.0034**
Targeted biopsies *n* (%)	26 (48)	21 (47.73)	5 (50)	1.00
Gleason score (%)				0.3036
6	24 (44)	18 (40)	6 (60)	
7	30 (54)	26 (58)	4 (40)	
7 (3 + 4)	24 (43)			
7 (4 + 3)	6 (11)			
8	1 (2)	1 (2)	0 (0)	
Mean cancer core length (− 1 SD/+ 1 SD)	5.7 (2.4–9)	5.50 (2.34–8.66)	6.64 (2.61–10.67)	0.51
Localization				NC
Base or mid	47 (86)	37 (82)	10 (100)	
Apex or anterior	8 (14)	8 (18)	0 (0)	
Cases with number of sextants with cancer *n* (%)				1.00
1	31 (56.4)	25 (55.56)	6 (60)	
≥ 2	24 (43.6)	20 (44.4)	5 (40)	

MRI characteristics	All cases ($n=55$)	Cases without untreated NCSC controlateral lesion $n=45$	Cases with untreated NCSC controlateral lesion ($n=10$)	p
Cancer seen at MRI *n* (%)	42 (78)	33 (75)	9 (90)	0.43
Mean prostatic volume at MRI in cc (− 1 SD/+ 1 SD)	51 (26.9–75.1)	49.41 (26.41–72.41)	59.17 (29.33–89.01)	0.42
Mean diameter of index lesion at MRI in mm (− 1 SD/+ 1 SD)	10.9 (6.5–15.3)	10.55 (6.41–14.69)	12.50 (7.21–17.79)	0.37
Suspicion score at MRI (Likert) *n* (%)				1.00
3	5 (12)	7 (19)	1 (11)	
≥ 4	37 (88)	29 (81)	8 (89)	

Bold values represents the statistically significant value at 95%

Impact of the presence of a NCSC on oncological results

In ten cases (18%) there was a contralateral untreated NCSC lesion. In all cases, lesions were Gleason 3 + 3 = 6. None of these lesions were visible at inclusion mp-MRI. Mean cancer core length of these lesions at inclusion was 1.33 mm (1–1 mm). Of these ten cases, only one (10%) of the NCSC lesions progressed at control MRI (occurrence of a previously non-visible lesion) with a 5/5 Likert score. This patient with MRI progression had a significant pathological progression [GS 6 (3 + 3), MCCL 7 mm] and was treated by radical prostatectomy. Presence or not of a NCSC in the untreated zone had no influence on the RTFS in univariate analysis ($p=0.29$) (Fig. 1). In addition, the presence of NCSC does not appear to interfere with CSC-free survival in all areas ($p=0.12$).

Oncological results and retreatment

Ten patients (18.2%) had a whole-gland salvage treatment, 8 (14.5%) as a second treatment, 2 (3.6%) as a third treatment. All patients were treated by radical prostatectomy. The median time between HIFU and whole-gland treatment was 26 months (SD 17–28 months). The RTFS was 92%, 80% at 2 years and 3 years, respectively (Fig. 2).

For the subgroup of patients with GS ≥ 7, 31 patients were analyzed, 6 had a whole-gland treatment (19.4%) with a median follow-up of 22 months (SD 14–31 months). The RTFS rates were 89% and 77% at 2 years and 3 years. There was no difference in oncologic results between patients treated by HIFU for GS = 6 or GS ≥ 7 ($p=0.79$). Regarding the histological recurrence, 15 patients (27%) had a clinically significant recurrence considering all areas. The median time between HIFU and CSC recurrence all areas

