CANCER DIAGNOSIS & PROGNOSIS
4: 715-721 (2024) doi: 10.21873/cdp.10386

Cribriform Pattern Is a Predictive Factor of PSA Recurrence in Patients Receiving Radiotherapy After Prostatectomy

MASAHIRO KAWAHARA[1], AKIRA TANAKA[2], KEIKO AKAHANE[1], MASASHI ENDO[3], YUKIKO FUKUDA[3], KOHEI OKADA[3], KAZUNARI OGAWA[3], SATORU TAKAHASHI[3], MICHIKO NAKAMURA[3], TSUZUMI KONISHI[4], KIMITOSHI SAITO[4], SATOSHI WASHINO[4], TOMOAKI MIYAGAWA[4], MASAHIRO HIRUTA[2], HISASHI OSHIRO[2], NORIKO OYAMA-MANABE[1] and KATSUYUKI SHIRAI[1,3]

[1]*Department of Radiology, Jichi Medical University Saitama Medical Center, Saitama, Japan;*
[2]*Department of Pathology, Jichi Medical University Saitama Medical Center, Saitama, Japan;*
[3]*Department of Radiology, Jichi Medical University Hospital, Tochigi, Japan;*
[4]*Department of Urology, Jichi Medical University Saitama Medical Center, Saitama, Japan*

Abstract. *Background/Aim: In prostate cancer, robotic total prostatectomy is a popular treatment modality. However, prostate-specific antigen (PSA) recurrence after prostate cancer surgery remains a concern. Salvage radiotherapy is commonly used to treat PSA recurrence, but the recurrence rate after salvage radiotherapy is high, highlighting the need for better predictive markers. This study aimed to retrospectively evaluate the association between cribriform pattern and PSA recurrence in patients receiving radiotherapy after radical prostatectomy. Patients and Methods: Data of 50 patients who underwent radiotherapy after total prostatectomy between January 2010 and May 2020 were retrospectively evaluated. The median age was 67 years. Among these patients, two cases involved postoperative irradiation, while 48 cases involved salvage irradiation after postoperative PSA recurrence. The median time from surgery to PSA recurrence was 38.3 months. The median radiation dose was 64 Gy in 32 fractions. Three-dimensional conformal radiation therapy was administered in 38 cases and intensity-modulated radiation therapy was used in 12 cases. Combined hormone therapy was administered in 21 cases. PSA levels were measured every 3 months after treatment. Statistical analysis between groups was performed by a t-test. Results: The median follow-up period after radiotherapy was 31 months. No local recurrences were observed at the prostate bed, and no deaths related to prostate cancer were recorded during follow-up. However, 18 patients (36.0%) had PSA recurrence. The PSA recurrence rate based on the cribriform pattern was 17.6% in the none to moderate group (34 patients) and 75.0% in the severe cribriform pattern group (16 patients). The PSA recurrence rate was significantly higher in patients with a severe invasive cribriform pattern (p=0.001). No significant differences were observed in other histopathological characteristics. Conclusion: The cribriform pattern in surgical pathology specimens was found to be a useful predictor of PSA recurrence after postoperative radiotherapy.*

Correspondence to: Masahiro Kawahara, Department of Radiology, Jichi Medical University Saitama Medical Center, 1-847 Amanumacho, Omiya-ku, Saitama-shi, Saitama 330-8503, Japan. Tel: +81 486472111, Fax: +81 486485188, e-mail: masahr.kawa@gmail.com

Key Words: Prostate cancer, postoperative radiation therapy, prostate-specific antigen (PSA) recurrence, Cribriform pattern.

Prostate cancer is the most common malignancy in men, and various treatment methods have been developed in recent decades. Surgery remains one of the most popular treatment options with robotic-assisted radical prostatectomy (RARP) becoming increasingly popular in many centers (1-2). Prostate-specific antigen (PSA) is a sensitive marker for prostate cancer, typically decreased to undetectable levels after radical prostatectomy. However, in some cases, PSA recurs after initially becoming undetectable. A Japanese study that analyzed the outcomes of cT1-2N0M0 prostate cancer patients who underwent radical prostatectomy without concomitant hormone therapy between 1993 and 2000 reported that PSA recurrence was observed in 25.3% of patients during a 45.6-month follow-up period (3).

