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ORIGINAL ARTICLE

The Significance of Accurate Determination of Gleason Score for Therapeutic Options and Prognosis of Prostate Cancer

Burkhard Helpap[1] · **Daniel Ringli**[1] · **Jens Tonhauser**[2] · **Immanuel Poser**[3] · **Jürgen Breul**[3] · **Heidrun Gevensleben**[4] · **Hans-Helge Seifert**[2]

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Abstract The Gleason score (GS) to date remains one of the most reliable prognostic predictors in prostate cancer (PCa). However, the majority of studies supporting its prognostic relevance were performed prior to its modification by the International Society of Urological Pathology (ISUP) in 2005. Furthermore, the combination of Gleason grading and nuclear/nucleolar subgrading (Helpap score) has been shown to essentially improve grading concordance between biopsy and radical prostatectomy (RP) specimens. This prompted us to investigate the modified GS and combigrading (Gleason/Helpap score) in association with clinicopathological features, biochemical recurrence (BCR), and survival. Core needle biopsies and corresponding RP specimens from 580 patients diagnosed with PCa between 2005 and 2010 were evaluated. According to the modified GS, the comparison between biopsy and RP samples resulted in an upgrading from GS 6 to GS 7a and GS 7b in 65 % and 19 %, respectively. Combigrading further resulted in an upgrading from low grade (GS 6/2a) to intermediate grade PCa (GS 6/2b) in 11.1 % and from intermediate grade (GS 6/2b) to high grade PCa (GS 7b/2b) in 22.6 %. Overall, well-differentiated PCa (GS 6/2a) was detected in 2.8 % of RP specimens, while intermediate grade (GS 6/2b and GS 7a/2b) and high grade cancers (≥ GS 7b) accounted for 39.5 % and 57.4 % of cases, respectively. At a mean follow-up of 3.9 years, BCR was observed in 17.6 % of patients with intermediate (9.8 %) or high grade PCa (30.2 %), while PSA relapse did not occur in GS 6/2a PCa. In conclusion, adding nuclear/nucleolar subgrading to the modified GS allowed for a more accurate distinction between low and intermediate grade PCa, therefore offering a valuable tool for the identification of patients eligible for active surveillance (AS).

Keywords Prostate · Carcinoma · Gleason and combigrading · Prognosis · PSA progress · Survival

Introduction

The Gleason grading system to date remains one of the most robust and powerful prognostic predictors in prostate cancer (PCa) [1]. Particularly during the past decade, Gleason scoring has experienced several refinements yielding better prognostic accuracy. In 2005, the Gleason score (GS) was essentially modified at the International Society of Urological Pathology (ISUP) conference. Several tumor growth patterns previously considered Gleason grade 3 were redefined as Gleason grade 4, resulting in disease upgrading [2]. Additionally, overall GS 2-4 were excluded altogether for the diagnosis of peripheral PCa [2, 3]. Recent recommendations by Jonathan Epstein in 2010 have further limited the definition of pattern 3 carcinomas [3]. However, the majority of studies supporting the prognostic relevance of the GS were performed prior to the aforementioned modifications [4–6], and so far only few more recent publications refer to the modified criteria of Gleason grading [7–10]. Furthermore, PCa with a GS 7 is considered one prognostic group in some studies, whereas other reports

✉ Burkhard Helpap
burkhard.helpap@hbh-kliniken.de

[1] Department of Pathology, Hegau-Bodensee Hospital of Singen, PO Box 720, 78207 Singen, Germany

[2] Department of Urology, Hegau-Bodensee Hospital of Singen, Singen, Germany

[3] Department of Urology and Urologic Oncology, Loretto Hospital, Freiburg, Germany

[4] Institute of Pathology, University Hospital Bonn, Bonn, Germany

respect the distinction between GS 7a (3 + 4) and GS 7b (4 + 3) [11–18].

