Defining Biochemical Cure After Low Dose Rate Prostate Brachytherapy: External Validation of 4-year Prostate-specific Antigen Nadir as a Predictor of 10- and 15-year Disease-free Survival

Introduction:

Surgery, external beam radiotherapy (EBRT), and low dose-rate brachytherapy with Iodine^{125} seeds (LDR) are all good curative therapeutic options for early prostate cancer [1], and upon completion of treatment, serial measurement of prostate specific antigen (PSA) is a useful biomarker of response, regardless of the modality used.

However, the degree of consensus on PSA thresholds that define both cure and relapse differ between each modality. Following radical prostatectomy, the absence of circulating PSA, or PSA <0.2ng/mL, is widely accepted as a biomarker of biochemical control [2-4]. Because a small rise in PSA is both physiological and common following EBRT [5], reaching such clear consensus of a definition of relapse was more challenging, but the Phoenix Criteria, which define biochemical failure as a PSA of 2.0ng/mL above the nadir value, have now been accepted and incorporated into standard practice [6]. In contrast, using the Phoenix definition following LDR brachytherapy is complicated by the well documented post treatment PSA-bounce phenomenon[7-9]. These studies show that 40% of men undergoing LDR brachytherapy show a PSA rise >0.2ng/ml above nadir before falling to pre-bounce, or lower levels again, and in 15% of men the rise is >2ng/ml [8], with the vast majority of these changes occurring between years 1 and 3 post implant [7-9].And PSA bounce notwithstanding, it has been shown that the Phoenix criteria can substantially delay the diagnosis of genuine relapse following LDR brachytherapy, in cases where it does occur [10].

Thus, bespoke PSA-response criteria for LDR brachytherapy, at a timepoint after the PSA bounce period has passed, are necessary. To address this unmet need, a recent large international study attempted to define a PSA threshold value 4 years after LDR prostate brachytherapy that predicts 10-year disease free survival, and could therefore be considered as biochemical evidence of cure [11]. The study showed that 98.7% of patients with PSA ≤0.2ng/ml at 4 years after low dose rate (LDR) prostate brachytherapy were disease free after 10 years, and the authors have concluded that it would be reasonable to adopt a biochemical definition of cure as PSA ≤0.2ng/mL at 4 years post LDR brachytherapy. The study was methodologically robust; the threshold was derived from analysis of a large Canadian database, and externally validated on separate Australian, Irish, and US cohorts.

Nonetheless, the data presented in this paper constitute a single retrospective study, and are therefore unlikely to underpin consensus guidelines in isolation. Furthermore, the validation cohorts used in this study were substantially smaller than the train dataset, and the proposed thresholds have not been validated on a cohort of UK patients. Therefore, we replicated the methodology of

Crook et al [11], by retrospective interrogation of a prospectively collated database of patient's treated as part of the *(removed for double-blind review)*Brachytherapy Service in *(removed for double-blind review)*over the last 20 years. In so doing, we sought to provide further robust external validation of the threshold proposed in this study, to examine the validity of these findings in a UK population, and to contribute to ongoing discussions about how to define cure after LDR brachytherapy for prostate cancer.

Methods

Patients

LDR brachytherapy as a therapeutic option for men with low and intermediate risk prostate cancer was first introduced at the *(removed for double-blind review)*in 2001. Over this time, and in conjunction with*(removed for double-blind review)*, this treatment has been delivered as part of a *(removed for double-blind review)*service. Within this national framework, a database (Microsoft Excel Corporation, Washington USA) of all patients treated at our centre since the service was implemented was prospectively collected and curated on institutional servers. The database records baseline demographic data including age, referring Health Board, presenting PSA, Gleason Score and Tumour (T) stage. Serial post-treatment PSA measurements are collected at a standardised interval of 3 monthly for 1 year post treatment, 4 monthly during year 2 post treatment, and 6 monthly thereafter. In addition, men undergo 6 monthly Clinical Nurse Specialist (CNS) led postal follow up, which includes IPSS score, and a QoL free text box in which patients are asked about ongoing LUTS, up to 3 years post-treatment. Clinical failure during follow up was considered to be local, nodal, distant, or biochemical failure which triggered salvage treatment with androgen deprivation therapy, external beam radiotherapy, or surgery. Where clinical failure or death were encountered, the date at which they occurred was recorded in the database.

