Advances in Radiation Oncology (2022) 8, 101112

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Definitions of "Cure" After Low-Dose-Rate Brachytherapy in Low- and Intermediate-Risk Prostate Cancer: Phoenix or Surgical?

Andreas Boehle, MD, PhD,[a,b,*] Dorothea Zywietz,[a] Irina Robrahn-Nitschke, MD,[d] Inke R. Koenig, MD, PhD,[c] and Achim Lusch, MD, PhD[a,b]

[a]*Department of Urology, University of Luebeck, Luebeck, Germany;* [b]*HELIOS Agnes-Karll Hospital Bad Schwartau, Bad Schwartau, Germany;* [c]*Institute for Medical Biometry and Statistics, University of Luebeck, Luebeck, Germany; and* [d]*CURAVID Radiology and Radiotherapy, Luebeck, Germany*

Received 18 August, 2022; accepted 6 October, 2022

Abstract

Purpose: The aim of this study was to compare a surgical with a Phoenix-derived definition of *cure* at 4 years after treatment by ^{125}J low-dose-rate brachytherapy (LDR-BT) in patients with low- and intermediate-risk prostate cancer.

Methods and Materials: A total of 427 evaluable men with low-risk (62.8%) and intermediate-risk (37.2%) prostate cancer were treated with LDR-BT (160 Gy). Cure was defined at 4 years either as not having experienced a biochemical recurrence by the Phoenix definition, or by a surgical definition, using a posttreatment prostate-specific antigen of ≤0.2 ng/mL. Biochemical recurrence−free survival (BRFS), metastasis-free survival (MFS), and cancer-specific survival were calculated at 5 and 10 years using the Kaplan-Meier method. Standard diagnostic test evaluations were used to compare both definitions with regard to later metastatic failure or cancer-specific death.

Results: At 48 months, 427 patients were evaluable with a Phoenix-defined and 327 with a surgical-defined cure. At 5 and 10 years BRFS was 97.4% and 89% and MFS was 99.5% and 96.3% in the Phoenix-defined cure cohort, and BRFS was 98.2% and 92.7% and MFS was 100% and 99.4% in the surgical-defined cure cohort. Specificity for cure was 100% for both definitions. Sensitivity was 97.4% for the Phoenix and 96.3% for the surgical definition. The positive predictive value was 100% for both, whereas the negative predictive value was 29% for the Phoenix and 7.7% for the surgical definition. Accuracies of a correct prediction of cure were 94.8% and 96.3% for the Phoenix and the surgical definition, respectively.

Conclusions: Both definitions are useful for a reliable assessment of cure after LDR-BT in patients with low-risk and intermediate-risk prostate cancer. Cured patients might follow a less stringent follow-up schedule from 4 years onward, whereas patients not achieving cure at 4 years should be monitored for an extended time.

Sources of support: This work had no specific funding.

Disclosures: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

All data generated and analyzed during this study are included in this published article (and its supplementary information files).

*Corresponding author: Andreas Boehle, MD, PhD; E-mail: boehle@urologie-bad-schwartau.de

Introduction

The optimal management of men with low- (LR) and intermediate-risk (IR) prostate cancer (PCa) is controversial, with a spectrum ranging from active surveillance[1] to

https://doi.org/10.1016/j.adro.2022.101112

curative approaches such as external beam radiation therapy (EBRT), low-dose-rate brachytherapy (LDR-BT), high-dose-rate brachytherapy, or radical prostatectomy.[1] Generally, time to failure for these different therapies is used to report results and compare treatments. For EBRT, a dynamic criterion (prostate-specific antigen [PSA] nadir + 2 ng/mL), was developed by consensus of the Phoenix group[2] and later extended for brachytherapy,[3,4] whereas for surgery, a fixed endpoint of PSA ≤0.2 ng/mL is used by default.[1]

Recently, a discussion emerged on the value of a fixed threshold-definition of *cure* similar to that used following surgery for all brachytherapy modalities[5-7] versus the standard use of the Phoenix criterion. Crook et al,[8] strongly supported by McNeill et al,[9] proposed that a fixed PSA level of <0.2 ng/mL at 4 years after LDR-BT should be the benchmark for cure.