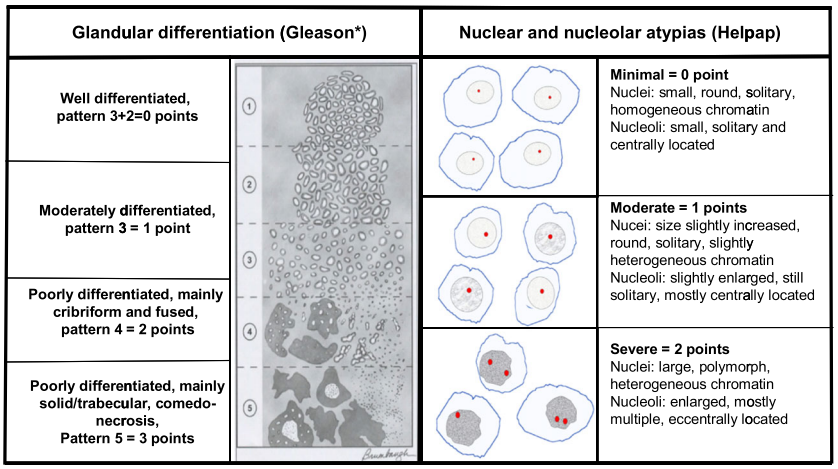
But how accurate is the Gleason grading for therapeutic decision making and prognosis? Recently, an upgrading from GS 6 to GS 7a (3 + 4) has been demonstrated by several studies addressing the significance of the GS modification [19–24]. However, the ISUP 2005 recommendations for Gleason grading are often misinterpreted, resulting in a high interobserver variability [25]. Comparative studies have shown increased agreement between biopsy and radical prostatectomy (RP) specimens using the modified GS, although not exceeding a concordance of 70 % [15]. In contrast, the combination of Gleason grading and nuclear/nucleolar subgrading (Helpap score) has been shown to improve grading accuracy, leading to an agreement of 85–90 % between biopsy and RP samples [26, 27]. Briefly, this histological and cytological combigrading (Gleason/Helpap score) is based on the five histological patterns of the Gleason grading system, as well as on the nuclear pattern (i.e. size, morphology, and chromatin quality) and nucleolar atypia (i.e. number, grade of nucleolar prominence, and location within the nucleus) (Fig. 1). It resembles the proposal made by Mostofi in 1999 to supplement the Gleason scoring with the WHO nuclear and nucleolar grading scheme [28] and was included in the modified WHO/Mostofi grading system of 2002 [29].

In the present study, we analyzed the modified GS and histological and cytological combigrading (Gleason/Helpap score) in biopsy and corresponding RP specimens in association with clinicopathological features, biochemical recurrence (BCR) and cancer specific death. In particular, we focused on the question as to whether combigrading may help to identify patients with insignificant PCa, which are eligible for active surveillance (AS) [30–34].

Methods

Core needle biopsies and corresponding RP specimens from 580 patients diagnosed with prostate cancer at the Department of Pathology, General Hospital Singen, Singen, Germany between 2005 and 2010 were included in the present study. Following tissue fixation in 4 % formaldehyde and paraffin-embedding, sections were cut and stained with hematoxylin-eosin.

Diagnostic analyses were performed by two independent observers (He, Oe). Biopsy and RP specimens were graded according to the modified Gleason grading (2010) as previously described (Fig. 1) [3]. For the overall GS, the most frequent and the worst GS pattern were assessed, and a tertiary pattern was included if present [22]. In addition to the evaluation of glandular differentiation using the Gleason grading system, nuclear and nucleolar atypia were determined [26, 27, 35]. Briefly, the scoring included nuclear size, chromatin quality, and the number and localization of nucleoli in the nuclei. Finally, four grades of decreasing glandular differentiation and three grades of increasing nuclear atypia were combined, resulting in the combined histoarchitectural and cytological grading (Gleason/Helpap score). The staging of PCa in RP specimens was based on the current TNM classification (UICC, 7th edition, 2010). The organ-confined tumor stage pT2 was further divided into subgroups (pT2a, pT2b, and pT2c) in accordance with the



Histol. score (Gleason)	Histol.-cytol. Pattern (Helpap)	Helpap score	Combined score (Gleason/Helpap)
2 – 5	0 or 1	1a, b	GS 2-5 / 1a, b
6, 7a, 7b	2 or 3	2a, b	GS 6 /2a, GS 7a, b/ 2b
8 – 10	4 or 5	3a, b	GS 8 – 10 / 3a, b

*Modification 2010

Fig. 1 Combined histological and cytological grading for prostate cancer including latest modification of Gleason grading [10], modified by Helpap and Köllermann [27]

Table 1 Comparison between biopsy and radical prostatectomy specimens according to Gleason grading