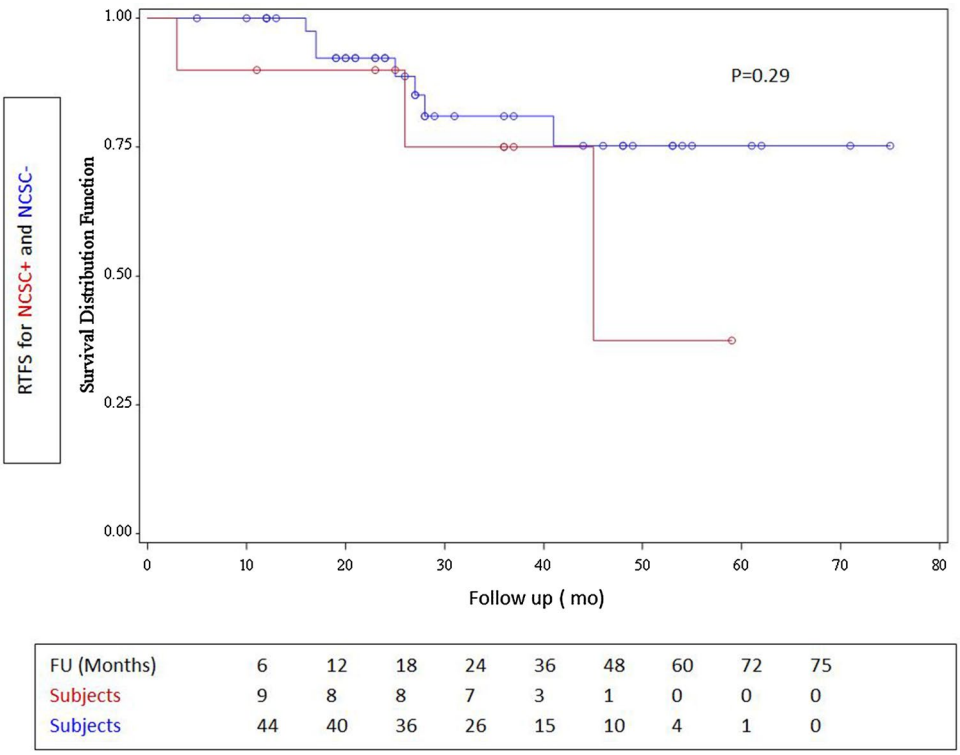

Fig. 1 Comparative RTFS depending on the presence (NCSC+) or not (NSCS−) of an untreated contralateral NCSC