To determine the value of a Phoenix-derived dynamic definition against a fixed surgical definition of cure, we analyzed a large cohort of patients with LR and IR PCa treated by LDR-BT monotherapy and compared both definitions of cure with regard to later biochemical, metastatic, and cancer-specific lethal failure by standard test evaluation calculations.

Methods and Materials

The protocol of this retrospective cohort analysis was approved by the local academic ethical committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent was not required.

Men diagnosed between 2005 and 2018 with low- and intermediate-risk PCa and deemed eligible for LDR-BT monotherapy with curative intend were identified. Every patient was seen independently by a urologist and by a radio-oncologist and provided written informed consent in both institutions. Patient data were recorded independently at each institution, anonymized, and entered into a shared database as described recently.[10]

Before therapy, all patients underwent routine staging according to the European Association of Urology (EAU) recommendations.[11,12] Patients with a follow-up <24 months and initial PSA ≥20 ng/mL were excluded from evaluation (Table 1).

For risk categorization, both the EAU[1,12] and the NCCN classification system[13] was applied, with Grade group 1 and PSA <10 ng/mL for LR PCa and grade group 1 or 2 and/or PSA 10 to 20 ng/mL for IR PCa.

^{125}J brachytherapy was performed according to guidelines[3,4] using the real-time intraoperative planning method[14] with the planning program Variseed (version 8.0; Varian Medical Systems, Palo Alto, CA). The prescription dose was 160 Gy as recommended.[3,4,15,16] Intraoperative and 6 week–postoperative radiation doses were documented for quality control as proposed by Stock and Stone[15] and are reported elsewhere.[10,17] All involved institutions provided independent follow-up. Follow-up visits were appointed every 3 months for 2 years, every 6 months for another 2 years, and yearly thereafter.

For this comparison, cure was assumed at 48 months as described recently[8] either by the surgical definition for patients with a posttreatment PSA of ≤0.2 ng/mL[12,18] or by the Phoenix definition for patients without a nadir + 2 ng/mL PSA.[2,18] These 2 cohorts were analyzed separately for "failure of cure." Biochemical failure was assessed specifically (surgical or Phoenix) within each group. Metastatic disease was defined as bone, visceral, or lymph-node metastases on imaging. PCa-specific death was defined if the last PSA before death was >10 ng/mL or if distant metastatic disease or systemic antineoplastic therapy (other than androgen deprivation therapy) was documented before death.

The Kaplan-Meier product-limit method and the log-rank test were applied to estimate survival probabilities and compare survival, respectively. Validation of both cure definitions were calculated as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy.

Definitions were applied for this situation (given in italics) as published recently[17]:

- Sensitivity (*of cure definition*): Probability that a test result (*cure*) will be positive when the disease (*metastases*) is not present.
- Specificity (*of cure definition*): Probability that a test result (*cure*) will be negative when the disease (*metastases*) is not present.
- PPV (*of cure definition*): Probability that no disease (*metastases*) is present when the test (*cure*) is positive.
- NPV (*of cure definition*): Probability that disease (*metastases*) is present when the test (*cure*) is negative.
- Accuracy (*of cure definition*): Overall probability that a patient will be correctly classified (*as cured*).

Confidence intervals (CIs) for sensitivity, specificity, accuracy, and the predictive values were "exact" Clopper-Pearson, and the standard logit CI.[19,20] All analyses were performed descriptively, and *P* values are reported as descriptive measure for the strength of the evidence. Analyses were performed with SPSS version 2.6 (IBM Corp).