Salvage radiotherapy is often performed in cases of PSA recurrence in patients following total prostatectomy (4).

However, in a study on a Japanese population, the PSA recurrence rate for postoperative salvage radiotherapy was 41.0%, suggesting that further studies are needed to improve the outcomes (5). Therefore, identifying factors that predict PSA recurrence after irradiation is crucial.

Predictors of prostate cancer recurrence include the rate of positive scores on prostate biopsy, PSA levels before prostatectomy, Gleason score, and T stage after surgery, all of which are associated with PSA recurrence. These postoperative risk factors contribute to predicting PSA recurrence (6). However, predictive factors specific to prostate cancer patients treated with salvage radiotherapy have not been fully evaluated. This study focused on histopathological factors as potential predictors of PSA recurrence in patients who underwent salvage radiotherapy. Specifically, we evaluated the cribriform pattern, Gleason score pattern 5 ratio, and perineural invasion, which are histopathological factors in prostate cancer specimens detected by our pathology department to investigate their association with postoperative PSA recurrence after irradiation.

By performing a pathological analysis using surgical specimens from patients who underwent total prostatectomy at our Institution, we aimed to determine whether there is a correlation between these pathological findings and PSA recurrence after postoperative salvage radiotherapy. This study aimed to clarify the relationship between pathological findings and PSA recurrence, potentially improving patient outcomes by identifying significant prognostic factors.

Patients and Methods

Patients. All 50 patients who underwent radiotherapy after total prostatectomy at our Center between 2010 and 2020 after total prostatectomy and pathological analysis were retrospectively evaluated. The prostate floor was delineated for the clinical target volume. The planning target volume included the clinical target volume with a 5-10 mm margin for set-up error. All patients provided written informed consent prior to radiotherapy. Gleason score pattern 5 ratio, cribriform pattern, and perineural invasion were evaluated as none, mild, moderate, or severe using surgical pathology specimens at our Hospital's pathology Department. Immunohistochemical analysis was performed to evaluate ETV1 and ERG protein expressions, together with PTEN loss, which were known as major chromosomal abnormalities in prostate cancer. Statistical analysis was performed using t-test and log-rank test. After treatment, PSA was measured every 3 months, and PSA >0.2 was considered PSA recurrence. $p<0.05$ was considered statistically significant. Analyses were performed using the SPSS software. This study was reviewed and approved by our Institutional Review Board (S20-055) and was performed in accordance with the Declaration of Helsinki.

Ethics approval and consent to participate. This study was reviewed and approved by our Institutional Review Board (S20-055) and was performed in accordance with the Declaration of Helsinki.

Results

Patient characteristics and treatment details. The median age was 67 (54-81) years. Among patients who underwent radiotherapy after total prostatectomy, the median time from prostatectomy to PSA recurrence was 12.0 months (range=1.94-60.35 months). The median time from prostatectomy to the start of irradiation was 13.6 months (2.6-61.8 months). Open radical prostatectomy was performed on 31 patients and RARP was performed on 19 patients. Postoperative radiotherapy was administered to 2 patients and salvage radiotherapy was administered to 48 patients. Three-dimensional conformal radiotherapy based on Computed Tomography (CT) simulation was performed on 38 patients, and the radiation dose was 64 Gy in 32 fractions. Intensity modulated radiation therapy based on CT simulation was performed on 12 patients, and the radiation dose was 66 Gy in 33 fractions. Hormonal therapy was not administered in all cases prior to undergoing total prostatectomy. Overall, 21 (42.0%) patients received neo-adjuvant or concurrent hormonal therapy (Androgen deprivation therapy: 14 patients, antiandrogen therapy: 7 patients).

