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Evaluation of outcomes following focal ablative therapy for treatment of localised clinically significant prostate cancer in patients >70 years: a multi-institute, multi-energy 15- year experience.

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Running head
Focal therapy in the older patient with prostate cancer

Key words
Prostatic neoplasms
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Ablation techniques
Aged

ABSTRACT

Purpose
In older patients who do not wish to undergo watchful waiting, focal therapy could be an alternative to the more morbid radical treatment. We evaluated the role of focal therapy (FT) in patients 70 years and older as an alternative management modality.

Materials and Methods
649 patients across 11 UK sites receiving focal high intensity focused ultrasound (HIFU) or cryotherapy between June 2006 - July 2020 reported within the UK based HIFU Evaluation and Assessment of Treatment and the International Cryotherapy Evaluation (ICE) registries were evaluated. Primary outcome was failure free survival (FFS) defined by need for more than one focal re-ablation, progression onto radical treatment, development of metastases, need for systemic treatment or prostate cancer specific death. This was compared to the FFS in patients undergoing radical treatment via a propensity score weighted analysis.

Results
Median age was 74 years (IQR: 72, 77) and median follow-up 24 months (IQR: 12, 41). 60% had intermediate risk disease and 35% high risk disease. 113 patients (17%)

required further treatment. 16 had radical treatment and 44 required systemic treatment. FFS was 82% (95% CI: 76-87%) at 5 years.

Comparing patients who had radical therapy to those who had focal therapy, 5-year FFS was 96%, (95% CI: 93-100%) and 82% (95% CI: 75-91%) respectively, p<0.001. 93% of those in the radical treatment arm had received Radiotherapy as their primary treatment with its associated use of Androgen Deprivation Therapy (ADT) thereby leading to potential over estimation of treatment success in the radical treatment arm, especially given the similar metastases free and overall survival rates seen.

Conclusions
We propose FT to be an effective management option for the older or comorbid patient who is unsuitable for or not willing to undergo radical treatment.

Introduction

Radical treatment for non-metastatic prostate cancer is not without its complications especially in the older patient. The decision to actively treat or commence monitoring in the older patient with a diagnosis of organ confined prostate cancer is becoming increasingly challenging especially in the setting of increasing comorbidity. Could FT, with its reduced side effect profile (1-5), represent an acceptable middle ground between watchful waiting and radical treatment?

Over the last 15 years in the UK, FT has been offered in several centers in which special arrangements included the requirement for the maintenance of prospective registries. The aim of this study was to explore the oncological outcomes of FT (HIFU and Cryotherapy) for the management of localized prostate cancer in patients 70 years and older. We have previously shown that FT compared to radical therapy regardless of age has no clinically meaningful difference in FFS and overall survival (OS).(6, 7) In this study we assessed outcomes and burden of treatment in those aged 70 years or more.

Materials and Methods

Evaluation of all patients aged ≥70 years with clinically significant localised prostate cancer treated across 11 UK sites with focal HIFU or cryotherapy between June 2006 and July 2020 reported within the UK based HIFU Evaluation and Assessment of Treatment (HEAT) and the International Cryotherapy Evaluation (ICE) registries were included.

Pre-ablative information collected included patient age, PSA, PIRADS score, prostate size, biopsy ISUP score and maximal core length (MCL). Ablative technique (HIFU, cryotherapy) and ablative pattern was recorded. Post-ablation PSA, MRI, repeat biopsy, subsequent cancer treatments (repeat FT, RP, radiotherapy, ADT or other systemic therapy), development of metastases and death due to prostate cancer were recorded.

For this study, informed consent from patients was not required as the data used represents a registered audit of clinical outcomes post-surgical intervention managed by Local Research and Development Departments for Service and Quality Assurance. The study was performed in accordance with the declaration of Helsinki.

The primary outcome was FFS, defined as the need for progression to a third ablative procedure, salvage radical treatment, development of metastases, need for systemic treatment or prostate cancer specific death(7-9). Secondary outcomes included retreatment-free survival, ADT-free survival and OS. Complications were reported using the Clavien-Dindo scale. Kaplan-Meier estimates were used to report survival outcomes. An assessment of the number of repeat biopsies and MRI scans post FT was assessed: this was to provide an assessment of the treatment burden associated with FT in this cohort. Post-treatment MRI scans were reviewed by expert Uro-radiologists in Multi Disciplinary Team (MDT) meetings and all scans were compared to the pre-treatment MRI.(10, 11)

A propensity score weighted analysis was performed to compare FFS between patients treated with radical therapy versus those treated with FT. Clinical details of patients who underwent laparoscopic RP or radiotherapy for clinically significant prostate cancer was obtained from a UK multicenter prospective prostate cancer registry between May 2007 and September 2018. Failure post RP was defined as the need for adjuvant or salvage radiotherapy, need for systemic therapy, development of metastases or prostate cancer-specific death. Failure post radiotherapy was defined as need for salvage local treatment (RP or ablative therapy), need for ADT beyond what was initially planned in the radiotherapy protocol, need for other systemic treatment, development of metastases and prostate cancer specific death.