Table 1 Patient characteristics, with 2 cohorts of cure definition analyzed separately

Variable		Total	Low risk	Intermediate risk
Treated, n		735		
iPSA ≥20 ng/mL		15		
Follow-up ≤24 mo		134		
No PSA 3.5-4.5 y		129		
Phoenix recurrence <3.5 y		30		
Cure@48mo (all), n (%)		427	268 (62.8)	159 (37.2)
GS	**GG**			
6	1	329 (87)	268 (100)	61 (38.4)
7a	2	98 (23)	0	98 (61.6)
iPSA (ng/mL)				
Mean (range)		7.4 (0.5-19.8)	6.0 (0.5-9.9)	9.9 (3.2-19.8)
Median		6.70	6.0	9.46
<10, n (%)		350 (82)	268 (100)	82 (51.6)
10 to <20, n (%)		77 (18)	0	77 (48.4)
ADT, n (%)				
No ADT		397 (93.0)	260 (97)	137 (86.2)
<6 mo		14 (3.3)	3 (1.1)	11 (6.9)
6-12 mo		16 (3.7)	5 (1.9)	11 (6.9)
Age (y)				
Mean (range)		66.84 (47-82)	65.78 (47-81)	68.63 (48-82)
Median		67	66	70
Follow-up (y)				
Mean (range)		6.7 (3.5-14.7)	7.3 (3.6-14.7)	6.3 (3.5-14.1)
Cure@48mo (Phoenix), n		427	268	159
Follow-up (y)				
Median		6.6	7.3	6.3
Mean (range)		7.5 (3.5-14.7)	7.8 (3.6-14.7)	7 (3.5-14.1)
Cure after 48 mo, n (%)				
Yes		396 (93)	255 (95.1)	141 (89)
No		31 (7)	13 (4.9)	18 (11)
Metastases, n (%)				
Yes		9 (2)	4 (1.5)	5 (3)
No		418 (98)	264 (98.5)	154 (97)
Time to metastasis (mo), n		7.2	13	6.7
Dead of PCa, n		2	1	1
Dead other cause, n		21	8	13
Cure@48mo (surgical)		327	207	120
Follow-up (y)				
Median		6.7	7.3	6.3
Mean (range)		7.5 (3.5-14.6)	7.8 (3.7-14.7)	7.1 (3.6-14.1)

(*continued on next page*)

Table 1 (*Continued*)

Variable	Total	Low risk	Intermediate risk
Cure after 48 mo, n (%)			
Yes	314 (96)	200 (96.6)	114 (95)
No	13 (4)	7 (3.4)	6 (5)
Metastases, n			
Yes	1	0	1
No	326	207	119
Time to metastasis (mo)	24.8	-	24.8
Dead of PCa, n	0	0	0
Dead other cause, n	18	6	12

Abbreviations: ADT = androgen deprivation therapy; Cure@48mo (Phoenix) = no biochemical recurrence according to Phoenix definition at 48 months; Cure@48mo (surgical) = no biochemical recurrence according to surgical definition at 48 months; GG = World Health Organization grade group; GS = Gleason score; GSS = Gleason sum score; iPSA = initial prostate-specific antigen; PCa = prostate cancer; PSA = prostate-specific antigen.

Results

Of 735 patients, 134 were excluded for follow-up <24 months and 15 for PSA >20 ng/mL. For a reliable definition of cure at 48 months, a PSA had to be available between 3.5 and 4.5 years of follow-up, which was not the case in 129 patients. A Phoenix-defined biochemical recurrence occurred in 30 patients before 3.5 years of follow-up, leading to exclusion for this analysis.

Of the remaining 427 patients in the Phoenix-defined cure cohort, 268 (62.8%) had LR and 159 (37.2%) had IR PCa. Mean follow-up time was 7.5 years (range, 3.5-14.7).

One hundred patients never achieved a PSA ≤0.2 ng/mL within 48 months, so these were excluded from the surgical-defined–cure cohort. Of the remaining 327 patients in this cohort, 207 (63.3%) had LR and 120 (36.7%) had IR PCa. Mean follow-up time was 7.5 years (range, 3.5-14.6).