	GS of RP					
GS of biopsy	6	7a	7b	8	9	total n/%
6	18 (16.2 %)	72 (64.9 %)	21 (18.9 %)	0	0	111 (19.1 %)
7a	0	129 (61.1 %)	77 (36.5 %)	2 (0.9 %)	3 (1.4 %)	211 (36.4 %)
7b	0	9 (5.0 %)	140 (77.8 %)	25 (13.9 %)	6 (3.3 %)	180 (31.0 %)
8	0	0	19 (34.6 %)	36 (65.4 %)	0	55 (9.5 %)
9	0	0	0	2 (8.7 %)	21 (91.3 %)	23 (4.0 %)
total n	18 (3.1 %)	210 (36.2 %)	257 (44.3 %)	65 (11.2 %)	30 (5.2 %)	580 (100 %)

proposal of several ISUP members regarding a prospective TNM classification. This proposed subclassification defines pT2a tumors as cancers with the largest tumor dimension ≤5 mm, pT2b tumors as cancers with the largest tumor dimension >5 mm but ≤16 mm, and pT2c tumors as cancers with the largest tumor dimension >16 mm in both lobes of the prostate [36]. Along with the tumor dimension, positive surgical margins, lymph node metastases, and tumor volume were recorded. A positive margin was documented if tumor cells extended to the margin marked with drawing ink.

Categorical variables were analyzed using the Chi square and Fisher's exact test. Follow-up data were retrieved in 86.4 % of cases (484/580) with a mean follow-up of 3.9 years. BCR, the rate of cancer specific death (death of disease, DoD), and death without disease (DwD) between 2005 and 2013 were recorded. Survival analysis was performed using the Kaplan-Meier method. A p value of 0.05 was considered statistically significant.

Results

The patients' mean age at diagnosis was 66.6 years (range 50–80 years). The comparison between biopsy and RP samples according to the modified Gleason grading resulted in an upgrading from GS 6 to GS 7a and GS 7b in 64.9 % (72/111) and 18.9 % (21/111), respectively (Table 1). Combigrading (Gleason/Helpap score) further resulted in an upgrading from GS 6/2a to GS 6/2b in 11.1 % ($p = 0.0068$). Within the intermediate group, GS 6/2b carcinomas were upgraded to GS 7a/2b and GS 7b/2b in 77.4 % (72/93) and 22.6 % (21/93), respectively ($p < 0.0001$), (Table 2). Additionally, the discrimination of GS 6 cancers by combigrading in biopsy and RP specimens was shown to be highly significant ($p < 0.0001$). The agreement within the high grade group (≥ GS 7b) on the other hand ranged from 65.5 % to 91.3 %, and 5.0–25.5 % of cases were downgraded (Table 2).

The overall frequency of well-differentiated PCa (GS 6/2a) was low, ranging between 3.1 % (all 580 cases) and 2.8 % (484 cases with clinical follow-up) in RP specimens (Tables 1 and 2). Intermediate grade carcinomas (GS 6/2b and GS 7a/2b) accounted for 39.9 % (193/484) of cases, while 57.4 % (278/484)($p = 0.0013$) of tumors were assigned to the high grade group (43.8 % GS 7b, 8.9 % GS 8, and 4.7 % GS 9), ($p < 0.0001$), (Tables 4 and 5). No significant difference was seen in the age of the patients (67.0–71.3 years).

A total of 49.7 % (241/484) of cancers presented as organ-confined disease (7.6 % pT2a, 42.1 % pT2b and pT2c), while extraprostatic extension (pT3-4) was documented in 50.3 % (243/484) of cases (Tables 4 and 5). Well-differentiated carcinomas according to the Gleason grading (GS 6) tended to be small (73.3 % pT2a, 20.0 % pT2b and pT2c, and 6.7 % pT3a),(<0.0001) (Table 3); an association that was highlighted in GS 6/2a carcinomas using the combigrading (84.6 % pT2a,

Table 2 Comparison between biopsy and radical prostatectomy specimens according to combigrading (Gleason/Helpap score)

	GS of RP						
GS of biopsy	6/2a	6/2b	7a/2b	7b/2b, 3a	8/2b, 3a	9/3a, 3b	total n/%
6/2a	16 (88.9 %)	2 (11.1 %)	0	0	0	0	18 (3.1 %)
6/2b	0	0	72 (77.4 %)	21 (22.6 %)	0	0	93 (16.0 %)
7a/2b	0	0	129 (61.1 %)	77 (36.5 %)	2 (1.0 %)	3 (1.4 %)	211 (36.4 %)
7b/2b, 3a	0	0	9 (5.0 %)	140 (77.8 %)	25 (13.9 %)	6 (3.3 %)	180 (31.0 %)
8/2b, 3a	0	1 (1.8 %)	1 (1.8 %)	17 (30.9 %)	36 (65.5 %)	0	55 (9.5 %)
9/3a, 3b	0	0	0	1 (4.3 %)	1 (4.3 %)	21 (91.3 %)	23 (4.0 %)
total n	16 (2.8 %)	3 (0.5 %)	211(36.4 %)	256(44.1 %)	64(11.0 %)	30 (5.2 %)	580 (100 %)