Statistical analyses

Baseline

For descriptive statistics median with corresponding interquartile range (IQR: Q1, Q3) were used for continuous data. Categorical data was depicted as absolute numbers with proportions. Baseline differences between groups as a whole and matched patients were statistically tested using the unpaired student's T-test or Mann–Whitney U test in case of normally and skewed distributed continuous variables. Fisher's exact test was used to test differences in categorical variables.

Propensity score matching

A propensity score was created for treatment type (i.e. radical or FT). For the propensity score matching, patients with grade group 4 disease were excluded from the FT group as there were no patients in the radical treatment group who had grade group 4 disease. The variables used in the logistic regression model to calculate the propensity score were age, the natural logarithm of PSA, grade group category, stage, MCCL and year of treatment. We used multiple imputation by chained equations (mice) to correct for missing data after which we performed subsequent analyses. Patients were matched 1:1 without replacement using the nearest neighbor method. A caliper of 0.10 of the sd logit (propensity score) was used to minimise baseline variables. The caliper was chosen more strictly due to persistent baseline differences at calipers ≥0.10. Standardised mean differences <0.10 were pursued. Furthermore, as sensitivity analysis, we performed a complete case analysis.

Survival analysis
Kaplan–Meier analysis was performed to assess differences in terms of the primary outcome (FFS) between FT and radical treatment. Statistical significance was tested using the stratified log-rank test. Finally, multivariable Cox regression correcting for the variables used in calculating the propensity score was performed.

Statistical software
SPSS version 25 was used for baseline descriptive statistics. R studio version 4.1.2 (http://www.R-project.org) was used for statistical testing of baseline characteristics, imputation ('mice' package), propensity score matching ('Matchthem' package after multiple imputation and ('MatchIt' and 'optmatch' packages for complete case analysis) and survival analyses ('rms' and 'survminer' package).

Results

649 patients aged ≥70 years underwent FT for prostate cancer between 2006 and 2020. Median follow-up was 24 months (IQR: 12, 41). 541 patients (83%) received HIFU and 108 (17%) cryotherapy. Median age was 74 years (IQR: 72, 77). 618 of 649 cases (95%) were done amongst 6 Urologist groups: Site 1 (252 cases), Site 2 (100), Site 3 (96), Site 4 (83), Site 5 (60), Site 6 (27) and other (31). The lower volume cases were performed by high volume clinicians working at multiple sites.

Pre-operative median PSA was 7.8 (IQR: 5.6, 11). 408 (63%) had a transperineal prostate biopsy and 8 (1.2%) had a transrectal biopsy; modality was unknown in 230 (36%). Median MCCL was 6mm (IQR: 4, 9). There were a median of 15 biopsies per patient (IQR: 12, 32) with a median of 4 positive cores per patient (IQR: 3, 7). 24 patients (4%) had T1 disease, 460 (71%) T2, 84 (13%) T3 and unknown in 81 (13%). 71 patients had ISUP 1 disease (11%), 395 (61%) ISUP 2, 136 (21%) ISUP 3, 16 (3%) ISUP 4 and two (0.3%) ISUP 5. 18 patients (3%) were in D'Amico low risk group, 382 (59%) intermediate risk, 230 (35%) high risk and unknown in 19 (3%). The 18 cases of low-risk disease by the D'Amico classification system were considered clinically significant by MDT/Tumour Board meetings due to high disease burden and/or size of lesion on MRI.

345 patients (53%) had focal ablation, 200 (31%) hemi-ablation, 22 (3%) hockey stick ablation, 41 (6%) anterior ablation, 1 (0.2%) posterior ablation and unknown in 40 (6%).

Post-operative surveillance included regular PSA checks, mpMRI scans and repeat prostate biopsies. A total of 716 follow-up MRI scans and 220 repeat biopsies were performed over 1459 patient years. Median time between first focal treatment and first prostate biopsy was 14 months (IQR 12-24).

Of those who failed the focal re-treatment, seven had a third ablative procedure, four had EBRT, one had a RALP and 10 were commenced on ADT (including EBRT related).