Patient characteristics are shown in Table 1.

During follow-up, the cure status remained unchallenged with regard to biochemical failure in 93% of patients (LR, 95.1%; IR, 89%) in the Phoenix-defined–cure cohort, and in 96% of patients (LR, 96.6%; IR, 96%) in the surgical-defined–cure cohort. Metastases occurred in 2% of the patients (n = 9; LR, 1.5; IR, 3%) in the Phoenix-defined cohort and in 1 patient (IR, 0.3%) in the surgical-defined cohort. Median time to metastasis was 7.2 and 24.8 months after a Phoenix-defined biochemical failure and a surgically defined failure, respectively. Cancer-specific death after cure was seen in 2 patients after Phoenix-defined cure and none after surgically defined cure (Table 1).

More patients experienced a biochemical recurrence (log-rank, $P = .062$; not significant.) (Fig. 1), and more patients developed metastasis in the Phoenix-defined–cure cohort compared with the surgical cohort (log-rank, $P = .033$) (Fig. 2). Biochemical recurrence–free survival at 5 and 10 years was 97.4% and 89%, respectively, for the Phoenix definition, and 98.2% and 92.7%, respectively, for the surgical definition. Metastasis-free survival at 5 and 10 years was 99.5% and 96.3%, respectively, for the Phoenix definition, and 100% and 99.4%, respectively, for the surgical definition (Table 2).

Next, we comparatively validated both definitions of cure with regard to "no metastatic failure" and "no cancer-specific death" using standard diagnostic test evaluations (Table 3). Both definitions of cure proved highly specific for the prediction of "no metastases" and "no cancer-specific death" (100% specificity for both predictions). Sensitivity of both definitions of cure predicting "no metastases" was 94.7% and 96.3% and for predicting "no cancer-specific death" 93.2% and 96.0% for the Phoenix and the surgical definition, respectively.

The PPV of both cure definitions reliably predicted cure (with the meaning of "no metastases or "no cancer-specific death") (both, PPV 100%), whereas the negative prediction of "no metastatic or no lethal failure" following a biochemical definition of cure was highly unreliable (NPV for "no metastases" 29% vs 7.7% and NPV for "no cancer-specific death" 6.4% vs 0% for Phoenix-defined cure vs surgical-defined cure, respectively). In summary, in this cohort of LR- and IR-PCa patients treated with LDR-BT, the overall probabilities (accuracies) of a correct prediction of cure with no metastases and no death of PCa were around 95% in all calculations (Table 3).

A comparison of cure rates of our LDR-BT cohorts to cure rates of published surgical interventions[21-24] was attempted using the surgical definition of cure (Table 4). Evidently, the results of LDR-BT favorably matched surgical cure rates at 5 and 10 years.

Discussion

In cancer therapy, and especially in the treatment of PCa, a definition of successful therapy resulting in cure is