Outcomes. The tumor stage was distributed as follows: pT2 (n=15; 30.0%), pT3a (n=18; 36.0%), and pT3b (n=17; 34.0%). A positive surgical margin was present in 27 cases (54.0%). The PSA levels before radiotherapy was distributed as follows: <0.2 (n=12; 24.0%), 0.2-0.5 (n=18; 36.0%), 0.5-1.0 (n=10; 20.0%), and >1.0 (n=9; 18.0%). The cribriform pattern was distributed as follows: none, <1% (n=1; 2.0%); small, 1<20% (n=16; 32.0%); moderate, 20<50% (n=17; 34.0%); and severe, >50% (n=16; 32.0%). Perineural infiltration was distributed as follows: none (n=6; 12.0%), small (n=22; 44.0%), moderate (n=15; 30.0%), and severe (n=7; 14.0%). Gleason pattern 5 ratio was distributed as follows: 0% (n=15; 30.0%), 0-10% (n=15; 30.0%), 10-30% (n=9; 18.0%), and >30% (n=11, 22.0%). No deaths related to prostate cancer were observed during follow-up; however, one patient died 48 months after radiotherapy owing to atrial fibrillation. Eighteen patients (36.0%) had PSA recurrence.

Statistical analysis. The correlation between clinical factors and PSA recurrence rate is shown in Table I, and the correlation between pathological factors and PSA recurrence rate is shown in Table II. The PSA recurrence rates of patients treated with and without hormonal therapy were 19.0% and 48.3%, respectively. The PSA recurrence rate based on the cribriform pattern was 17.6% in the none to moderate group (34 patients) and 75.0% in the severe group (16 patients). The PSA recurrence rate was significantly higher in cases with a severe cribriform pattern ($p=0.001$; Figure 1). The PSA recurrence rate for perineural invasion within the capsule was 34.9% for the none to moderate group (43 cases) and 42.9% for the severe group (7 cases), with no significant difference

Table I. *Correlation between clinical factors and PSA recurrence rate*.

Characteristics		N	%	PSA failure	%	*p*-Value
Pathological status	T2	15	30	5	33	
	T3a	18	36	8	44	
	T3b~T4	17	34	5	29	0.240
Surgical margin status	Negative	23	46	10	43	
	Positive	25	50	7	28	
	Unknown	2	4	1	50	0.272
Type of surgery	Open radical prostatectomy	19	38	8	42	
	RARP	31	62	10	32	0.491
Gleason Score	~6	1	2	0	0	
	7	23	46	8	35	
	8~10	26	52	10	38	0.593
RT techniques (Total dose)	3DCRT (64 Gy/32fr.)	38	76	16	42	
	IMRT (66 Gy/33fr.)	12	24	2	17	0.114
ADT	Yes	21	42	4	19	
	No	29	58	14	48	0.027
PSA level, before radiotherapy	<0.2	12	24	3	25	
	0.2~0.5	18	36	6	33	
	0.5~1.0	10	20	3	30	
	1.0<	9	18	6	67	
	Unknown	1	2	0	0	0.084

PSA, Prostate-specific antigen; RARP, robot-assisted laparoscopic radical prostatectomy; RT, radiation therapy; 3DCRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; Gy, gray; fr., fraction; ADT, androgen deprivation therapy.

Table II. *Correlation between pathological factors and PSA recurrence rate*.

Characteristics		N	%	PSA failure	%	*p*-Value
Cribriform pattern	None	1	2	0	0.0	
	Small	16	32	3	18.8	
	Moderate	17	34	3	17.6	
	Severe	16	32	12	75.0	0.001
Extracapsular extension	None	9	18	4	44.4	
	Small	17	34	3	17.6	
	Moderate	7	14	3	42.9	
	Severe	17	34	8	47.1	0.373
Perineural infiltration	None	6	12	2	33.3	
	Small	22	44	10	45.5	
	Moderate	15	30	3	20.0	
	Severe	7	14	3	42.9	0.679
Gleason pattern 5 ratio	0%	15	30	7	46.7	
	0~10%	15	30	5	33.3	
	10~30%	9	18	3	33.3	
	30%~	11	22	3	27.3	0.333

PSA, Prostate-specific antigen.

(p=0.679). The PSA recurrence rate for the group with a Gleason pattern 5 ratio of >30% was 27.3% in 11 cases, which was not significantly different (p=0.333).

ERG, and ETV1 chromosomal rearrangement were evaluated by immunostainings. ERG positive case was observed only 1, and ETV1 was positive in 19 cases, respectively. In addition, substantial areas with loss of PTEN expression was observed in 17 patients. However, these findings were not associated with cribriform pattern (Table II).

