Title: Focal therapy compared to radical prostatectomy for non-metastatic prostate cancer: a propensity matched study

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Word count: 2890

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Abstract

Importance

Focal therapy involves treating only the cancerous area within the prostate rather than the whole gland. Comparative effectiveness data for oncological and functional outcomes are lacking.

Objective

To evaluate oncological and functional outcomes of focal therapy in comparison to radical prostatectomy in patients with clinically significant, non-metastatic prostate cancer.

Design

A 1:1 propensity score matched study, reviewing patients undergoing focal therapy or radical prostatectomy between November 2005- September 2018.

Setting

Prospective multicentre databases for focal therapy (high intensity focused ultrasound and cryotherapy) and radical prostatectomy were analysed for eligibility.

Participants

Patients with PSA<20ng/ml, Gleason</=4+3 and stage</=T2c that underwent radical prostatectomy or focal therapy were matched for treatment year, age, PSA, Gleason score, T-stage, maximum cancer core length and neoadjuvant androgen deprivation therapy use.

Intervention

Focal therapy compared to radical prostatectomy.

Main outcome and measures

Primary outcome was failure-free survival (FFS) defined by need for salvage whole-gland or systemic therapy or metastases. Secondary outcomes were all-cause mortality, erectile and urinary functional outcomes.

Results

335/572 patients underwent radical prostatectomy, and 501/761 patients underwent focal therapy, high intensity focused ultrasound (n=626) and cryotherapy (n=135) were eligible for matching. After

propensity score matching, 246 radical prostatectomy (mean [SD] age 63.4 [5.6] years, median [IQR] PSA 7.9g/ml [6-10]) and 246 focal therapy (mean [SD] age 63.3 [6.9] years, median [IQR] PSA 7.9ng/ml [5.5-10.6]) cases were identified. The median [IQR] follow-up for radical prostatectomy was 64 [30-89] months and after focal therapy 49 [34-67] months.

At 3, 5 and 8 years, FFS (95%CI) was 86% (81-91%), 82% (77-88%) and 79% (73-86%) for radical prostatectomy, compared to 92% (88-96%), 89% (84-94%) and 86% (79-92%) following focal therapy (p=0.03). No difference was noted in 8-year overall survival (96% [95%CI 92-99%]) after radical prostatectomy vs. 99% [95%CI 98-100%] after focal therapy, p=0.24). Reported erectile function sufficient for penetrative sex was 39% and 68% (p<0.0005) and pad-free continence 86% and 97% (p=0.0007), after radical prostatectomy and focal therapy, respectively.

Conclusions and Relevance

In well selected patients with non-metastatic clinically significant prostate cancer, focal therapy can achieve similar oncological outcomes to radical prostatectomy but with improved functional outcomes.

Introduction

Patients diagnosed with non-metastatic prostate cancer are offered whole-gland radical treatments such as radical prostatectomy or radiotherapy. Data on oncological outcomes for men with low risk disease show an overall survival of 99.9% at 10 years and there is general agreement that men with intermediate to high risk prostate cancer have the most to benefit from active treatment(1). However, radical treatments can sometimes lead to treatment related complications and side-effects with urinary incontinence requiring pads in 1-2 in every 10 and erectile dysfunction in 3-5 in every 10 men. In addition to these, radiotherapy can also cause rectal problems.

Focal therapy (FT) has emerged over the last decade to improve the therapeutic ratio. Focal therapy involves ablating only the areas of cancer within the prostate in order to achieve cancer control without damaging collateral tissues such as the neurovascular bundles, external urinary sphincter and rectum(2). A focal treatment strategy is not uncommon in solid tumours and is often applied in lung, renal and breast cancers(3-5). In prostate cancer, following early phase studies, data from large multicentre prospective prostate cancer registries have shown encouraging cancer control rates in the medium term when using ablative technologies such as High Intensity Focused Ultrasound (HIFU) and cryotherapy with low rates of sexual dysfunction, urinary and rectal side-effects (6-11).

There is, however currently a paucity of level 1 evidence evaluating the efficacy and side-effect profiles of focal therapy in comparison to radical therapy, although RCTs are in preparation(11-13). We thus performed a propensity score matched analysis to compare oncological and functional outcomes for patients who underwent focal therapy or radical prostatectomy.

Methods

Study design and patient population

We performed a propensity score matched analysis on data collected in two prospective multicentre registries (focal HIFU and focal cryotherapy) and one prospective single centre laparoscopic radical prostatectomy registry (November 2005-September 2018). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Inclusion and exclusion criteria

All patients with serum PSA <20ng/ml at diagnosis, Gleason score </=7, and MRI stage </= T2c were included in the analysis. We excluded patients who had radiological or clinical T3 disease and men who had previous prostate cancer treatment. In addition, all men who received adjuvant (salvage) therapy within 12 months of radical prostatectomy were excluded to reduce bias against this treatment as our primary outcome was rate of salvage therapy and early adjuvant therapy was only given in the radical cohort for adverse post-operative pathological findings rather than for failure.

Intervention

All patients underwent standardised focal HIFU (Sonablate, Sonacare) or cryotherapy (SeedNet or Visual ICE cryotherapy device, Boston Scientific) as previously described. Cryotherapy was performed in anterior tumours or in larger prostates with an anterior-posterior distance of >3cm or those with prostatic calcifications. All other patients with peripheral/posterior tumours were offered HIFU. This stratification of treatment allowed optimum treatment delivery for patients. Patients with apical disease and those with large bilateral tumours were excluded.

Comparator

Laparoscopic Radical Prostatectomy (LRP). All patients underwent a standardised LRP procedure with unilateral or bilateral nerve sparing which was determined by the operating surgeon and patient tumour characteristics.