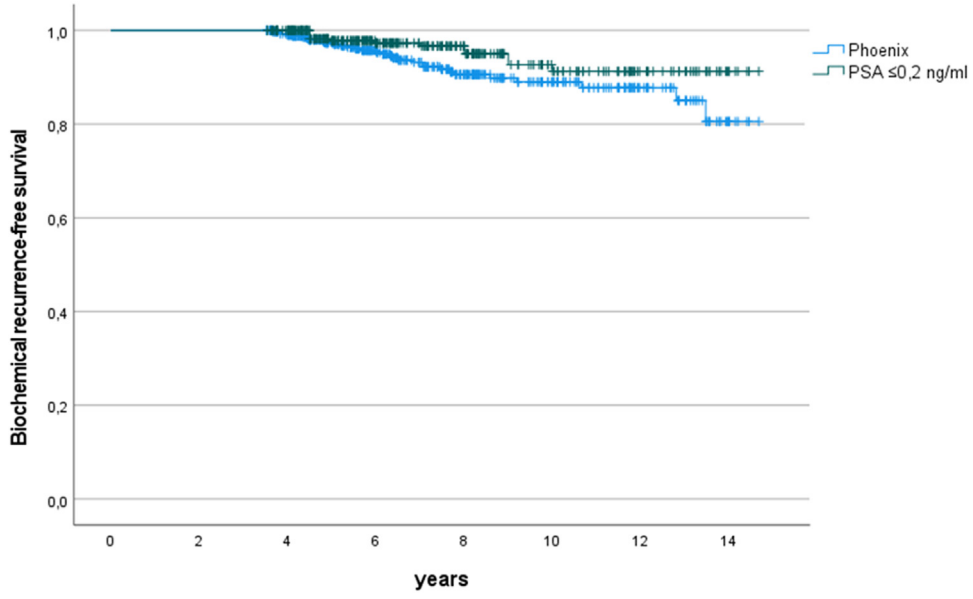

Figure 1 Biochemical recurrence–free survival of patients defined as "cured" at 48 months after low-dose-rate brachytherapy by Phoenix (blue) and surgical (green) definition (log-rank, $P = .062$; n.s.). *Abbreviations:* n.s. = not significant.

highly desirable because it may influence the pattern and frequency of follow-up and might convey confidence to the patient. Moreover, if a common definition of cure is found, results may be comparable across different treatment options. Previous reports have shown that, in contrast to other radiation modalities, LDR-BT may result in very low PSA levels which predict a sustained disease-free status.[25,26] In a post hoc analysis of the ASCENDE-RT trial[5,27] PSA ≤0.2 ng/mL was highly prognostic for recurrence-free survival in the subgroup of patients undergoing EBRT with a brachytherapy boost. In high-risk patients, a surgical PSA ≤0.2 ng/mL threshold for direct comparison of biochemical outcomes after combined-modality radiation therapy to surgery was recently suggested.[17] Finally, using a large heterogenous database of LR, IR, and high-risk patients treated by brachytherapy-monotherapy or

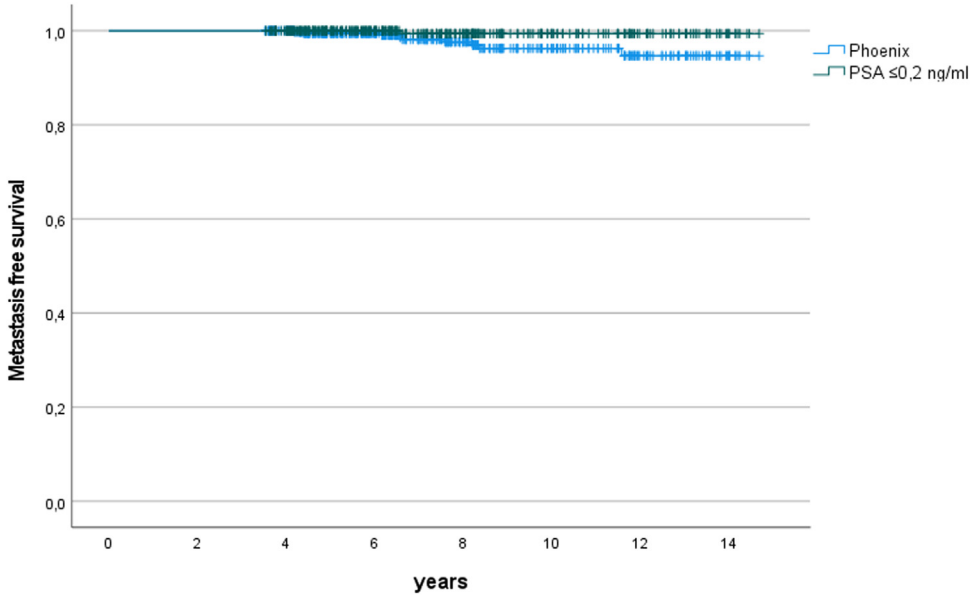

Figure 2 Metastasis-free survival of patients defined as "cured" at 48 months after low-dose-rate brachytherapy by Phoenix (blue) and surgical (green) definition (log-rank, $P = .033$).