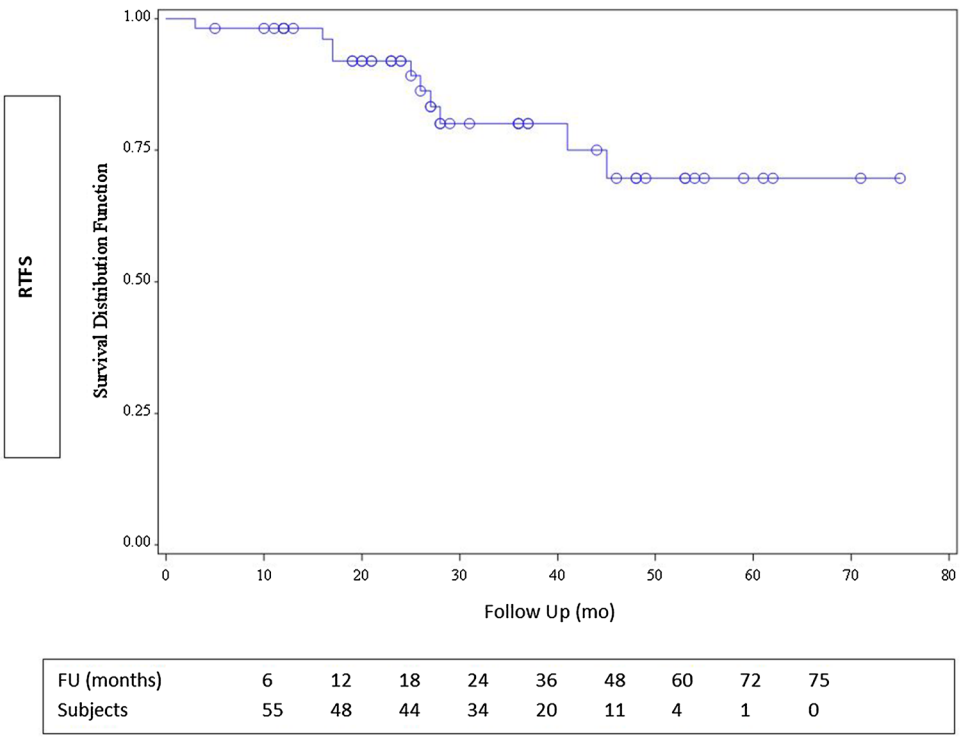

Fig. 2 Radical treatment-free survival all Gleason

was 17 months (SD 9–25 months), CSC-free survival all areas rates were 78% and 61% at 2 years and 3 years (Fig. 3). Twelve patients (22%) had a clinically significant recurrence in the treated area with a median time before recurrence of 21 months (SD 12–29.5 months) The CSC recurrence-free survival rates in treated area at 2 years and 3 years were 86% and 72%, respectively. These recurrences were localized for 6 (40%) in the apex or anterior area and 9 (60%) in base or

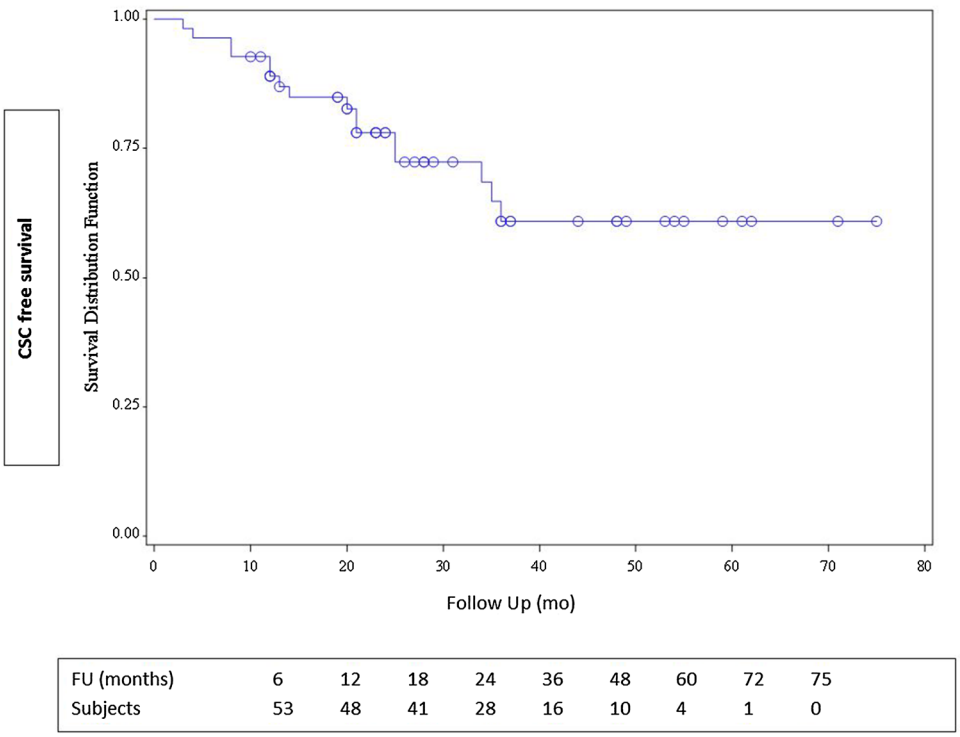

Fig. 3 Clinically significant cancer-free survival

mid posterior areas. Two patients had a clinically significant recurrence and were not retreated, these patients have decided not to be treated and are under active surveillance because of Gleason 3 + 4 with minority grade 4 and MCCL of 7 mm. No patients had a metastatic progression or died from prostate cancer.

The factors affecting the RTFS at univariate analysis were a high-PSA nadir (HR = 1.44; CI 95% 1.13–1.8, $p = 0.0016$) and a low percentage of PSA decrease (HR = 0.981; CI 95% 0.97–0.99, $p = 0.003$). GS (6 or ≥ 7) ($p = 0.79$), number of positive biopsies (≤ 3/> 3) ($p = 0.25$), MCCL (≤ 6 mm/6 mm) ($p = 0.36$), number of sextants involved by tumor (1/> 1) ($p = 0.28$) and biochemical recurrence (Phoenix criteria) ($p = 0.45$) were not predictive factors of the reduction of the RTFS. The factors affecting RTFS and CSCFS are presented in Table 2.