Table 3 Association of Gleason score with tumor stage

	pT2a	pT2b, c	pT3a	pT3b	pT4	total n/%
GS 6	11 (73.3 %)	3 (20.0 %)	1 (6.7 %)	0	0	15 (3.1 %)
GS 7a	19 (9.9 %)	118 (61.7 %)	47 (24.6 %)	4 (2.1 %)	3 (1.6 %)	191 (39.5 %)
GS 7b	0	77 (36.3 %)	103 (48.6 %)	16 (7.5 %)	9 (4.3 %)	212 (43.8 %)
GS 8	0	6 (13.9 %)	13 (30.2 %)	10 (23.3 %)	14 (32.6 %)	43 (8.9 %)
GS 9	0	0	9 (39.1 %)	8 (34.8 %)	6 (26.1 %)	23 (4.7 %)
total n	16 (2.8 %)	204 (42.1 %)	173(35.8 %)	38 (7.9 %)	32(6.6 %)	484 (100 %)

15.4 % pT2b and pT2c) (Table 4) and shown to be significant ($p = 0.0034$), despite the small number of well-differentiated carcinomas. Positive surgical margins (R1) were observed in 23.1 % (112/484) of patients with intermediate grade carcinomas (10.9 %, 21/193) and high grade PCa (32.7 %, 91/278) (Table 5). Lymph node metastases were found in 3.6 % (12/329) of cases, including only intermediate grade (1.4 %, 3/212) and high grade carcinomas (13.6 %, 9/66) (Table 5).

At a mean follow-up of 3.9 years, BCR was recorded in 17.6 % (85/484) of cases (74 patients with RP, 5 patients with RP and radiation therapy, 3 patients with RP and hormone treatment, and 3 patients with RP and combined radiation and hormone treatment). PSA relapse was observed in 9.8 % of GS 7a carcinomas with an average interval of 3.8 years after RP, in 22.6 % of GS 7b carcinomas 2.7 years after RP, and in 27.3 % of GS 8-9 carcinomas 3 years after RP (Table 5). PSA levels were not available for 58 patients. For further details on BCR in association with clinicopathological parameters see Table 5.

Between 2005 and 2013, only four patients died with or from PCa, resulting in low DwD and DoD rates of 1.7 % and 0.8 %, respectively (Table 5). All patients with disease-related cause of death (DoD) presented with poorly differentiated PCa (GS 8-9), extraprostatic tumor extension (pT3), positive resection margins (R1), and lymph node metastases at the time of RP. The cancer specific mortality rate for GS 8-9 PCa was 6.1 %. The Kaplan-Meier plot revealed a decreasing probability of prostate-specific survival (0.998 after 33 months, 0.995 after 42 months, 0.992 after 43 months, and 0.985 after 71 months) (Fig. 2).

Discussion

Gleason Grading and Treatment The modifications of the Gleason grading system in 2005 and 2010 have resulted in an upgrading from GS 6 to GS 7a (3 + 4) in biopsy and RP specimens [3, 15, 21, 24, 37]. The redefined criteria for the accurate diagnosis of GS 6 exclude poorly formed and fused glands. Cytological criteria (e.g. size, prominence, number and localization of nucleoli within nuclei) have been shown to further limit the diagnosis of low grade, early stage pT2a PCa [27]. These amendments have clearly narrowed the definition of patients eligible for the therapeutic option of AS [26, 38].

Comparative studies on biopsy and RP specimens have shown that GS 6 carcinomas with activated nucleoli, hence resembling GS 7a (3 + 4) PCa, are associated with increased tumor stages (pT2c) [35]. This group of tumors may correspond with the low grade cancer group of D'Amico and Epstein, which were upgraded from GS 6 to GS 7 in 32–34 %. As a result, low grade cancers without further subgrading may potentially receive undergrading in up to 30 % of primary biopsies [39]. According to our previous results, 35 % of GS 7a (3 + 4) cancers present with a tumor stage pT3 at the time of diagnosis [35]. Compared to low grade PCa, these cancers show significant differences in grading and staging and are therefore assigned to the intermediate grade group [35], which in principle, does not qualify for the therapeutic option of AS. However, the question as to whether these cancers might also be eligible for AS ultimately needs to be ascertained by future clinical trials such as the German cancer study PREFERE [40].