1142 patients with low or intermediate risk early prostate cancer were treated from the 28th August 2001 and 17th November 2020, at which time the data was locked. As this was a retrospective analysis of data pertaining to a standard treatment protocol, prospectively collated within the framework of a national service, no further ethical approval for the study was required or sought.

In order to replicate the methodology of Crook et al. as accurately as possible, the same exclusion criteria were used for this study [11]. A total 512 patients were excluded, leaving 632 for analysis of the primary endpoint. Reasons for exclusion from the study included <4 years follow up from time of

treatment, missing a 4-year PSA (4YrPSA) reading, disease relapse prior to this timepoint, and NCCN high-risk disease [12]. Specific numbers, and exclusion sequence are shown in the Consort diagram in Figure 1. The primary endpoint for the study was disease free survival (DFS) at 10 years, defined as freedom from clinical, radiological, or PSA progression requiring androgen deprivation therapy. The secondary endpoint was DFS at 15 years.

Replicating the original study, we assessed the predictive value of 4-yearPSA measurements for 10-, and 15-year DFS. For patients included in the final cohort, the PSA within the time-window 3.5-4.5 years post implant was regarded as 4YrPSA. This 4YrPSA value was used to categorise patients using the same thresholds as Crook et al (ref): ≤0.2 ng/mL, >0.2 to ≤0.5ng/mL, >0.5 to ≤1.0ng/mL and >1.0ng/mL.

Treatment

Diagnostic workup prior to LDR brachytherapy was undertaken according to standard clinical protocols. Biopsies were performed using a standard trans-rectal technique, and all pathology was reviewed centrally in the multi-disciplinary meeting (MDT). Further details regarding the number of positive cores sampled, the proportions of malignancy within cores, and the percentage of Gleason pattern 4 disease were reported and discussed at MDT, but were not routinely collated on the database from which the data for this study was derived. MRI was mandated for all patients in whom LDR brachytherapy was considered, and bone scan was mandated for all patients with a Gleason score >6, or PSA ≥10ng/ml. Patients with radiological, clinical, or biopsy evidence of T-stage >2, N-stage >0, or M-stage >0 were not considered eligible for LDR brachytherapy. Details of the treatment technique used for the patients in this study are described in detail in a previously publication [10]. In brief, patients underwent general anaesthesia, and trans-perineal insertion of 0.379mCi/0.481 U Iodine^{125}seeds under real-time trans-rectal ultrasound guidance. Implant dosimetry was calculated via post-procedure CT scan 4 weeks post-implant. 10.3% (65/632) of the patients in this study received 3-6 months of neo-adjuvant hormone therapy, to downsize the prostate gland to below 50cc volume.

Statistics

Kaplan-Meier (KM) analysis to 10 and 15 years follow up was carried out for each of the 4 PSA categories. Disease relapse as defined was the endpoint for all 4 categories, and patients were censored at this event, or most recent PSA. In patients who were lost to follow up, or died of non-oncological causes during the follow up period, the most recent PSA prior to this event was used,

with censorship at this point. Competing risks for these patients were considered, and thought likely to be equivalent to those still under surveillance. The starting date for the KM analysis was the date of insertion of the brachytherapy implant and the final date was that of disease relapse, or last recorded follow up PSA.

The null hypothesis that failure rates in all 4 groups were equivalent was tested with the log-rank test, assuming proportional hazards across the study period. Following the methodology of Crook et al, these results were checked by repeating the analysis with Wilcoxon-Breslow-Gehan test, which does not assume proportional hazards [13]. 10-year DFS rates for all 4 groups are presented as percentages, with 95% confidence intervals, and compared to those reported in Cook et al.'s training dataset [11].