Discussion

This study investigated whether cribriform pattern was associated with biochemical recurrence-free survival in the 50

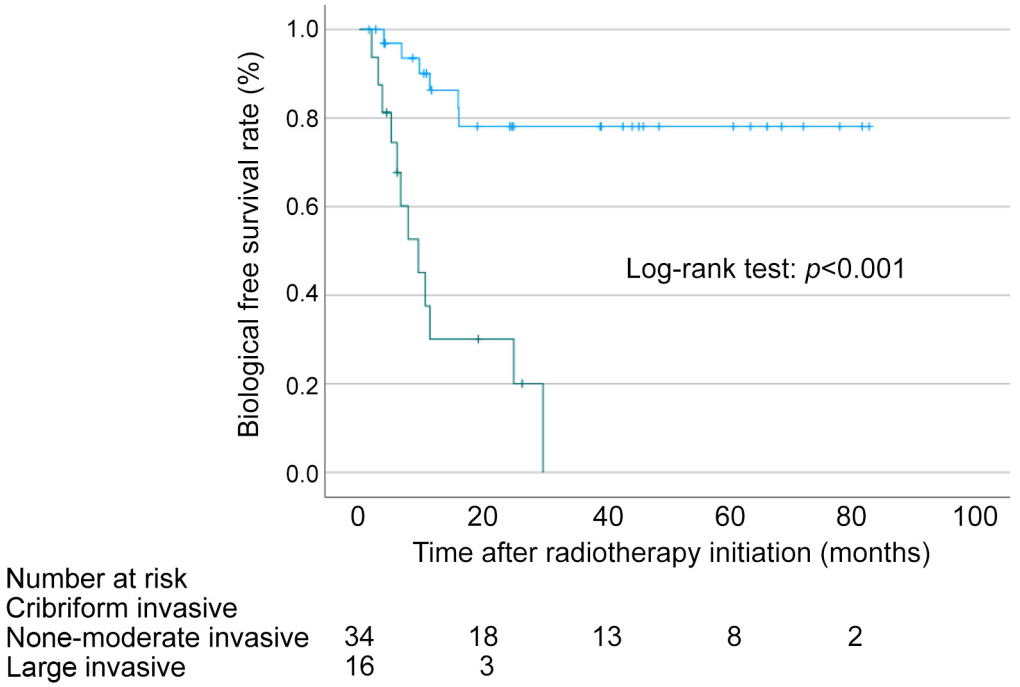

Figure 1. *Log-rank test of time to recurrence after irradiation for prostate-specific antigen recurrence after prostate cancer surgery, according to the incidence of cribriform pattern. Blue line: None to moderately invasive, green line: largely invasive.*

patients who received radiotherapy after radical prostatectomy. The PSA recurrence rates when the two groups were divided by the cribriform pattern of the prostate of surgical pathology specimens were 17.6% for the none to moderate (34 cases) group and 75.0% for the severe (16 cases) group; there was a significant difference (p=0.001). Other histopathological factors, such as the perineural invasion inside and outside the capsule and Gleeson pattern 5 ratio, did not show significance for PSA recurrence.

Gleason grade 4 prostate cancer comprises four main architectural growth patterns, specifically poorly formed, fused, and cribriform glands (Figure 2) (6-7). It is now well-established that, among these growth patterns, cribriform architecture in biopsies or radical prostatectomy specimens is strongly associated with a less favorable outcome (8-9).

Several reports have shown postoperative and radical radiotherapy outcomes for cribriform patterns using biopsy and resected pathology specimens. Ramotar *et al*. studied the improvement of treatment methods based on the results of radiation therapy and treatment after prostatectomy by observing the intraductal carcinoma and cribriform architecture and by using a 22-gene decipher genomic classifier. The study revealed that intraductal carcinoma, cribriform architecture, and the 22-gene decipher genomic classifier predict biochemical relapse and metastasis beyond conventional clinicopathologic indexes in a post-prostatectomy radiotherapy setting (10).