Table 2 Biochemical recurrence–free survival rates and metastasis-free survival rates at 5 and 10 years in patients defined as "cured" at 48 months according to cure definition

"Cure" by definition	5-y survival	10-y survival	
Biochemical recurrence–free survival			
Phoenix	97.4%	89%	
Surgical	98.2%	92.7%	
Metastasis-free survival			
Phoenix	99.5%	96.3%	
Surgical	100%	99.4%	
"Cure" by definition	**No metastases**	**Metastases**	**Total**
Phoenix cure	396	0	396
No Phoenix cure	22	9	31
Total	418	9	427
Surgical cure	314	0	314
No surgical cure	12	1	13
Total	326	1	327
	No cancer-specific death	**Cancer-specific death**	
Phoenix cure	396	0	396
No Phoenix cure	29	2	31
Total	425	2	427
Surgical cure	314	0	314
No surgical cure	13	0	13
Total	327	0	327

combined-modality radiation therapy, Crook et al[8] proposed that a fixed PSA level of <0.2 ng/mL at 4 years after LDR-BT should be the new benchmark for cure instead of the established Phoenix criterion.

To assess the value of a fixed surgical definition of cure against the conventional Phoenix-derived dynamic definition,[2] we analyzed a more homogenous group of patients with LR and IR PCa treated with LDR-BT monotherapy and compared both definitions of cure with regard to later biochemical, metastatic, and cancer-specific lethal failure by standard test evaluation calculations. Further subclassification into favorable IR and unfavorable IR categories, as proposed recently,[28] was not done here. Still, with regard to different follow-up schedules after curative therapy, this may turn out promising.

Cure by both definitions was validated as highly sensitive, specific, and accurate. While the PPV of cure can be considered safe (PPV, 100% for both definitions), the

Table 3 Number of patients with "cure" at 48 months as defined by either Phoenix or surgical definition, patients who later experienced metastases or cancer-specific death, and corresponding validity analysis for cure by both definitions

Validity of "cure" at 48 mo	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
For no metastases					
By Phoenix definition	94.7% (92.1-96.7)	100% (66.4-100)	100%	29.0% (92.3-96.7)	94.8% (92.3-96.7)
By surgical definition	96.3% (93.6-98.1)	100% (2.5-100)	100%	7.7% (4.5-12.7)	96.3% (93.7-98.1)
For no cancer-specific death					
By Phoenix definition	93.2% (90.3-95.4)	100% (15.8-100)	100%	6.4% (4.6-8.9)	93.2% (90.4-95.4)
By surgical definition	96.0% (93.3-97.9)	-	100%	0	-

Abbreviations: CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value.

Table 4 Results of selected publications on long-term biochemical recurrence–free survival outcomes after radical prostatectomy and comparison with results after low-dose-rate brachytherapy using Phoenix-defined and surgically defined thresholds

	LDR brachytherapy		Radical prostatectomy surgical "cure"			
Risk Group	Phoenix "cure" (n = 427)	Surgical "cure" (n = 327)	Lantz et al[21] (n = 3232)	Zumsteg et al22* (n = 4760)	Sauter et al[23*] (n = 9228)	Meissner et al[24*] (n = 5693)
Follow-up (y)	5		-	5	5	5
LR	98.8%	98.9%	-	85%	95%	90%
IR	94.8%	96.9%	-	65%	83%	85%
Follow-up (y)	10		8	10	-	10
LR	91.6%	94%	84.2%	80%	-	80%
IR	84.4%	90.2%	71.6%	50%	-	75%

Abbreviations: LR = low risk; IR = intermediate risk; Phoenix "cure" = biochemical recurrence–free survival by Phoenix definition, prostate-specific antigen nadir + 2ng/mL; surgical "cure" = biochemical recurrence–free survival by surgical definition, prostate-specific antigen >0.2 ng/mL.
* Estimated from Kaplan-Meier plots.