Outcome measures and definitions

Our primary outcome was failure free survival (FFS) defined as transition to local salvage whole-gland therapy or systemic therapy or development of metastases. We allowed for up to two repeat focal treatments as part of the focal therapy intervention, any further interventions were classified as treatment failure. Adjuvant radiotherapy or hormones within 12 months after LRP were excluded.

Secondary outcomes included overall survival and functional outcomes (potency and pad-free urinary continence) after LRP or FT. Potency was defined as the ability to maintain an erection sufficient for penetrative intercourse, with or without the use of oralmedications. Cancer specific survival was not available. Functional outcomes were based on validated patient reported outcome measures (PROMS) (International Index of Erectile Function-5 [IIEF-5], EPIC Urinary domain, International Prostate Symptom Score [IPSS]) for FT, and by clinician assessment following LRP. Urinary continence was defined as no pad usage. In the FT cohort this was defined as a score of 2-5

on question 2 of the IIEF-5 questionnaire whereas after LRP cohort it was based on physician reporting.

Data Points

Data was collected on patient age, treatment modality, operation year, use of neoadjuvant hormonal treatment, serum Prostate Specific Antigen (PSA) level at diagnosis, overall Gleason Score, maximum cancer core length (MCCL), tumour stage, follow-up duration, time to failure/ last follow up without failure, time to death (if applicable), patient/physician reported potency, patient/physician reported pad free continence, management of recurrence, and outcomes after recurrence/ failure of treatment.

Statistical Analyses

Baseline characteristics

Descriptive statistics were performed in which continuous data was depicted as mean +/- SD or as median with corresponding interquartile range (IQR), as appropriate. Absolute numbers are depicted with percentages. Differences in continuous variables were tested with the unpaired students' T-test or Mann-Whitney U test, for normally and non-normally distributed data, respectively. Differences in functional outcomes were tested with Fisher's Exact Test.

Patients were matched according to the following variables: year of surgery, age (years), PSA (ng/ml), Gleason score (3+3, 3+4, 4+3), maximum cancer core length (MCCL), use of neoadjuvant hormonal therapy, and T- stage (unilateral T1c, T2a, T2b, or bilateral T2c). T- stage was determined using MRI in the focal therapy cohort, and a combination of clinical DRE, MRI and biopsy in the LRP cohort.

Propensity score

A propensity score for the probability of receiving LRP rather than FT was constructed to correct for baseline imbalances using logistic regression. The variables used to perform propensity score matching were age, use of neoadjuvant ADT, PSA at diagnosis, Gleason Grade Category, MCCL, tumour stage and year of treatment. Nearest neighbour matching without replacement was used and groups were matched 1:1 (one patient receiving LRP for one patient receiving FT).

Patients outside the range of matched propensity scores were not included. A caliper of 0.20 of the standard deviation of the logit of the propensity score was used to minimize the differences

between the groups in baseline characteristics described above (14). Missing data was assumed to be missing at random and therefore eligible for imputation. Single imputation was performed to correct for missing data before creation of the propensity score. After matching an absolute standardized difference of <0.1 for each matching variable was considered a balanced match. Patients with any missing matching variables as outlined below were excluded. For patients missing formal T-staging in the LRP group, biopsy histology was used to infer staging, if demonstrated as bilateral disease, T2c staging was applied.

Sensitivity Analyses

Weight-adjusted 1-2 matching with and without imputation and a 1-1 matching without imputation and analysis of unmatched cases were performed to determine if the results matched our primary analysis. Further analyses with different definitions of FT failure were used using the same matching cohorts described:

1) transition to systemic or salvage whole gland treatment or diagnosis of metastases,
2) transition to systemic or salvage whole gland treatment or diagnosis of metastases, or requirement of second repeat FT treatment (total of three FT sessions)
3) transition to systemic or salvage whole gland treatment or diagnosis of metastases, or requirement of any repeat FT treatment (two or more FT sessions)

Survival analysis

Kaplan-Meier analysis was performed on the original dataset, the matched dataset and on the original dataset corrected for the inverse probability of treatment weights (IPTW). The log-rank test was used to ascertain statistical significance of differences in FFS and OS in the treatment groups. A multivariable Cox-model was used to assess whether treatment type was associated with failure. The model was corrected for the covariates used to create the propensity score. In addition, a Cox-model was created using treatment type corrected for the IPTW and the propensity score separately (15). The proportional hazards assumption was checked using Schoenfeld residuals and log-log curves. Because this assumption was violated for treatment type (decreased hazard of failure over time), Weibull accelerated regression modelling was used. Statistical analysis of categorical data was analysed using SPSS, version 25 (SPSS inc). All further statistical analyses were performed using R version 3.5.3 (http://www.R-project.org). The 'MatchIt' and 'optmatch' packages were used for propensity score analysis. The 'mice' package was using for imputation and the 'rms' and 'survminer' package for survival analyses.

Results

A total of 1333 patients underwent either LRP (N=572) or FT (N=626 HIFU, N=135 Cryotherapy) during the study period. After applying our inclusion/exclusion criteria, 335 patients were eligible in the LRP group and 501 patients in the FT group (420 HIFU, 81 Cryotherapy). 1-1 propensity score matching resulted in in 246 patients in each group [Figure 1]. Patients were well matched according to age, tumour grade, maximum cancer core length, stage of disease and use of neoadjuvant treatment, with delta =/<0.1 [Table 1]. In the LRP group, mean [SD] age was 63.4 [5.6] years, median [IQR] PSA 7.9g/ml [6-10] and in the FT group, mean [SD] age was 63.3 [6.9] years, median [IQR] PSA 7.9ng/ml [5.5-10.6]. The median [IQR] follow-up for LRP was 64 [30-89] months and after FT 49 [34-67] months [Table 1].