Hollemans *et al*. found that both invasive cribriform and intraductal carcinoma of the prostate have an impact on prognosis in radical total prostatectomy (11). The study reviewed 420 prostatectomy specimens from patients with The International Society of Urological Pathology (ISUP) grade 2 prostate cancer, assessed the percentages of Gleason grade 4 and tertiary 5, and performed immunohistochemistry for basal cells to differentiate intraductal carcinoma from invasive cribriform growth. Severe cribriform architecture was associated with older age, higher percentage of Gleason grade 4, extraprostatic expansion, and more frequent lymph node metastases. In multivariable Cox regression analysis, pT-stage, positive surgical margins, and severe cribriform growth were independent predictors for biochemical recurrence-free survival, whereas intraductal carcinoma, small cribriform growth, and percentage of Gleason grade 4 were not.

Tom *et al*. evaluated the effect of cribriform pattern and/or intraductal carcinoma on radiotherapy for prostate cancer patients with a Gleeson score of 7 (12). The study revealed that cribriform pattern with intraductal carcinoma was associated with adverse outcomes in men with Gleason 7 prostate cancer treated with radiotherapy, whereas cribriform pattern without intraductal carcinoma was not associated with adverse outcomes.

Radiation therapy for prostate cancer is effective in combination with radical external radiation and hormone

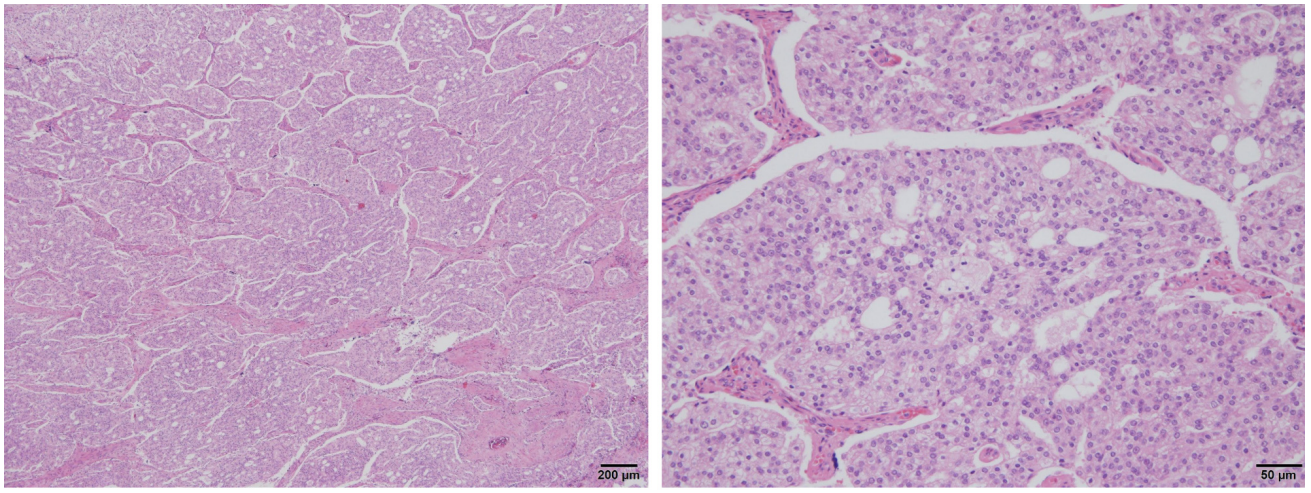

Figure 2. *Typical case of a high cribriform pattern. Low-magnification image (left) and high-magnification image (right).*

therapy, and as a control for recurrent cases after total prostatectomy, external irradiation to the prostate bed is effective as salvage therapy. However, the control rate of salvage radiotherapy was lower than that of radical radiotherapy. Therefore, we believe that some countermeasures are necessary in cases with severe cribriform disease. For this purpose, it is necessary to increase the prescribed irradiation dose. In our study, salvage radiotherapy was performed at 64-66 Gy; however, it is necessary to use a dose of 66 Gy or higher to avoid adverse events.

Pisansky *et al*. determined whether a dose-response relationship exists for salvage radiotherapy of biochemical failure after prostatectomy for prostate cancer. The study revealed that dose escalation to levels >66 Gy are associated with a reduced likelihood of biochemical failure after salvage radiotherapy in patients with post-radical prostatectomy (RP) detectable PSA levels (4).