NPV was unreliable. Thus, a patient who is considered cured at 4 years after brachytherapy, will reliably not have metastasis or die of PCa. On the other hand, a patient who is not considered cured at 4 years by any definition might nonetheless not experience metastasis or die of PCa.

Which definition of cure is to be preferred? In contrast to the opinion of McNeill et al,[9] there is no easy answer to this. First, it has to be kept in mind that the Phoenix definition of failure is highly accepted among radio-oncologists, and the discussion on cure selectively applies to patients treated by LDR-BT alone or in combination with EBRT. Therefore, as stated by Crook et al,[8] the established nadir + 2 ng/mL definition of failure should still be followed and should remain unchallenged. From this, it would only be a small step to define cure by having no Phoenix-defined failure at 48 months.

The most relevant benefit of a fixed surgical definition of cure using the ≤0.2 ng/mL threshold at 4 years after brachytherapy is to compare cure rates over different treatment modalities. Evidently, the results of LDR-BT in our analysis favorably matched surgical cure rates at 5 and 10 years. However, for this calculation, only patients with cure at 48 months after LDR-BT were assessed for a failure thereafter, leading to an exclusion of all patients who had a Phoenix-defined biochemical failure within these 4 years and of patients who never achieved a surgical-defined cure within 48 months. In contrast, assessment of surgical cure rates begins with the first PSA determination at 3 months after radical prostatectomy, leading to a lead-time bias favoring the results of radiation therapy. Thus, while we do not see a clear advantage of a fixed surgical definition of cure, the value of the concept still is appealing, as both definitions reliably predicted cure at 48 months. We therefore suggest that, regardless of the definition, patients cured after LDR-BT might follow a less stringent follow-up schedule from 4 years onward, whereas patients not achieving this status at 4 years should be closely monitored for an extended time.

Conclusion

We provided evidence that both definitions are useful for a reliable prediction of cure after LDR-BT.

References

1. Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer-2020 update. Part 1: Screening, diagnosis, and local treatment with curative intent. *Eur Urol*. 2021;79:243-262.
2. Abramowitz MC, Li T, Buyyounouski MK, et al. The Phoenix definition of biochemical failure predicts for overall survival in patients with prostate cancer. *Cancer*. 2008;112:55-60.
3. Davis BJ, Horwitz EM, Lee WR, et al. American brachytherapy society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy. *Brachytherapy*. 2012;11:6-19.
4. Rosenthal SA, Bittner NH, Beyer DC, et al. American Society for Radiation Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the transperineal permanent brachytherapy of prostate cancer. *Int J Radiat Oncol Biol Phys*. 2011;79:335-341.
5. Morris WJ, Pickles T, Keyes M. Using a surgical prostate-specific antigen threshold of >0.2 ng/ml to define biochemical failure for intermediate- and high-risk prostate cancer patients treated with definitive radiation therapy in the ascende-rt randomized control trial. *Brachytherapy*. 2018;17:837-844.
6. Taussky D, Lambert C, Meissner N, et al. Risk factors for biochemical recurrence after a tissue-ablative prostate-specific antigen <0.2 ng/ml. *Brachytherapy*. 2018;17:794-798.
7. Soyano T, Yorozu A, Natsume N, et al. Time to achieve a prostate-specific antigen nadir of ≤0.2 ng/ml and related factors after permanent prostate brachytherapy. *Brachytherapy*. 2021;20:29-37.
8. Crook JM, Tang C, Thames H, et al. A biochemical definition of cure after brachytherapy for prostate cancer. *Radiother Oncol*. 2020;149:64-69.