Primary Outcome

Failure-free survival (95% CI) at 3, 5 and 8 years in the LRP vs. FT cohorts was 86% (81-91%) vs. 92% (88-96%), 82% (77-88%) vs. 89% (84-94%) and 79% (73-86%) vs. 86% (79-92%), respectively (adjusted log rank p-value 0.031) [Figure 2a].

Secondary outcomes

Overall Survival

After LRP 6/246 (2.4%) patients died; one of these patients underwent salvage radiotherapy (Figure 4b). Mean time to death after LRP was 41.6 (SD 3.5) months. After FT, 2/246 (0.8%) died with one of these patients undergoing re-do FT [Figure 3a]. Mean time to death after FT was 3.5 (SD 1.3) months. Neither patient that died after FT underwent any form of salvage/systemic treatment. Therefore, OS (95% CI) at 3, 5 and 8 years following LRP vs. FT was 99% (98-100%) vs. 99% (95% CI 98-100%), 98% (96-100%) vs. 99% (95% CI 98-100%) and 96% (92-99%) vs. 99% (95% CI 98- 100%), respectively (log rank test p=0.24) [figure 2b].

Additional local treatments

No patients in the matched cohort developed metastases after LRP during the study period. 39/246 (15.9%) of LRP patients underwent EBRT to the prostate bed. One patient that underwent salvage EBRT died [Figure 3a]. After FT, 186/246 (75.6%) required no further treatment, and remained metastases free. 42/246 (17.1%) underwent repeat FT and 4/246 (1.6%) required a third FT session. 7/246 (2.8%) required whole-gland treatment after second FT session with either EBRT (n=6; 2.4%) or radical prostatectomy (n=1; 0.4%). 16/246 (6.5%) underwent whole-gland treatment straight after

the first FT session due to failure, without a second FT session. No patient that underwent three FT sessions later underwent whole-gland treatment [figure 3b].

Functional Outcomes

After LRP, all 246 patients had completed continence reports, and 237/ 246 had erectile function outcomes reported during consultation. After FT, 144/246 patients completed continence PROMs, and 148/246 patients completed erectile function PROMs. After LRP 212/246 (86.2%) reported pad-free continence compared to 139/144 (96.5%) reporting pad-free continence after FT ($p < 0.0007$). After LRP, 92/247 (38.8%) patients reported having erectile function compared to 101/148 (68.2%) after FT $p<0.0005$ [Figure 4].

Sensitivity analysis

Within the unmatched cohort, when using failure definition 1, the hazard ratio when corrected for propensity score matching, IPTW, and the Weibull accelerated model varied from 1.85-2.28 (p=0.01-p=0.0006), with LRP demonstrating a higher chance of failure. However, the significance in the Weibull accelerated failure model was lost when applying failure definition 2, in which the HR varied from 1.53-1.75 (p=0.18-p=0.01) corrected for the PS, IPTW and the Weibull accelerated failure model. In reviewing failure definition 1 and 2, FT led to improved FFS compared with LRP [eTable 2 in the Supplement]. Our main analysis results were supported by the results of various matching methodologies, using failure definition 1 and 2. Improved FFS was observed after FT in all groups, either significantly improved after log-rank test, or by trend in absolute numbers. Failure definition 3 demonstrated higher FFS after LRP in all matching methodologies.

Discussion

In summary, our propensity matched comparison of FT and LRP in the treatment of non-metastatic prostate cancers shows that patients undergoing FT had similar cancer control and overall survival to those undergoing LRP.

Albisinni *et al* recently reported a propensity matched analysis of 55 patients treated with focal HIFU to 55 patients undergoing radical prostatectomy finding no significant difference in terms of need for salvage treatment but with better functional outcomes after focal therapy with a median follow-up of 36 months (IQR16-56)(11). Another group reported on a propensity matched comparison of 50 patients undergoing another type of ablation called irreversible electroporation to 50 radical

prostatectomy patients but with only 12 months follow-up. Again, functional outcomes were superior with focal therapy, but failure was significantly higher with 4 patients undergoing salvage therapy whilst none in the radical prostatectomy group experienced biochemical failure at 12-months(16). Although not a directly comparable study, Tay *et al* assessed outcomes from whole-gland cryotherapy to focal cryotherapy and showed that using the Phoenix definition for biochemical failure there was no statistically significant difference in the 5-year biochemical disease-free survival rates (76.4% whole-gland vs. 70.0% focal, p=0.26)(17). Additionally, although there was no difference in incontinence (94.1% vs. 95.1%, p=0.803), erectile function was better preserved in those undergoing focal cryotherapy (29.5% vs. 46.8%, p=0.003). The only RCT on FT randomized 413 patients with very low to low-risk cancer to either active surveillance or focal vascular target photodynamic therapy (VTP)(18). After a median follow-up of 24 months, 58% had higher risk cancer in the active surveillance arm compared to 28% in the VTP arm. These results are not directly comparable to our patient cohort and have been criticised for applying FT in a group of men who do not stand to benefit from any form of treatment (19).

Unlike the above studies, the unique quality of our dataset comes from the fact that both focal HIFU and focal cryotherapy have been used in a manner that suits the patients' disease characteristics. Our results support the increasing body of evidence that demonstrates acceptable oncological outcomes as well as improved functional outcomes after FT, to those seen after radical treatment. Additional benefits, which we have not been able to evaluate, may include lower upfront cost of treatment, decreased length of hospital stay, and shorter recovery time and return to normal activities of life(20, 21). A formal health economics analysis is needed to investigate this further.