King *et al*. analyzed through a systematic review and a meta-analysis, from 1996 to 2015, identified the pathologic, clinical, and treatment factors associated with relapse-free survival after salvage radiotherapy. The study reviewed level 2a evidence for dose-escalated salvage radiotherapy dose of 70 Gy or higher. Salvage radiotherapy dose–response for microscopic disease supports the hypothesis that prostate cancer is inherently radioresistant (13).

We also considered the significance of hormonal therapy in salvage treatment for the control of recurrent cases after total prostatectomy. In this study, we found that PSA recurrence after irradiation was suppressed in patients who received concomitant hormone therapy. Hormonal therapy in prostate cancer increases the control rate when combined with radiation therapy. The principle of hormone therapy is to reduce or block the male hormones (androgens) that contribute to prostate cancer development, thereby reducing the effect of testosterone on prostate cancer and temporarily suppressing its growth (14-16). Radiation therapy for localized prostate cancer is generally categorized according to risk, presence or absence of adjuvant hormone therapy, and duration of adjuvant hormone therapy (12-14). In the current study, there was a significant difference in PSA recurrence rates between patients with and without hormonal therapy for the first PSA after prostate cancer surgery. This suggests that hormonal therapy may be beneficial in patients with a large cribriform pattern (17, 18). Recently, a brand-new drug, oral recombinant methioninase, has been reported to suppress PSA level in advanced prostate cancer patients (19). Further studies are warranted to establish the strategy for a combination of drugs and radiotherapy.

Clinical and pathological factors that predict cribriform pattern are important. Mikoshi *et al*. reported that MRI-detectability of prostate cancer was associated with cribriform pattern (20). ERG, PTEN, and ETV1 rearrangements were reported as potential molecular markers for cribriform lesion (21, 22); However, this study did not show the associations. Future studies are needed to identify radiological or molecular markers that can assist in diagnosing the cribriform pattern.

Recently, the efficacy of prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT)-guided salvage radiotherapy has been reported (23). A complete clinical response of approximately 70% at one year after irradiation especially in patients with low PSA levels, indicating that early detection of PSA recurrence and appropriate salvage radiotherapy contribute to improved prognosis. Juracek *et al*. reported that a logistic regression model combining the miR-335:miR-501 ratio, PSA, and prostate volume data was significantly more discriminating in

predicting prostate biopsy results than standalone parameters (24). Considering the results of our study on Cribriform pattern and prognosis prediction, it is expected that the relationship between Cribriform pattern and PSMA PET/CT or miR-335:miR-501 can lead to the development of more sophisticated prognostic predictions (23, 24).

The present study had several limitations. It was a retrospective single-center study with a small sample size. Further prospective studies are warranted to evaluate cribriform pattern as a predictive factor in prostate cancer.

Conclusion

Cribriform pattern in surgical pathology specimens was found to be a useful predictor of PSA recurrence after postoperative radiotherapy.

Conflicts of Interest

The Authors declare that there are no conflicts of interest.

Authors' Contributions

Kawahara M, Tanaka A and Shirai K established the study design and directed the analysis. Tanaka A, Hiruta M and Oshiro H contributed to validation of pathological data. Kawahara M and Shirai K analyzed the data and contributed to the analysis of the results and performed the statistical analysis. Tanaka A, Miyagawa T and Shirai K supervised the project. All Authors reviewed the manuscript.

Acknowledgements

We would like to thank Editage (www.editage.com) for English language editing.

References

1 Du Y, Long Q, Guan B, Mu L, Tian J, Jiang Y, Bai X, Wu D: Robot-assisted radical prostatectomy is more beneficial for prostate cancer patients: a system review and meta-analysis. Med Sci Monit 24: 272-287, 2018. DOI: 10.12659/msm.907092

2 Cao L, Yang Z, Qi L, Chen M: Robot-assisted and laparoscopic vs open radical prostatectomy in clinically localized prostate cancer: perioperative, functional, and oncological outcomes: A Systematic review and meta-analysis. Medicine (Baltimore) 98(22): e15770, 2019. DOI: 10.1097/MD.0000000000015770