Discussion

In this retrospective study, we evaluated the implication of extra-target contralateral NCSC on oncological results of HIFU hemiablation of CSC. There was no statistical difference in leaving out an extra-target NCSC ($p = 0.29$). In our study, 10% of the untreated NCSC have progressed at MRI at 1 year with Likert score 5/5 confirmed by histology, and was treated by radical treatment.

This is consistent with the findings of large active surveillance cohort of Klotz et al. with 75.7% of patients untreated at 5 years [13]. In a consensus report, Tay et al. [15] stated that it is acceptable to leave untreated these NCSC lesions, non-visible at MRI, and to follow them in the same way as NCSC lesion on AS.

HIFU is a well-known energy for treatment of PCa. Crouzet et al. reports good results in whole-gland treatment with RTFS of 81% at 5 years and 68% at 8 years. The cancer-specific survival rate at 10 years is 97% [16]. In a review by Valerio [3], six series about focal HIFU at least ideal stage 2a published between 2011 and 2016 were reported [17–22]. This meta-analysis showed that median follow-up is 12 months (ICR 0 to 28.5 months) with good oncologic results (in treated area 0% of CSC recurrence at control biopsies and 23.3% for any cancer stage). Since this review, two prospective series on partial HIFU were published by Rischmann et al. ($n = 111$) [14] Gazer et al. ($n = 54$) [23]. Our study (of which 16 out of the 55 cases were part of the study by Rischmann et al.) shows a RTFS at 2 years of 92%, which is acceptable and comparable to the results of the previous publication by Rischmann with 89% (CI 95% 81–94%). Our CSC-free survival is 88% in all area and 92% in treated area at 1 year that is also similar to the results of Rischmann et al. [14] with 88% free of CSC (CI 95% 82–94%) at 1 year, of Ganzer et al. [23] with 91.8% at 1 year in treated area, of Feijoo et al. [21] with 74.6% at 1 year and of Ahmed et al. [20] with 80.8% at 6 months (CI 95% 67.5–90.4%) in all areas and 84.6% (CI 95% 70–92%) in treated area.

In a series of 599 cases with 6-month follow-up, RTFS rate was 92% (95% CI 90–95%) at 3 years [24]. These rates

Table 2 Univariate analysis of the variables affecting CSCFS and RTFS

Predictive factors investigated	Cut off	Hazard ratio [CI 95%] for RTFS	*p* value (log-rank test or Chi square) for RTFS	Hazard ratio [CI 95%] for CSCFS	*p* value (log-rank test or Chi square) for CSCFS
T score	1c/2	–	0.88	–	0.07
Risk group	Low or intermediate	–	0.29	–	0.76
Pre op PSA	–	HR 1007 [0.77–1301]	0997	HR 0.859 [0689–1072]	0.18
Number of positive biopsies	≤ 3/> 3		0.25	–	NC
Percentage of positive biopsies	–	HR 1035 [0974–1.1]	0.27	HR 1056 [1.008–1.107]	**0.02**
Presence of targeted biopsies	–	–	0.24	–	0.053
Gleason score	≤ 6/> 6	–	0.79	–	0.26
MCCL	≤ 6 mm/> 6 mm	–	0.36	–	NC
Significativity of the treated lesion	–	–	0.78	–	0.12
Lesion localisation	Base or mid/apex or anterior	–	0.32	–	0.53
Number of positive sextant	1/> 1	–	0.28	–	0.56
Presence of NCSC	–	–	0.29	–	0.12
Lesion visibility at MRI	–	–	0.45	–	0.55
Diameter of the lesion at MRI	–	HR 1045 [0869–1256]	0.64	HR 1.150 [1.005–1314]	**0.04**
Presence of positive biopsies in the suspect zone at MRI.	–	–	NC	–	0.49
MRI Likert score	Non suspect/suspect	–	0.65	–	0.74
Security margin to the apex	–	HR 1208 [0896–1627]	0.22	HR 1.038 [0851–1267]	0.71
Volume treated	–	HR 0603 [0320–1138]	0.12	HR 0.966 [0711–1313]	0.83
Slice treated	–	HR 0.9 [0.7–1159]	0.41	HR 1 [0851–1174]	0.99
TURP before or during procedure	–	–	0.73	–	0.84
Percentage decrease in PSA rate	–	HR 0981 [0970–0993]	**0.0016**	HR 0.985 [0976–0.994]	**0.0013**
PSA Nadir	–	HR 1442 [1131–1838]	**0.0032**	HR 1237 [1.027–1490]	**0.0251**
Presence of Phoenix biochemical recurrence	–	–	0.45	–	0.56

Bold values represents the statistically significant value at 95%

are superior to our results, but only 222 patients underwent per-protocol or for cause biopsies.