Our study was not a randomised trial. Whilst historical RCTs such as SPCG-4, PIVOT and PROTECT have successfully recruited, many other RCTs have failed to recruit where the interventions are very different as a result of difficulty in maintaining physician and patient equipoise. A recent pilot RCT comparing focal HIFU with radical prostatectomy, called the Partial Ablation versus Radical Therapy (PART) study, required an extended accrual time than originally intended and the radical arm had approximately 80% compliance(12) . Within the UK, two RCTs are due to open in 2019. The main PART RCT will be now be comparing the use of focal VTP to radical prostatectomy (ISRCTN99760303). The Comparative Health Research Outcomes of Novel Surgery in prostate cancer (CHRONOS) (clinicaltrials.gov NCT04049747) will aim to randomise men to either radical treatment (radiotherapy, brachytherapy or prostatectomy) or FT (HIFU or cryotherapy), as well as test neoadjuvant strategies that might reduce failure after FT.

There are some limitations requiring discussion. First, we observed a slightly better FFS following FT. This may be explained by potential staging bias. Both MRI and clinical staging with DRE were used in much of the LRP group whereas staging in the FT group was entirely based on MRI. In addition, we could not match for tumour volume, so it is possible that even with PSA, stage and grade matching, a selection bias exists whereby larger tumours underwent LRP. To control for such a phenomenon, we used MCCL as a surrogate for tumour volume as previously shown (22). Second, a selection bias may also exist in favour of LRP as we excluded patients who received adjuvant therapy within 12-months after LRP. Our primary definition for failure was transition to local or systemic salvage treatment or prostate cancer metastases, rather than the recognised biochemical failure definition for radical prostatectomy of either any rising PSA or a PSA 0.2ng/ml or greater. Use of these definitions would have resulted in a higher number of LRP failures but would have made comparisons to FT difficult as there are no validated PSA thresholds that define FT failure. Third, although functional outcomes for potency and urinary continence were assessed prospectively the outcomes were determined slightly differently. This is unlikely to create a significant bias for urinary continence but physician-reporting of erectile function in the LRP cohort may have led to a higher proportion being classified as potent. Further bias may have been introduced as data regarding pre-operative function was not recorded. The analysis of functional outcomes assumes all patients were continent and potent prior to treatment, however the decision to undergo FT vs LRP may have been guided by lack of/compromised function prior to treatment.

Conclusion

In well selected patients with non-metastatic clinically significant prostate cancer, FT can achieve similar oncological outcomes as LRP but with improved genitourinary functional outcomes. Whilst clinicians await the results of RCTs directly comparing FT to radical therapy, data such as these may be used to better counsel patients about their treatment options.

Authorship

TS and DR were responsible for data collection, analysis of the data. TS, DR and MP were responsible for production of the first draft and completed the data analysis. All authors were involved in data collection, manuscript preparation/drafting and approval of the final draft. HUA and MW had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. HUA and MW are guarantors of the study.

Declaration of Interests

Ahmed's research is supported by core funding from the United Kingdom's National Institute of Health Research (NIHR) Imperial Biomedical Research Centre. Ahmed currently receives funding from the Wellcome Trust, Medical Research Council (UK), Cancer Research UK, Prostate Cancer UK, The Urology Foundation, BMA Foundation, Imperial Health Charity, NIHR Imperial BRC, Sonacare Inc., Trod Medical and Sophiris Biocorp for trials in prostate cancer. Ahmed is a paid medical consultant for Sophiris Biocorp and Sonacare Inc.

Mark Emberton's research is supported by core funding from the United Kingdom's National Institute of Health Research (NIHR) UCLH/UCL Biomedical Research Centre. He was awarded NIHR Senior Investigator in 2015. Emberton receives funding from NIHR-i4i, MRC (UK), Cancer Research UK, Sonacare Inc., Trod Medical, Cancer Vaccine Institute and Sophiris Biocorp for trials in prostate cancer. Emberton is a medical consultant to Sonacare Inc., Sophiris Biocorp, Steba Biotech, Exact Imaging and Profound Medical.

Moore receives funding from the National Institute for Health Research, The European Association of Urology Research Foundation, MRC, Cancer Research UK, Prostate Cancer UK, Movember and the Cancer Vaccine Institute, for clinical prostate cancer research. She has received advisory board fees for Genomic Health.

Shah receives funding from Prostate Cancer UK and the St Peters Trust for clinical research and has received funding for conference attendance from Astellis, Ferring and Galil Medical.

Ahmed, Emberton, Hindley, Moore and Arya are all proctors for HIFU and are paid for training other surgeons in this procedure. Ahmed and Arya are proctors for cryotherapy and are paid for training other surgeons in this procedure. Emberton is a proctor for Irreversible Electroporation (Nanoknife) and is paid for training other surgeons in this procedure. Ahmed and Hindley are paid proctors for Rezum for the treatment of benign prostate hyperplasia.

Emberton, Freeman and Hindley have loan notes/stock options in Nuada Medical Ltd (UK).

Winkler receives a travel grant and a loan of device from Zicom Biobot.
E. Gómez-Gómez has received funds from The Carlos III Health Institute (ISCIII) and the European Social Funds (FSE) which funds his Rio Hortega research grant contract (CM16/00180).

None of the other authors have anything to declare.