3 Yokomizo A, Murai M, Baba S, Ogawa O, Tsukamoto T, Niwakawa M, Tobisu K, Kinukawa N, Naito S: Percentage of positive biopsy cores, preoperative prostate-specific antigen (PSA) level, pT and Gleason score as predictors of PSA recurrence after radical prostatectomy: a multi-institutional outcome study in Japan. BJU Int 98(3): 549-553, 2006. DOI: 10.1111/j.1464-410X.2006.06379.x

4 Pisansky TM, Agrawal S, Hamstra DA, Koontz BF, Liauw SL, Efstathiou JA, Michalski JM, Feng FY, Abramowitz MC, Pollack A, Anscher MS, Moghanaki D, Den RB, Stephans KL, Zietman AL, Lee WR, Kattan MW, Stephenson AJ, Tendulkar RD: Salvage radiation therapy dose response for biochemical failure of prostate cancer after prostatectomy—a multi-institutional observational study. Int J Radiat Oncol Biol Phys 96(5): 1046-1053, 2016. DOI: 10.1016/j.ijrobp.2016.08.043

5 Shirai K, Suzuki M, Akahane K, Takahashi Y, Kawahara M, Yamada E, Wakatsuki M, Ogawa K, Takahashi S, Minato K, Hamamoto K, Saito K, Oshima M, Konishi T, Nakamura Y, Washino S, Miyagawa T: Dose-volume histogram-based predictors for hematuria and rectal hemorrhage in patients receiving radiotherapy after radical prostatectomy. In Vivo 34(3): 1289-1295, 2020. DOI: 10.21873/invivo.11904

6 Verhoef EI, van Cappellen WA, Slotman JA, Kremers GJ, Ewing-Graham PC, Houtsmuller AB, van Royen ME, van Leenders GJLH: Three-dimensional analysis reveals two major architectural subgroups of prostate cancer growth patterns. Mod Pathol 32(7): 1032-1041, 2019. DOI: 10.1038/s41379-019-0221-0

7 van Leenders GJLH, Verhoef EI, Hollemans E: Prostate cancer growth patterns beyond the Gleason score: entering a new era of comprehensive tumour grading. Histopathology 77(6): 850-861, 2020. DOI: 10.1111/his.14214

8 van Leenders GJLH, Kweldam CF, Hollemans E, Kümmerlin IP, Nieboer D, Verhoef EI, Remmers S, Incrocci L, Bangma CH, van der Kwast TH, Roobol MJ: Improved prostate cancer biopsy grading by incorporation of invasive cribriform and intraductal carcinoma in the 2014 grade groups. Eur Urol 77(2): 191-198, 2020. DOI: 10.1016/j.eururo.2019.07.051

9 van der Kwast TH, van Leenders GJ, Berney DM, Delahunt B, Evans AJ, Iczkowski KA, McKenney JK, Ro JY, Samaratunga H, Srigley JR, Tsuzuki T, Varma M, Wheeler TM, Egevad L: ISUP consensus definition of cribriform pattern prostate cancer. Am J Surg Pathol 45(8): 1118-1126, 2021. DOI: 10.1097/PAS.0000000000001728

10 Ramotar M, Chua MLK, Truong H, Hosni A, Pintilie M, Davicioni E, Fleshner NE, Dicker AP, Bristow RG, He HH, van der Kwast T, Den RB, Berlin A: Subpathologies and genomic classifier for treatment individualization of post-prostatectomy radiotherapy. Urol Oncol 40(1): 5.e1-5.e13, 2022. DOI: 10.1016/j.urolonc.2021.08.013

11 Hollemans E, Verhoef EI, Bangma CH, Rietbergen J, Helleman J, Roobol MJ, van Leenders GJLH: Large cribriform growth pattern identifies ISUP grade 2 prostate cancer at high risk for recurrence and metastasis. Mod Pathol 32(1): 139-146, 2019. DOI: 10.1038/s41379-018-0157-9

12 Tom MC, Nguyen JK, Lucianò R, Mian OY, Stephans KL, Ciezki JP, Smile TD, Wei W, McKenney JK, Magi-Galluzzi C, Tendulkar RD: Impact of cribriform pattern and intraductal carcinoma on gleason 7 prostate cancer treated with external beam radiotherapy. J Urol 202(4): 710-716, 2019. DOI: 10.1097/JU.0000000000000316