In 2014, Donaldson et al. [4] established an expert consensus on focal prostatic therapy laying the groundwork for patient selection, treatment modalities and oncology goals. The committee considered a whole-gland retreatment rate of 10% at 1 year an acceptable cancer control.

A strength of our study is the medium term follow-up, [mean follow-up of 33 months (SD 17–49 months)] and a series over 50 patients, all with 1 year control biopsy results. There are few publications which show results with this length of follow-up and this order of magnitude of population.

In our study, no predictor of improvement or impairment of RTFS was found among patient characteristics. There was no significant difference in RTFS between the patient group with SG ≤ 6 and that with SG ≥ 7 ($p = 0.79$). We also found no difference in treating patients with more than three initial biopsies reached ($p = 0.25$) or with an initial biopsy length greater than 6 mm ($p = 0.36$), patients with two prostate sextants affected ($p = 0.28$). These results are weighted by the lack of power of our study but would allow to widen the criteria of selection of the patients initially dictated by the consensus of Donaldson et al. [4].

Our study had several limitations mainly related to the monocentric nature, medium follow-up and the recent character of this ablation technique. There is a lack of power related to the small size of the population. Lost to follow-up, missing data during data collection represent selection and classification biases that could have influenced the results. Another limitation to our study is the fact that at the beginning of the inclusion period, some patients with low-risk non-significant cancer were treated. These patients would have benefit more from active surveillance and this is probably overtreatment.

Conclusion

In this preliminary study, presence or not of a NCSC in the untreated part of the gland seems to have no impact on RTFS and CSCFS. NCSC lesion could be left untreated and actively monitored. RTFS was 80% at 3 years which support the concept of partial treatment as a treatment option of low-intermediate-risk prostate cancer.