In order to test the accuracy of a 4YrPSA ≤0.2 ng/mL as a standalone diagnostic test independent of co-variate factors, the sensitivity and specificity of this threshold for 10-year DFS was calculated. The sensitivity, or true-positive rate of this threshold was defined by calculating the proportion of patients with a positive test (4YrPSA ≤0.2 ng/mL, numerator), from the cohort who reached the outcome of interest (disease-free at 10 years, denominator). Specificity, or true negative rate, was defined by calculatingthe proportion of patients with a negative test (4YrPSA was >0.2 ng/mL, numerator) from the group who did not have the outcome of interest (relapse within 10 years, denominator). 95% confidence intervals for sensitivity and specificity were calculated using the Clopper-Pearson method for computing binomial confidence intervals.

Finally, we sought to understand the impact of disease parameters at baseline on long-term treatment efficacy in our cohort. Therefore, Kaplan-Meier analysis to 10 and 15 years was repeated, splitting the cohort by NCCN risk group [12]. As with the 4-year PSA analysis, we tested the null hypothesis that failure rates across all 3 NCCN risk groups were equivalent with the log-rank test (assuming proportional hazards), and validated this with the Wilcoxon-Breslow-Gehan test (proportional hazards not assumed). Statistical analysis was done using the R open source software package (R version 4.0.2) and Kaplan-Meier plots were produced with ggplot2 (version 3.3.2).

Results

Details of the final 632 patient cohort are presented in Table 1. By NCCN risk stratification criteria [12], 39.9% had low risk, 36.7% favourable intermediate risk, and 23.4% unfavourable intermediate

risk. Median follow up for this cohort was 9.1 years (range 3.5 to 18.7 years). The number of patients available for analysis at 10 and 15 years respectively were 248, and 46. The median number of post treatment PSA measurements in the cohort was 9. During the full study period, 64 patients of the initial cohort (10.1%) suffered disease relapse.

The number of patients in each 4YrPSA category were as follows (proportions in brackets): PSA ≤0.2ng/ml – 402 (63.6%) , PSA 0.2 to ≤0.5 ng/ml –122 (19.3%), PSA 0.5 to ≤1.0ng/ml – 55 (8.7%), and PSA≥1.0ng/ml – 53 (8.4%). The proportion of patients in each NCCN risk stratification group with a 4YrPSA ≤0.2ng/ml was also calculated. In the low-risk group, 160/252 (63.5%) were in this group, and figures were 155/232 (66.8%), and 87/148 (58.8%) for favourable-intermediate and unfavourable-intermediate groups respectively.

Actuarial probabilities of being disease free over the entire follow up period, for patients in each 4YrPSA category, are shown in Figure 2. Associations between 4-year PSA measurement, and the probability of remaining disease free throughout the follow up period, were highly significant on log-rank test ($p < 0.0001$). This analysis was repeated with the Wilcoxon-Breslow-Gehan test, which was also statistically significant ($p < 0.0001$). Disease free survival probabilities at 10 and 15 years, with 95% confidence intervals, are shown in Table 2, with data from the study of Crook et al. [11] for comparison.

There were 248 patients who reached 10 years of follow up disease free. Of these, 154 were in the 4YrPSA≤0.2 ng/mL category, thus the sensitivity of this threshold for 10-year DFS was 62.1% (95% CI 55.7% - 68.2%). There were 52 cases of disease relapse (events) before the 10 year follow up point. Of these, only 6 patients had 4YrPSA ≤0.2 ng/mL; thus, specificity of this threshold for being disease free at 10 years was 88.5% (95% CI 76.6% - 95.7%).

Actuarial probabilities of being disease free over the follow-up period, with the cohort split by NCCN risk group, are shown in Figure 3. The probability of being disease-free at 10 and 15 years for each NCCN risk group, with 95% CIs, are presented in table 3.