See graphs 1, 2, 3 and 4 for FFS by risk group, ADT free survival by risk group, re-treatment free survival by risk group and OS by risk group respectively. 5-year FFS for

high-risk patients is 75% (95% CI: 66-86%) and for intermediate-risk 86% (95% CI: 79-93%). 5-year ADT-free survival for high-risk patients is 88% (95% CI: 81-95%) and for intermediate-risk is 90% (95% CI: 85-96%). 5-year re-treatment free survival for high-risk patients is 49% (95% CI: 39-62%) and for intermediate-risk is 65% (95% CI: 56-77%). 5-year OS for high-risk patients is 94% (95% CI: 89-99%) and for intermediate-risk is 97% (95% CI: 95-100%).

11 patients (1.7%) had urinary retention, 17 (2.6%) UTIs, 3 (0.5%) epididymitis and 18 with other mixed complications. There were no clavien-dindo 3-5 complications.

A total of 524 patients were matched in the propensity score analysis (262 in each arm). At baseline patients differed in PSA, grade group and stage category. Afterwards patients were well matched (see table 1). Five-year FFS in the FT group was 82% (95% CI: 75-91%) and in the radical treatment group 96%, (95% CI: 93-100%) p<0.001 – graph 5. The difference in FFS between FT and radical therapy at 1 year was 0.9% (95%-CI: 0.3-2%, p=0.15), at 3 years 7.9% (95%: CI 2.3-14%, p=0.006) and at 5 years 14% (95%: CI 5.7-23%, p=0.001). The HR from the univariable Cox model was 7 (95% 3.2-16, p<0.001). HR's from the multivariable Cox regression post imputation are depicted in table 2. Corrected for these variables, FT versus RT showed a HR of 8.7 (95%-CI 3.7-20, p<0.001). Complete case analysis showed a concordant HR for treatment modality although less precise (HR 10 (95% CI 3.4 – 301)), p<0.001.

Discussion

To our knowledge, this is the first study to focus on ablative therapies for localized clinically significant prostate cancer in the older patient. 612 of the 649 patients had intermediate or high-risk disease. Most published studies focus on the role of FT in the cure of low and intermediate-risk prostate cancer (12-14). While the concept of FT for high-intermediate and high-risk disease has been mentioned,(15) to our knowledge, this is the first study to explore its role in this cohort. We have demonstrated a 5-year FFS of 82% (95% CI: 75-91%) and an OS of 96% (95% CI: 93-98%).

We have previously shown that in patients of any age, 8-year FFS was 83% (96% CI: 76-90%) following FT and 79% (95% CI: 73-86%) for RP (p=0.12). There was no difference in 8-year OS, 99% after FT and 96% after RP (p=0.24).(7) Reported erectile function sufficient for penetrative intercourse was 68% and 39% (p<0.001) and pad-free continence 97% and 86% (p<0.001) after FT and RP respectively.(7) Similar positive functional outcomes from FT using cryotherapy and HIFU have been well reported (2, 12, 13). Functional outcomes were not the focus of this present study.

The International Society of Geriatric Oncology have published a recommendation on the management of Prostate Cancer in 2014. The options of management put forward for clinically significant localised disease included radical treatment or watchful waiting; the role of FT was still as yet considered under investigation.(16) RP in the older patient for intermediate and high-risk disease does offer a cancer-specific survival benefit but this comes at the expense of a 1% 30 day post-operative mortality, a lower long-term continence rate of 86% (compared to 95% for patients aged <50 years) and a higher rate of erectile dysfunction.(17-19) A recent meta-analysis showed that primary radiotherapy is associated with significant rates of genitourinary toxicity (grade ≥2,

32% acute and 28% late) and gastrointestinal toxicity (grade ≥2, 22% acute and 13% late).(20) Older patients are more likely to have higher risk disease than younger patients.(21) While we do not here propose FT to be a replacement of radical treatment for the fitter older patient with high-risk disease, yet in those patients who are comorbid or in those who do not wish to pursue radical treatment due to its side effects, FT may be a minimally invasive low-risk means of providing comparable oncological outcomes to radical treatment. Whether it can be demonstrated to prevent or delay the development of metastases or the need for systemic treatment still needs to be tested in a direct comparison between watchful waiting and FT, an acknowledged limitation of this study. We would propose that based on the outcomes of this study, a randomized trial between FT and watchful waiting could be a feasible study to undertake.

The burden of the treatment protocol especially with its requirements for follow-up MRI scans and repeat biopsy is of increasing significance in the older patient. Here we demonstrate that follow-up in these patients is not as burdensome as perhaps initially thought. On average, a patient can be expected to have one repeat MRI and 1 in 3 patients expected to have a repeat biopsy. We propose that this would represent an acceptable burden of treatment. PSA surveillance would be similar regardless of the management approach taken (that is, watchful waiting, radical treatment or FT).