13 King CR: The dose-response of salvage radiotherapy following radical prostatectomy: A systematic review and meta-analysis. Radiother Oncol 121(2): 199-203, 2016. DOI: 10.1016/j.radonc.2016.10.026

14 Grozescu T, Popa F: Prostate cancer between prognosis and adequate/proper therapy. J Med Life 10(1): 5-12, 2017.

15 Van Poppel H, Abrahamsson PA: Considerations for the use of gonadotropin-releasing hormone agonists and antagonists in patients with prostate cancer. Int J Urol 27(10): 830-837, 2020. DOI: 10.1111/iju.14303

16 Spratt DE: Evidence-based risk stratification to guide hormone therapy use with salvage radiation therapy for prostate cancer. Int J Radiat Oncol Biol Phys 102(3): 556-560, 2018. DOI: 10.1016/j.ijrobp.2018.06.037

17 Shipley WU, Seiferheld W, Lukka HR, Major PP, Heney NM, Grignon DJ, Sartor O, Patel MP, Bahary JP, Zietman AL, Pisansky TM, Zeitzer KL, Lawton CA, Feng FY, Lovett RD, Balogh AG, Souhami L, Rosenthal SA, Kerlin KJ, Dignam JJ, Pugh SL, Sandler HM, NRG Oncology RTOG: Radiation with or without antiandrogen therapy in recurrent prostate cancer. N Engl J Med 376(5): 417-428, 2017. DOI: 10.1056/NEJMoa1607529

18 Carrie C, Hasbini A, de Laroche G, Richaud P, Guerif S, Latorzeff I, Supiot S, Bosset M, Lagrange JL, Beckendorf V, Lesaunier F, Dubray B, Wagner JP, N'Guyen TD, Suchaud JP, Créhange G, Barbier N, Habibian M, Ferlay C, Fourneret P, Ruffion A, Dussart S: Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial. Lancet Oncol 17(6): 747-756, 2016. DOI: 10.1016/S1470-2045(16)00111-X

19 Han Q, Hoffman RM: Chronic treatment of an advanced prostate-cancer patient with oral methioninase resulted in long-term stabilization of rapidly rising PSA levels. In Vivo 35(4): 2171-2176, 2021. DOI: 10.21873/invivo.12488

20 Mikoshi A, Miyai K, Hamabe F, Edo H, Ito K, Matsukuma S, Tsuda H, Shinmoto H: MRI-detectability and histological factors of prostate cancer including intraductal carcinoma and cribriform pattern. Prostate 82(4): 452-463, 2022. DOI: 10.1002/pros.24291

21 Han B, Suleman K, Wang L, Siddiqui J, Sercia L, Magi-galluzzi C, Palanisamy N, Chinnaiyan AM, Zhou M, Shah RB: ETS gene aberrations in atypical cribriform lesions of the prostate. Am J Surg Pathol 34(4): 478-485, 2010. DOI: 10.1097/PAS.0b013e3181d6827b

22 Downes MR, Satturwar S, Trudel D, Van Der Kwast TH: Evaluation of ERG and PTEN protein expression in cribriform architecture prostate carcinomas. Pathol Res Pract 213(1): 34-38, 2017. DOI: 10.1016/j.prp.2016.10.007

23 Tamburo M, Buffettino E, Pepe P, Marletta G, Pepe L, Cosentino S, Ippolito M, Pennisi M, Marletta F: Salvage radiotherapy PSMA PET/CT-guided in men with PSA recurrence. Anticancer Res 44(5): 2205-2210, 2024. DOI: 10.21873/anticanres.17027

24 Juracek J, Madrzyk M, Trachtova K, Ruckova M, Bohosova J, Barth DA, Pichler M, Stanik M, Slaby O: Combination of urinary MiR-501 and MiR-335 with current clinical diagnostic parameters as potential predictive factors of prostate biopsy outcome. Cancer Genomics Proteomics 20(3): 308-316, 2023. DOI: 10.21873/cgp.20383

Received June 3, 2024
Revised July 30, 2024
Accepted August 20, 2024