Role of Funding Source
None of the funding sources had any role or input into the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

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Figures

Figure 1: flow diagram demonstrating matching variables and cohort development

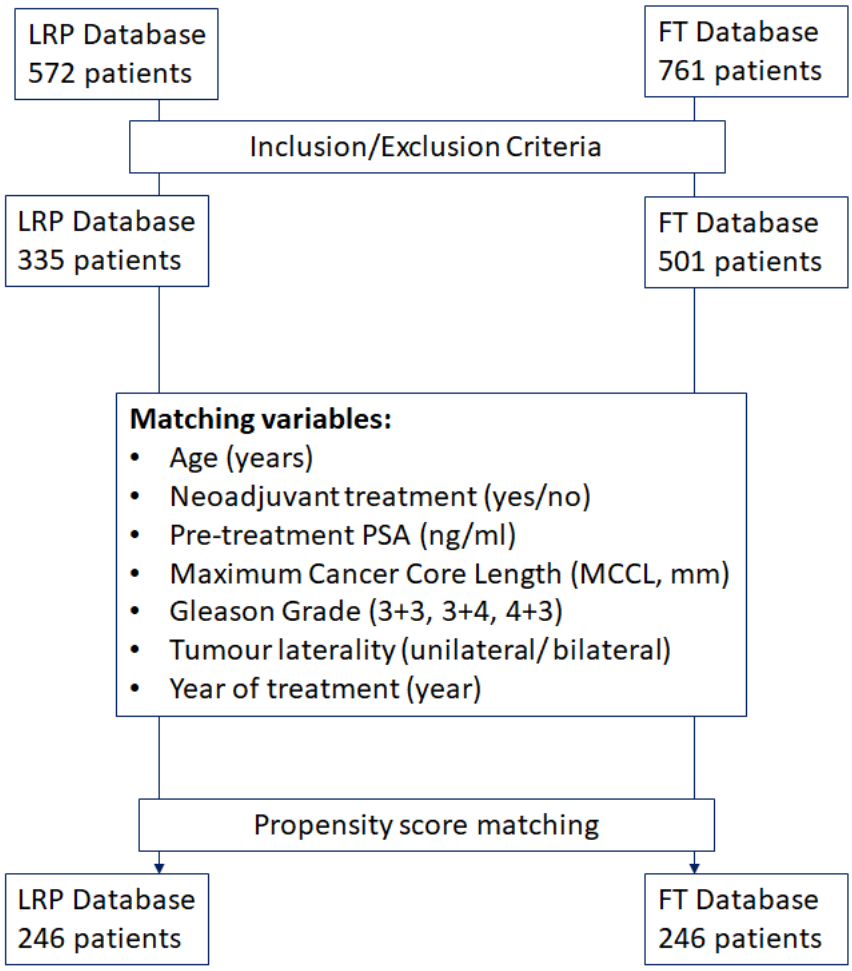


Table 1: Characteristics of LRP vs FT prior to matching, and after 1:1 matching and single imputation with caliper 0.20.

	LRP before matching	FT before matching	p-value	SMD before matching	LRP after matching	FT after matching	p-value	SMD after matching
N	N= 335	N= 501			N=246	N=246		
Age (years), mean ± SD	62.1 (±6.1)	65.3 (±7.4)	<0.001	0.48	63.4 (±5.6)	63.3 (±6.9)	0.79	0.02
Number of neoadjuvant ADT given	13 (3.9%)	56 (11.2%)	<0.001	0.28	11 (4.5%)	7 (2.8%)	0.47	0.08
PSA (ng/ml), median (IQR)	7.9 (5.9-10)	7.4 (5.3-10.3)	0.04	0.12	8.47 (6-10)	8.5 (5-10)	0.59	0.002
Gleason grade			0.001	0.27			0.75	0.05
Grade 3+3	132 (39.4%)	135 (26.9%)			94 (38.2%)	91 (36.9%)		
Grade 3+4	169 (50.4%)	310 (61.9%)			128 (52.0%)	134 (54.5%)		
Grade 4+3	34 (10.1%)	56 (11.2%)			24 (9.6%)	20 (8.1%)		
Stage (bilateral)	147 (43.9%)	136 (27.1%)	<0.001	0.66	116 (47.2%)	106 (43.1%)	0.47	0.07
MCCL (mm), median (IQR)	6 (3-9)	6 (4-8)	0.53	0.04	6 (3-8)	6 (4-8)	0.48	-0.007
Year, median (IQR)	2012 (2010-2015)	2011 (2010-2013)	<0.001	0.46	2012 (2010-2014)	2011 (2010-2013)	0.42	0.10

Abbreviations: LRP=laparoscopic radical prostatectomy, FT=focal therapy, ADT= Androgen Deprivation Therapy, PSA= Prostate-Specific Antigen, MCCL= Maximum Cancer Core Length
SMD= standardised mean difference, SD= Standard Deviation, IQR= Inter-Quartile Range

Figure 2a: Kaplan-Meier graph reporting failure free survival against time for Laparoscopic radical prostatectomy and focal therapy, after 1:1 matching and single imputation.