Discussion

A diagnosis of prostate cancer causes great distress and uncertainty [14], not least because it can be so hard to reassure patients that they have been ‘cured’ once treatment is completed. Being in a position to provide such reassurance is a key priority for both patients, and their treating physicians

[15]. This issue becomes increasingly relevant to UK practice, as both the number of centres offering LDR brachytherapy, and experience with the technique increases [16-20]. The *(removed for double-blind review)* database is one of the most mature databases of prostate low dose rate brachytherapy within the UK, with sufficient duration of follow up to answer these important clinical questions.

In this paper, we aimed to externally validate the findings of Crook et al. [11], in a UK population, and test the hypothesis that a PSA nadir of ≤0.2ng/ml at 4 years after implantation predicts for a very high probability of being cured after LDR brachytherapy for prostate cancer. Results from the training dataset of this study suggest that 98.7% of patients with a 4YrPSA ≤0.2ng/ml are disease free at 10 years [11]. Our result of 97.5% is notably similar, with significant overlap of 95% confidence internals. It is worth noting that the proportion of patients in this study (63.6%) with a 4YrPSA ≤0.2ng/ml was lower than that in the Crook et al. training dataset (77.1%), and validation datasets 2 and 3 (73.5% and 85.7% respectively), but higher than that reported in validation cohort 1 (54.6%) [11]. Other authors report similarly excellent relapse-free survival for patients meeting this threshold, albeit with a shorter duration of follow up [21,22]. Put another way, our data suggest that for patients with 4YrPSA ≤0.2ng/ml, the odds of clinically meaningful prostate cancer relapse by 10 years post-implant are 1 in 40.

The sensitivity of 4YrPSA ≤0.2ng/ml to 10-year disease free status seems a little less impressive at 62.1%(95% CI 55.7% - 68.2%). However, this is because 94 of the 248 patients who were disease-free at 10 years had a 4YrPSA >0.2ng/ml; many patients in this category are still likely to be cured. Specificity was higher at 88.5%(95% CI 76.6% - 95.7%). This might be expected from the survival analysis, but emphasises that PSA ≤0.2ng/ml is a good predictor of 10-year DFS. In this cohort, only 6 patients with a 4YrPSA ≤0.2ng/ml suffered relapse by year 10. Five of these 6 did have unfavourable-intermediate risk disease, but the high specificity of this threshold suggests that 4YrPSA ≤0.2ng/ml is a good predictor of 10-year DFS regardless of baseline NCCN risk group.

Overall, our results confirm the findings not only of Crook et al [11], but other authors who have tested the utility of this PSA threshold for predicting long term outcome following LDR brachytherapy for prostate cancer [21,22]. Furthermore, it is worth noting that between 2017 and 2019, mean life expectancy of a Scottish male was 77.1 years [23], whilst the median age of patients in this study is 63 years (range 36-78, data not presented). Therefore, our data suggest that the overwhelming majority of patients receiving LDR brachytherapy will require no further treatment for their prostate cancer. Even those men with a slightly higher PSA nadir of >0.2-≤0.5ng/ml had an 89% and 85% probability of remaining disease free by years 10 and 15 respectively.

A strength of our study is the duration of follow up for many patients, and these data show some late relapses occurring between years 10 and 15. Interestingly, the data presented by Crook et al. show a similar phenomenon [11], and it is not easy to explain these very late events. It is known that poor dose coverage, and D90 <140Gy in particular associate with worse outcomes [18, 20, 24], but our treatment protocol is a standard technique, and previously published dosimetry data align with results from other groups [10,20]. Furthermore, it seems likely that differences in results caused by dosimetric discrepancies would manifest before 10 years post-implant. One possibility could be that with ageing, immune surveillance may decrease, allowing previously senescent cells to reactivate [25]. It may also reflect incomplete tumour eradication as measured by nadir PSA. The lowest limit of PSA detection currently recorded in our unit is <0.1ng/ml, yet the PSA can be measured to <0.003ng/ml in ultra-sensitive assay systems [26], and it is well documented that nadir PSA predicts long term outcome for patients undergoing external beam radiotherapy [27, 28]. It would be of interest to investigate if a supersensitive PSA nadir at year 4 in the late relapsing patients was indeed higher than those who did not relapse. There is also the possibility that these are actually second cancers within the prostate within areas of the gland that were not fully ablated from the initial implant. Perhaps the most likely explanation lies with the definition of relapse used in this paper and by Crook et al. [11]. This specifies "PSA progression requiring androgen deprivation therapy", and we suggest that by this definition, a small number of patients have low, but steadily rising PSA values between years 5 and 10, but do not require hormone treatment before the 10-15 year window.