Author contributions AA: Manuscript writing/editing, data collection or management/protocol/project development. JO: Manuscript writing/editing. PV: Data collection or management. VD: Data analysis. XL: Data collection or management. PP: Data collection or management. AV: Manuscript writing/editing, data collection or management/protocol/project development.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Formal consent For this type of study formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M et al (2017) EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: Screening, diagnosis, and local treatment with curative intent. Eur Urol 71(4):618–629
2. Resnick MJ, Koyama T, Fan K-H, Albertsen PC, Goodman M, Hamilton AS et al (2013) Long-term functional outcomes after treatment for localized prostate cancer. N Engl J Med 368(5):436–445
3. Valerio M, Cerantola Y, Eggener SE, Lepor H, Polascik TJ, Villers A et al (2017) New and established technology in focal ablation of the prostate: a systematic review. Eur Urol 71(1):17–34
4. Donaldson IA, Alonzi R, Barratt D, Barret E, Berge V, Bott S et al (2015) Focal therapy: patients, interventions, and outcomes—a report from a consensus meeting. Eur Urol 67(4):771–777
5. Nevoux P, Ouzzane A, Ahmed HU, Emberton M, Montironi R, Presti JC Jr et al (2011) Quantitative tissue analyses of prostate cancer foci in an unselected cystoprostatectomy series. BJU Int 110(4):517–523
6. Yoon GS, Wang W, Osunkoya AO, Lane Z, Partin AW, Epstein JI (2008) Residual tumor potentially left behind after local ablation therapy in prostate adenocarcinoma. J Urol 179(6):2203–2206
7. Villers A, McNeal JE, Freiha FS, Stamey TA (1992) Multiple cancers in the prostate. Morphologic features of clinically recognized versus incidental tumors. Cancer 70(9):2313–2318
8. Liu W, Laitinen S, Khan S, Vihinen M, Kowalski J, Yu G et al (2009) Copy number analysis indicates monoclonal origin of lethal metastatic prostate cancer. Nat Med 15(5):559–565
9. Ahmed HU et al (2009) The index lesion and the origin of prostate cancer. N Engl J Med 361(17):1704
10. Karavitakis M, Winkler M, Abel P, Livni N, Beckley I, Ahmed HU (2011) Histological characteristics of the index lesion in whole-mount radical prostatectomy specimens: implications for focal therapy. Prostate Cancer Prostatic Dis 14(1):46–52
11. Huang CC, Deng F-M, Kong MX, Ren Q, Melamed J, Zhou M (2014) Re-evaluating the concept of "dominant/index tumor nodule" in multifocal prostate cancer. Virchows Arch 464(5):589–594
12. Arora R, Koch MO, Eble JN, Ulbright TM, Li L, Cheng L (2004) Heterogeneity of Gleason grade in multifocal adenocarcinoma of the prostate. Cancer. 100(11):2362–2366
13. Klotz L, Vesprini D, Sethukavalan P, Jethava V, Zhang L, Jain S et al (2015) Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol 33(3):272–277
14. Rischmann P, Gelet A, Riche B, Villers A, Pasticier G, Bondil P et al (2017) Focal high intensity focused ultrasound of unilateral localized prostate cancer: a prospective multicentric hemiablation study of 111 patients. Eur Urol 71(2):267–273
15. Tay KJ, Scheltema MJ, Ahmed HU, Barret E, Coleman JA, Dominguez-Escrig J et al (2017) Patient selection for prostate focal therapy in the era of active surveillance: an International Delphi Consensus Project. Prostate Cancer Prostatic Dis 20(3):294–299
16. Crouzet S, Chapelon JY, Rouvière O, Mege-Lechevallier F, Colombel M, Tonoli-Catez H et al (2014) Whole-gland ablation of localized prostate cancer with high-intensity focused ultrasound: oncologic outcomes and morbidity in 1002 patients. Eur Urol 65(5):907–914
17. Muto S, Yoshii T, Saito K, Kamiyama Y, Ide H, Horie S (2008) Focal therapy with high-intensity-focused ultrasound in the treatment of localized prostate cancer. Jpn J Clin Oncol 38(3):192–199
18. Ahmed HU, Hindley RG, Dickinson L, Freeman A, Kirkham AP, Sahu M et al (2012) Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study. Lancet Oncol 13(6):622–632
19. Van Velthoven R, Aoun F, Limani K, Narahari K, Lemort M, Peltier A (2014) Primary zonal high intensity focused ultrasound for prostate cancer: results of a prospective phase iia feasibility study. Prostate Cancer 2014:1–6

20. Ahmed HU, Dickinson L, Charman S, Weir S, McCartan N, Hindley RG et al (2015) Focal ablation targeted to the index lesion in multifocal localised prostate cancer: a prospective development study. Eur Urol 68(6):927–936
21. Feijoo ERC, Sivaraman A, Barret E, Sanchez-Salas R, Galiano M, Rozet F et al (2016) Focal high-intensity focused ultrasound targeted hemiablation for unilateral prostate cancer: a prospective evaluation of oncologic and functional outcomes. Eur Urol 69(2):214–220
22. Fegoun ABE, Barret E, Prapotnich D, Soon S, Cathelineau X, Rozet F et al (2011) Focal therapy with high-intensity focused ultrasound for prostate cancer in the elderly: a feasibility study with 10 years follow-up. Int Braz J Urol 37(2):213–222
23. Ganzer R, Hadaschik B, Pahernik S, Koch D, Baumunk D, Kuru T et al (2018) Prospective multicenter phase II study on focal therapy (hemiablation) of the prostate with high intensity focused ultrasound. J Urol 199(4):983–989
24. Guillaumier S, Peters M, Arya M, Afzal N, Charman S, Dudderidge T et al (2018) A multicentre study of 5-year outcomes following focal therapy in treating clinically significant nonmetastatic prostate cancer. Eur Urol. https://doi.org/10.1016/j.eururo.2018.06.006