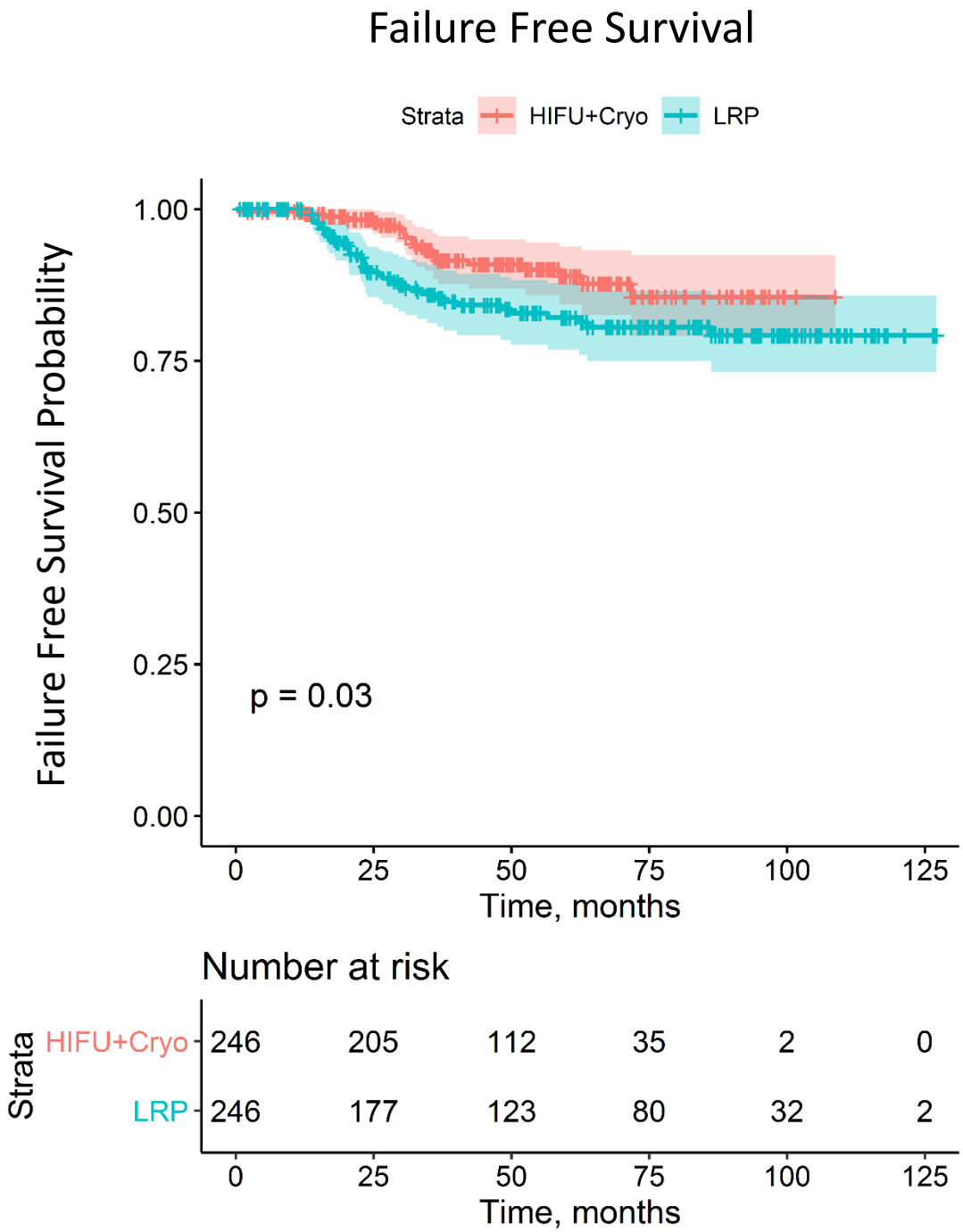


Figure 2b: KM for overall survival in 1-1 matched patients after single imputation