Within our data set, NCCN low and favourable-intermediate risk patients had excellent, and very similar 10 and 15-year DFS, as shown in figure 3. These data strongly support the use of LDR brachytherapy in low intermediate risk patients as per the latest ASCO guideline [29]. Outcomes were significantly inferior for unfavourable-intermediate risk patients, with observed DFS of 75.9% (+/-8.6%), and 71.3% (+/-10.2%) at 10 and 15 years respectively, and it is interesting to contrast these data with results of the ASCENDE–RT trial [30]. In the brachytherapy-based treatment escalation arm of this study, patients received an LDR seed boost after 46y of external-beam radiotherapy to the prostate and pelvic nodes, alongside 12 months of androgen deprivation therapy [30]. For the 63 patients with NCCN high-intermediate risk disease who received this treatment within ASCENDE–RT, reported 9-year biochemical-PFS was 94% [30], noticeably better than the 10-year results reported in this paper. Interestingly however, our results are still at least as good and possibly better than the 78Gy dose escalated external beam cohort (69.8% +/-14.6 % at 9 years) [30], infering that local dose escalation may be more important than covering the pelvic nodes. However, it is important to state that this is not a like for like, or statistically significant

comparison, and that an accurate assessment of the risk of both extra-capsular and pelvic lymphatic disease requires careful consideration of a range of factors, not just NCCN risk group. Nonetheless, we suggest that the multi-modality protocol delivered in ASCENDE–RT [30] may provide the extra dose rate required from external beam for unfavourable-intermediate risk disease, in addition to the systemic and local benefits of ADT for those patients who would have done poorly with LDR alone. Clearly however,this theoretical benefit needs to be weighed against the potentially increased toxicity risks conferred by this approach. In our unit, and following the publication of the ASCENDE–RT trial [30], we have added the combination of 12 months of ADT with 46Gy in 23 fractions to the prostate, seminal vesicles and the pelvic lymph-nodes before a 115Gy LDR Brachytherapy boost 2 weeks later, as a treatment option for men with unfavourable-intermediate risk disease.

Previous studies have suggested that patients with a 4YrPSA ≤0.2ng/ml could be safely discharged from long-term PSA follow-up [22]. Given the very low risk of clinically significant relapse reported in this, and other studies [11, 21-22], we suggest that our data support this conclusion. However, the observation of ongoing relapse events between years 10 and 15 seen in both Crooks paper and this study [11], mean that in our view, patients should be counselled of this risk, and given the choice. Furthermore, and as inferred by the relatively low sensitivity of 4YrPSA ≤0.2ng/ml, it is important to state that a PSA nadir of >0.2ng per ml at 4 years does not mean the patient has failed brachytherapy, as the majority of these patients remain free of clinically relevant disease by 10 years post-implant. However, it would suggest that these patients should continue long-term PSA follow-up to detect relapse should it occur.

Finally, it is worth noting that the small proportion of patients with a 4YrPSA >1.0ng/ml (8.4%) do poorly, with a failure rate of nearly 60% by year 10. With rapidly increasing access to more sensitive imaging tools such as PSMA-PET-CT [31], we further suggest a PSMA-PET-CT for patients with a 4YrPSA >1.0ng/ml may detect oligometastatic disease amenable to salvage stereotactic body radiotherapy (SBRT) within trials such as COMET-3 [32], or indeed local salvage therapies such as focal LDR, HDR or prostatectomy in the hope that it may improve long term outcomes.