Regarding the propensity matched comparison between radical treatment and FT, the limitations of this type of comparison is fully recognized. This was performed as there is no randomised or observational study where these two treatments arms are directly compared. The five-year FFS is 14% better in the radical treatment arm than in the focal therapy arm. While the exact cause of this difference cannot be identified from our study, we would propose that a large part of this difference can be explained by the effect that ADT would have on patients undergoing radical radiotherapy, with 93% of the patients in the radical treatment arm being treated with radiotherapy. The ADT is likely to slow disease progression and slow biochemical recurrence in the short to medium term. While this is a good thing, the morbidity of the ADT needs to be considered. The second factor that we believe would likely contribute to this difference is that some patients in the FT treatment arm would have received a second biopsy as a matter of treatment protocol rather than for clinical reasons. This of course would not be done in the radiotherapy treatment arm.

Being a multicenter study, the presence of heterogeneity of follow-up and heterogeneity of surgeons, whilst could be considered a limitation, is also advantageous as it improves external validity. A patient's clinical needs and health priorities would have changed during the follow-up period and this was reflected in how each patient's prostate cancer was ultimately managed. Unless the patients preference or clinical condition required a deviation from the usual post ablation follow-up, patients would have received a PSA check 3 monthly for a year, 6 monthly for another year and then yearly thereafter, an MRI at 12 months and a biopsy at 12 months (or earlier if indicated).(10)

A further limitation of this study is the relatively short median follow-up time of 24 months (IQR: 12, 41). The short median follow-up time is likely due to the increased uptake of FT in the later years of this study period.

Conclusions

FT in the older or comorbid patient with clinically significant prostate cancer may represent an acceptable treatment option that confers oncological control at a rate comparable to that of radical treatment. With its previously demonstrated lower side-effect profile compared to radical therapy, FT may therefore represent an acceptable middle ground for this cohort of patients whilst potentially reducing the burden associated with palliative systemic therapy. A direct comparison between FT and watchful waiting would be invaluable.

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Table 1: Characteristics of radical treatment versus focal therapy prior to matching and after 1:1 matching and single imputation.

	RT before matching	FT before matching	p-value	Missing n (%)	SMD before matching	RT after matching	FT after matching	SMD after matching
n	282	602				262	262	
Age (median (IQR))	74 (72, 77)	74 (72, 77)	>0.9	0	0.001	74 (72, 77)	74 (72, 77)	0.06
Log(PSA) (median (IQR))	2.3 (2.1, 2.6)	2.1 (1.7, 2.4)	<0.001	5 (0.6%)	0.5	2.3 (2, 2.6)	2.3 (1.9-2.6)	0.05
MCCL (median, (IQR))	7 (3.5, 10)	6 (4, 9)	0.4	155 (18%)	0.07	6.5 (3.5, 9)	6 (4, 9)	0.03
ISUP Grade (%)			0.002	0	0.3			0.03
1	45 (16)	71 (12)				42 (16)	40 (15)	
2	150 (53)	395 (66)				146 (56)	149 (57)	
3	87 (31)	136 (23)				74 (28)	73 (28)	
Stage (%)			<0.001	61 (7)	0.6			0.04
1	38 (13)	23 (4)				22 (8)	19 (7)	
2	241 (85)	442 (73)				240 (92)	243 (93)	
3	0	79 (13)				0	0	
Year (median (IQR))	2015 (2013, 2017)	2016 (2013, 2017)	0.2	0	0.1	2015 (2013, 2017)	2015 (2013, 2017)	0.06

Abbreviations: FT = Focal Therapy, RT = Radical Treatment, PSA = Prostate Specific Antigen, SMD = Standardised mean difference, SD = Standard Deviation

Table 2: Multivariable analysis for failure after imputation

Comparison	HR	95% CI	p-value
FT Vs RT	8.70	3.7 – 20	<0.001
Age, per year increase	1	0.9 - 1.1	0.7
Log PSA, per unit increase	1.8	1.1 – 2.8	0.02
Grade 2 Vs 1	2.	0.9 – 4.6	0.1
Grade 3 Vs 1	2.6	1.0 – 6.7	0.06
MCCL per mm increase	1	0.9 – 1.1	>0.9
Stage 2 Vs 1	0.8	0.3 – 2.3	0.7
Stage 3 Vs 1	0.9	0.3 – 3.1	0.9
Year	1.	0.9 – 1.2	0.5