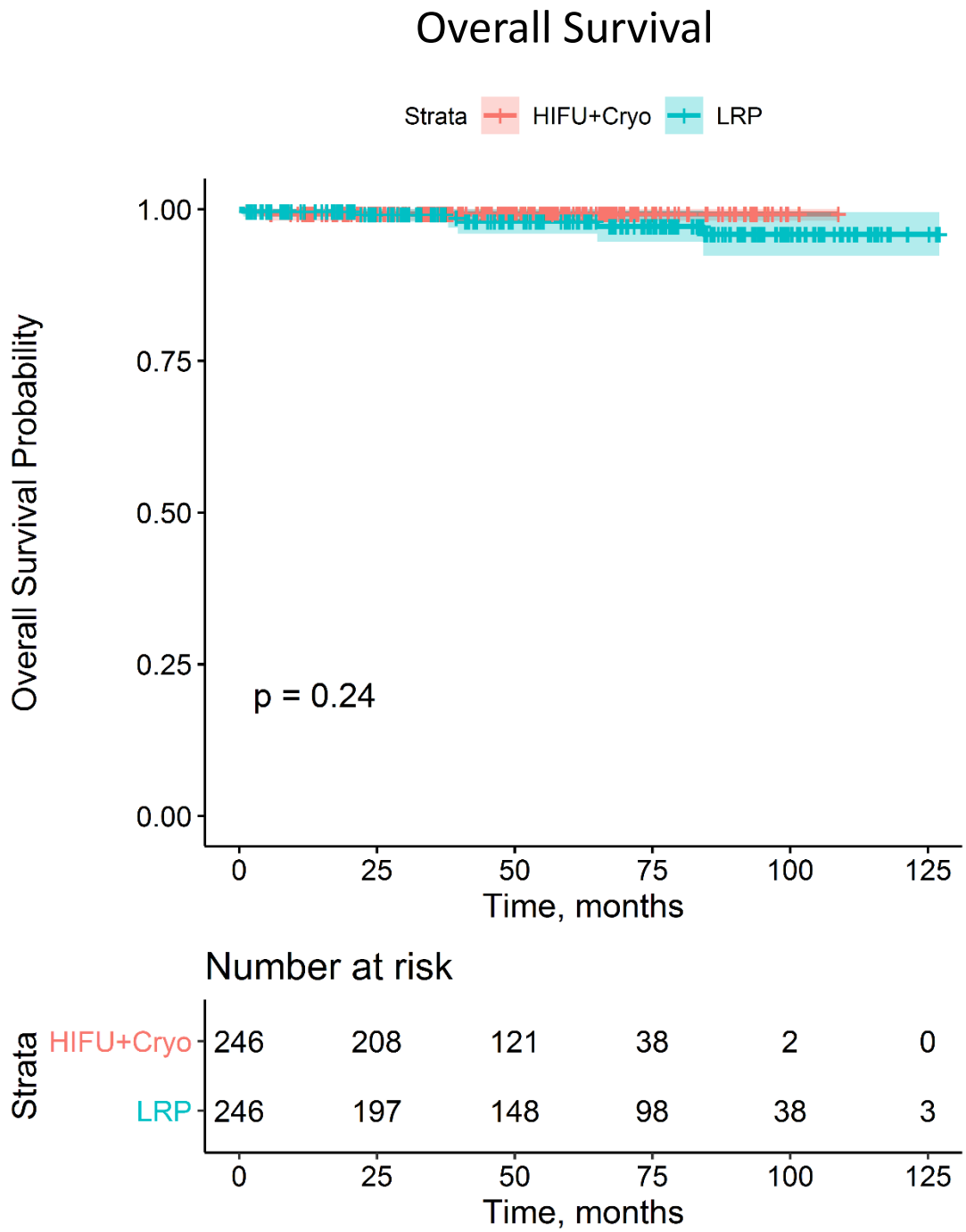


Figure 3a: Management outcomes of patients undergoing LRP

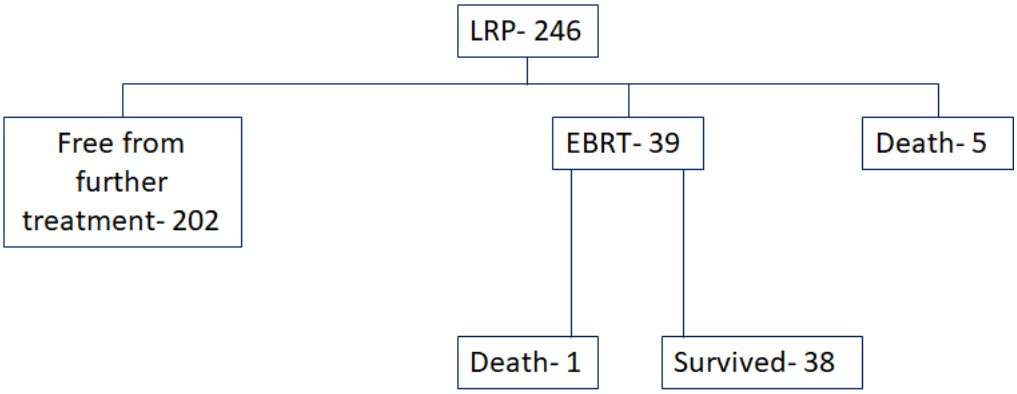


Figure 3b: management outcomes of patients undergoing FT

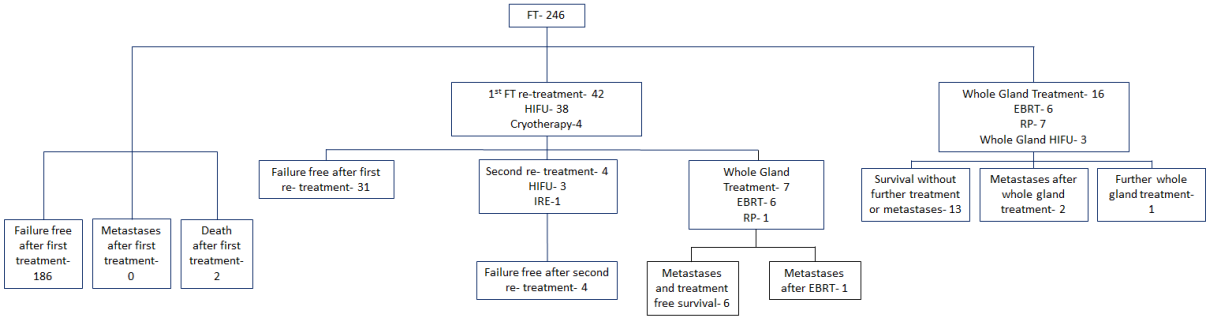
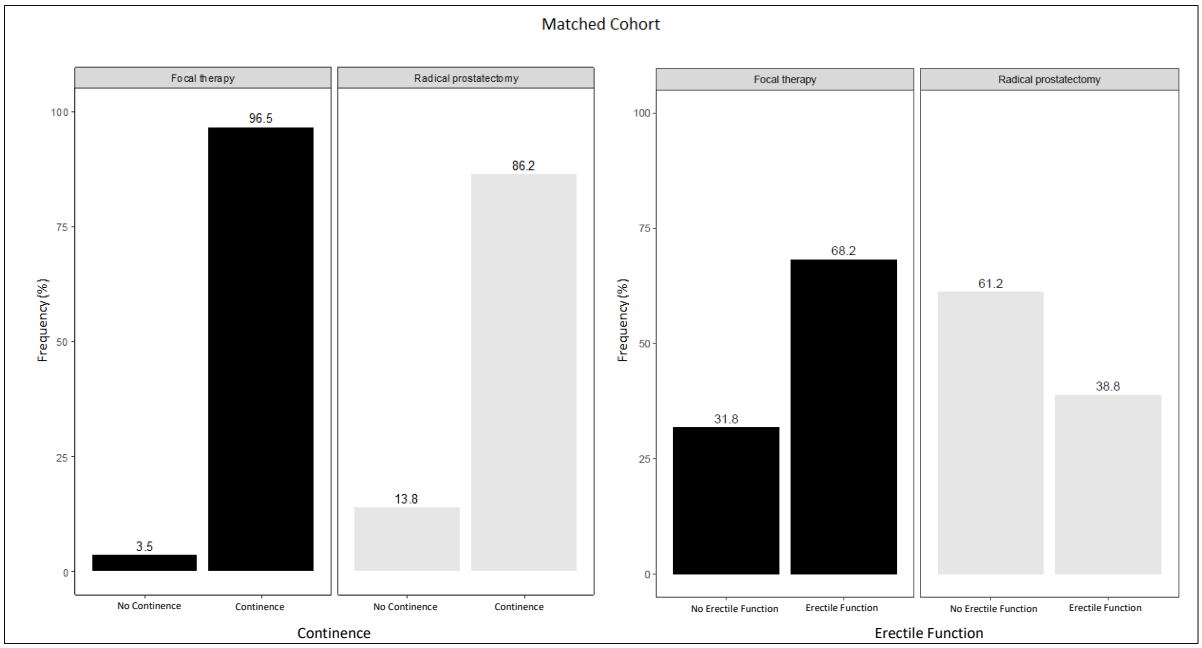
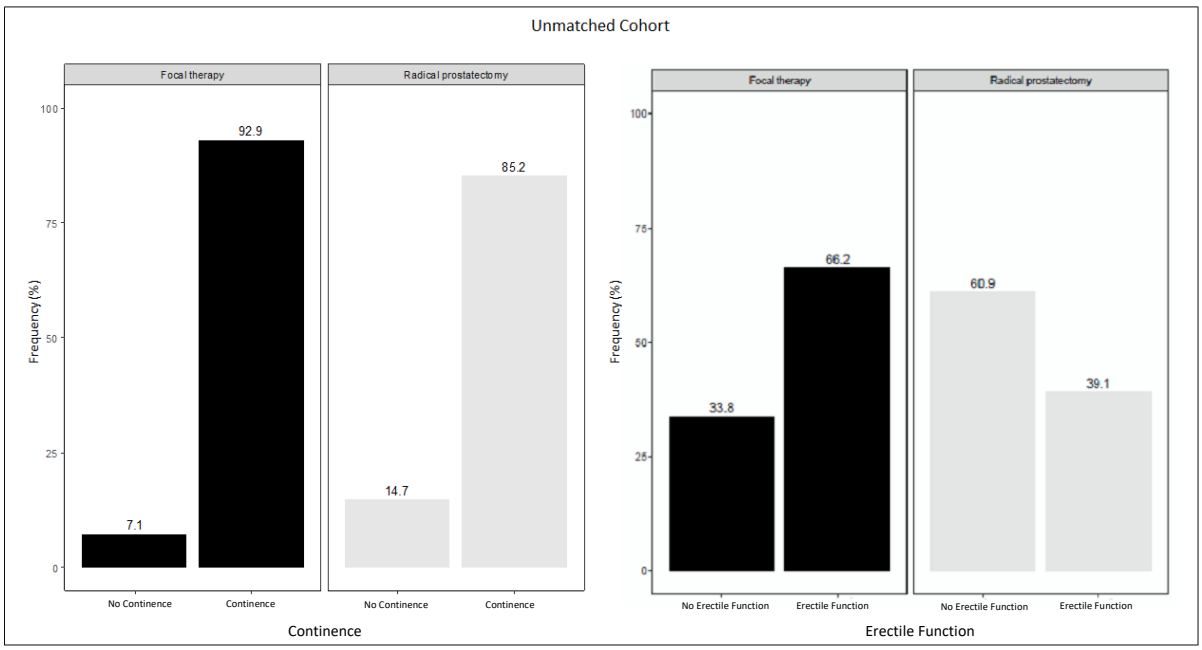