Conclusion

This study confirms that 4 years after LDR brachytherapy, a nadir PSA of ≤0.2ng/ml equates to cure, through validation in a UK population. These patients could be discharged back to GP follow up. For men with low and favourable-intermediate risk prostate cancer presenting as a new patient to the clinic, LDR Brachytherapy offers excellent outcomes with an approximately 90% chance of remaining disease free at 10-15 years, rising to 97.5% if a PSA nadir of ≤0.2ng/ml is reached by year 4 post

treatment. The early use of PSMA-PET-CT should be considered for those men with a PSA >1.0ng/ml at 4 years post treatment to establish if they require salvage therapy at the earliest opportunity.

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Characteristic	**No of patients (%)**
Patients	632
Baseline PSA (ng/ml):	
median	6.7
<4	67 (10.6)

≥4-<10	432 (68.4)
≥10-<20	132 (21)
≥20-<30	0
≥30	0
Gleason Score:	
≤6	356 (56.3)
3+4=7	222 (35.1)
4+3=7	54 (8.6)
8	0
9 or 10	0
T category:	
T1a-T2a	459 (72.6)
T2b-T2c	173 (27.4)
T3a-T3b	0
NCCN risk group:	
low	252 (39.9)
intermediate (low)	232 (36.7)
intermediate (high)	148 (23.4)
Age (years)	
median	63
<50	13 (2.1)
≥50-<60	169 (26.7)
≥60-<70	378 (59.8)
≥70	72 (11.4)
Neo-adjuvant hormones	
yes	65 (10.3)
no	567 (89.7)
No. of PSA measurements	
<10	333 (52.7)
≥10-<20	299 (47.3)
≥20	0
PSA follow up (years)	
median	9.1
maximum	18.7

Table 1: Patient and disease characteristics

	Edinburgh Cancer Centre		**Crook et al. (Train dataset) [11]**	
4-year PSA (ng/ml) (number in each group)	10-year DFS (95% CI)	15-year DFS (95% CI)	10-year DFS (95% CI)	15-year DFS (95% CI)