9. Alan McNeill S, Gallagher KM, Clyde D. Re: A biochemical definition of cure after brachytherapy for prostate cancer. *Eur Urol*. 2021;80:762-764.
10. Boehle A, Katic K, Konig IR, et al. Combined-modality (125)J-seed-brachytherapy, external beam radiation and androgen deprivation therapy of unfavorable-risk prostate cancer: Report of outcomes and side-effects. *World J Urol*. 2019;37:2355-2363.
11. Aus G, Abbou CC, Bolla M, et al. EAU guidelines on prostate cancer. *Eur Urol*. 2005;48:546-551.
12. Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: Screening, diagnosis, and local treatment with curative intent. *Eur Urol*. 2017;71:618-629.
13. Carroll PR, Parsons JK, Andriole G, et al. NCCN clinical practice guidelines prostate cancer early detection, version 2.2015. *J Natl Compr Canc Netw*. 2015;13:1534-1561.
14. Stock RG, Stone NN, Wesson MF, et al. A modified technique allowing interactive ultrasound-guided three-dimensional transperineal prostate implantation. *Int J Radiat Oncol Biol Phys*. 1995;32:219-225.
15. Stock RG, Stone NN. Importance of post-implant dosimetry in permanent prostate brachytherapy. *Eur Urol*. 2002;41:434-439.
16. Zelic R, Garmo H, Zugna D, et al. Predicting prostate cancer death with different pretreatment risk stratification tools: A head-to-head comparison in a nationwide cohort study. *Eur Urol*. 2020;77:180-188.
17. Boehle A, Katic K, Konig IR, et al. Comparison of outcome endpoints in intermediate- and high-risk prostate cancer after combined-modality radiotherapy. *Brachytherapy*. 2020;19:24-32.
18. Philipson RG, Romero T, Wong JK, et al. Patterns of clinical progression in radiorecurrent high-risk prostate cancer. *Eur Urol*. 2021;80:142-146.
19. Mercaldo ND, Lau KF, Zhou XH. Confidence intervals for predictive values with an emphasis to case-control studies. *Stat Med*. 2007;26:2170-2183.
20. Cornford P, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: Treatment of relapsing, metastatic, and castration-resistant prostate cancer. *Eur Urol*. 2017;71:630-642.
21. Lantz A, Bock D, Akre O, et al. Functional and oncological outcomes after open versus robot-assisted laparoscopic radical prostatectomy for localised prostate cancer: 8-year follow-up. *Eur Urol*. 2021;80:650-660.
22. Zumsteg ZS, Zelefsky MJ, Woo KM, et al. Unification of favourable intermediate-, unfavourable intermediate-, and very high-risk stratification criteria for prostate cancer. *BJU Int*. 2017;120:E87-E95.
23. Sauter G, Steurer S, Clauditz TS, et al. Clinical utility of quantitative gleason grading in prostate biopsies and prostatectomy specimens. *Eur Urol*. 2016;69:592-598.
24. Meissner VH, Woll M, Ankerst DP, et al. Long-term and pathological outcomes of low- and intermediate-risk prostate cancer after radical prostatectomy: Implications for active surveillance. *World J Urol*. 2021;39:3763-3770.
25. Lo AC, Morris WJ, Lapointe V, et al. Prostate-specific antigen at 4 to 5 years after low-dose-rate prostate brachytherapy is a strong predictor of disease-free survival. *Int J Radiat Oncol Biol Phys*. 2014;88:87-93.
26. Niwa N, Matsumoto K, Nishiyama T, et al. Selection of patients who would not require long-term prostate-specific antigen monitoring after low-dose-rate brachytherapy. *Brachytherapy*. 2018;17:899-905.
27. Gharzai LA, Jiang R, Wallington D, et al. Intermediate clinical endpoints for surrogacy in localised prostate cancer: An aggregate meta-analysis. *Lancet Oncol*. 2021;22:402-410.
28. Zumsteg ZS, Spratt DE, Pei I, et al. A new risk classification system for therapeutic decision making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy. *Eur Urol*. 2013;64:895-902.