Figure 4: Continence and Potency rates after focal therapy or laparoscopic prostatectomy





Supplement

E-Table 2: Failure free survival after LRP or FT with various matching methodology

Matching Methodology	Failure definition	FFS after LRP (% [95%CI])			FFS after FT (% [95%CI])			P value
		3 years	5 years	8 years	3 years	5 years	8 years	
No matching	1	84% (80-88)	81% (76-86)	78% (73-84)	95% (93-97)	91% (88-94)	86% (81-91)	0.0001
1:1 no imputation	1	88% (83-93)	85% (79-91)	82% (76-90)	93% (88-97)	89% (83-95)	89% (83-95)	0.23
1:1 imputation	1	86% (81-91)	82% (77-88)	79% (73-86)	92% (88-96)	89% (84-94)	86% (79-92)	0.03
1:2 no imputation	1	86% (81-91)	82% (77-88)	79% (73-86)	94% (91-97)	89% (86-93)	85% (81-92)	0.28
1:2 imputation	1	86% (81-91)	82% (77-88)	79% (73-86)	94% (91-97)	89% (86-93)	86% (81-92)	0.009
No matching	2	84% (80-88)	81% (76-86)	78% (73-84)	94% (92-96)	88% (85-92)	82% (76-88)	0.006
1:1 no imputation	2	88% (83-93)	85% (79-91)	82% (76-90)	92% (88-97)	86% (79-93)	86% (79-93)	0.44
1:1 imputation	2	86% (81-91)	82% (77-88)	79% (73-86)	91% (87-95)	86% (81-92)	83% (76-90)	0.12
1:2 no imputation	2	88% (83-93)	85% (79-91)	82% (76-90)	93% (89-96)	85% (80-91)	84% (78-90)	0.53
1:2 imputation	2	86% (81-91)	82% (77-88)	79% (73-86)	93% (90-96)	87% (83-92)	83% (77-89)	0.06
No matching	3	84% (79-88)	81% (76-86)	78% (72-83)	82% (79-86)	72% (68-77)	64% (59-71)	0.01
1:1 no imputation	3	88% (83-93)	85% (79-91)	91% (76-90)	86% (80-92)	76% (68-84)	72% (63-83)	0.08
1:1 imputation	3	86% (81-90)	82% (76-87)	79% (73-85)	81% (76-86)	72% (65-79)	64% (55-75)	0.02
1:2 no imputation	3	88% (83-93)	85% (79-91)	82% (76-90)	83% (78-88)	73% (67-80)	63% (53-76)	0.007
1:2 imputation	3	86% (81-90)	82% (76-87)	79% (73-85)	82% (78-86)	72% (67-78)	64% (56-72)	0.01