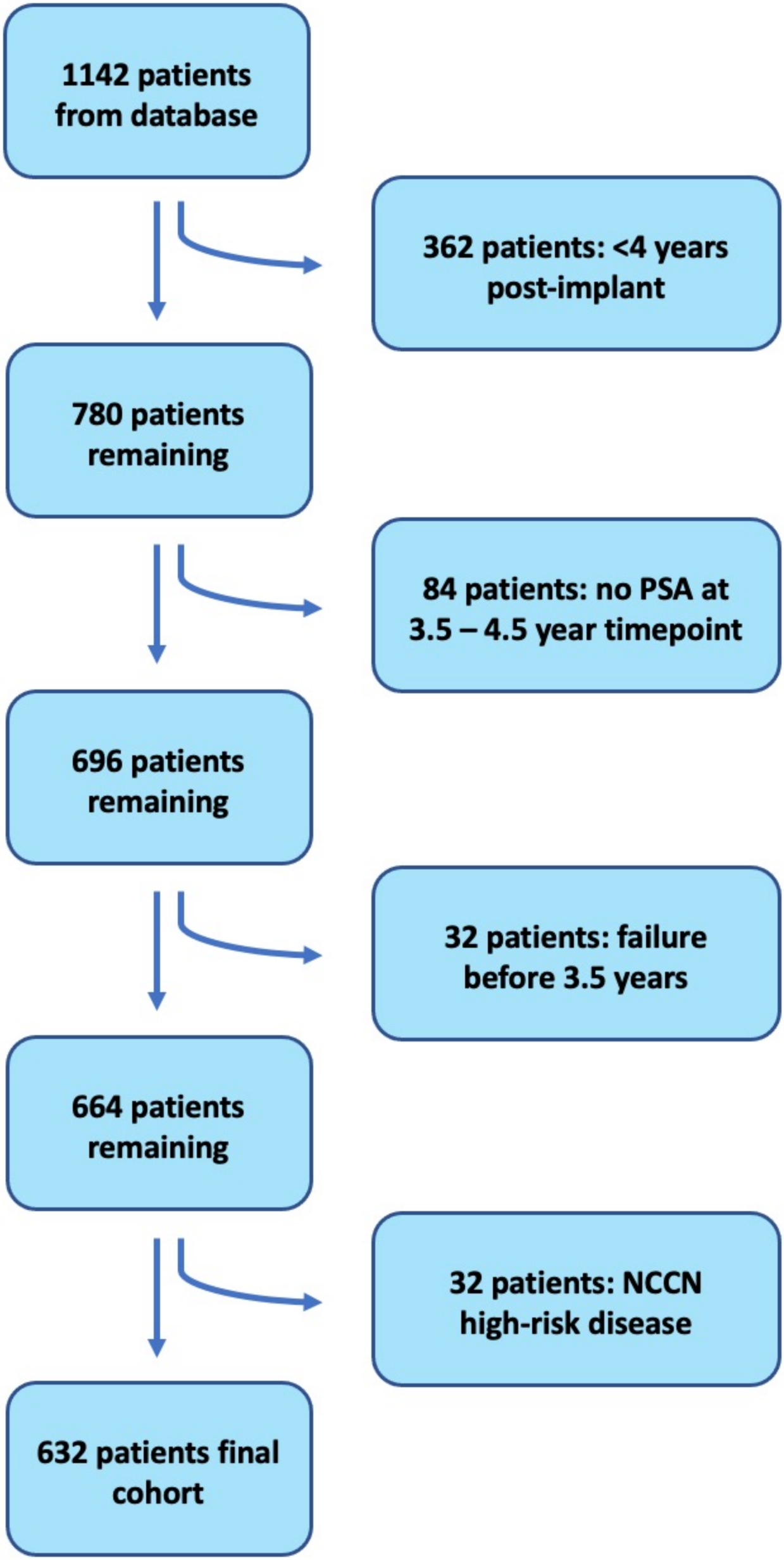
≤0.2 402 (63.6%)	97.5% (95.4-99.6)	90.2% (83.3-97.7)	98.7% (98.3-99.0)	96.1% (94.8-97.2)
>0.2 to ≤0.5 122 (19.3%)	89.0% (82.4-96.1)	84.5% (76.0-94.0)	93.5% (91.0-95.3)	86.8% (81.4-90.7)
>0.5 to ≤1.0 55 (8.7%)	81.5% (70.5-94.2)	73.4% (59.6-90.4)	85.9% (80.6-89.8)	78.2% (68.6-85.2)
>1.0 53 (8.4%)	41.8% (29.7-58.9)	41.8% (29.7-58.9)	48.0% (41.8-53.8)	33.2% (24.9-41.6)

Table 2: 10 and 15-year DFS by 4-year PSA strata, comparing results with those published by Crook et al [11].

NCCN risk group (number in each group)	**10-year DFS** (95% CI)	**15-year DFS** (95% CI)

Low (252 - 39.9%)	93.1% (89.6-96.7%)	86.6% (80.4-93.3%)
Favourable-intermediate (232 - 36.7%)	92.1% (87.6-96.9%)	88.8% (82.7-95.5%)
Unfavourable-intermediate (148 - 23.4%)	75.9% (67.8-84.9%)	71.3% (61.8-82.2%)

Table 3: 10 and 15-year DFS by NCCN risk groups


1142 patients from database
362 patients: <4 years post-implant
780 patients remaining
84 patients: no PSA at 3.5 – 4.5 year timepoint
696 patients remaining
32 patients: failure before 3.5 years
664 patients remaining
32 patients: NCCN high-risk disease
632 patients final cohort