Table 4 Association of combigrading (Gleason/Helpap score) with tumor stage

	pT2a	pT2b, c	pT3a	pT3b	pT4	total n/%
GS 6/2a	11(84.6 %)	2 (15.4 %)	0	0	0	13 (2.7 %)
GS 6/2b	0	1 (50.0 %)	1 (50.0 %)	0	0	2 (0.4 %)
GS 7a/2b	19 (9.9 %)	118 (61.7 %)	47 (24.6 %)	4 (2.1 %)	3 (1.6 %)	191 (39.5 %)
GS 7b/2b	7 (3.3 %)	77 (36.3 %)	103 (48.6 %)	16 (7.5 %)	9 (4.3 %)	212 (43.8 %)
GS 8/2b, 3a	0	6 (13.9 %)	13 (30.2 %)	10 (23.3 %)	14 (32.6 %)	43 (8.9 %)
GS 9/2b, 3a	0	0	9 (39.1 %)	8 (34.8 %)	6 (26.1 %)	23 (4.7 %)
total n	37 (7.6 %)	204 (42.1 %)	173(35.8 %)	38(7.9 %)	32(6.6 %)	484 (100 %)

Table 5 Association of combigrading, Gleason score, stage (pT), surgical margins (R) and lymph node metastases (pN1) with PSA-recurrence, DoD, and DwD after RP (2005–2013)

Hist.-Cyt. Combi-Score of PCa after RP			Bioch. Rec.			DoD		DwD
	n	%	N	%	yrs p.op.	n	yrs p.op.	n
GS 6/2a	13	2.7	-			-		-
GS 6/2b	2	0.4	-			-		-
GS 7a/2b	191	39.5	19	9.8	3.8	-		4
GS 7b/2b, 3a	212	43.8	48	22.6	2.7	-		4
GS 8/2b, 3a	43	8.9	13	30.2	2.6	2	4.3	-
GS 9/3a	23	4.7	5	21.7	3.5	2	3.5	-
pT2a	37	7.6	-			-		-
pT2b, c	204	42.1	25	12.3	3	-		6
pT3a	173	35.8	36	20.8	3.3	-		2
pT3b	38	7.9	13	34.2	2.9	1	3.6	-
pT4	32	6.6	11	34.4	2	3	4.1	-
R1	112/484	23.1	28	25.0	2.9	4	3.9	1
Intermediate	21/193	10.9	2		-	-		-
high grade	91/278	32.7	26	28.6	2.7	4	3.9	1
pN1	12/329	3.6	4	33.3	1.7	4	3.9	-
GS 7b	3/212	1.4	1					
GS 8, 9	9/66	13.6	3					
total n	484		85	17.6	2.8	4	3.9	8
Average time of observation	5.3 yrs							

Certainly, these results emphasize the pressing need for discriminators to reliably distinguish between low and intermediate grade PCa; particularly since intermediate grade cancers were predominantly classified as GS 6 prior to the modification of Gleason grading [17, 20, 21, 41].

Biochemical Recurrence and Survival According to the criteria of ISUP and combigrading, none of the patients with low grade PCa (GS 6/2a) in our study developed BCR, while PSA relapse occurred in 9.8 % of GS 7a (3 + 4) carcinomas 3.8 years after surgery and in 22.6 % of GS 7b (4 + 3) cancers

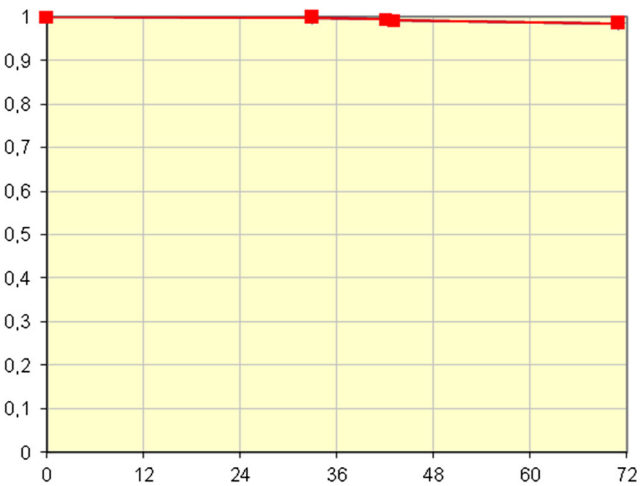


Fig. 2 Kaplan-Meier plot showing prostate-specific survival (months)

2.7 years after RP. These results are in line with previous findings based on the data of 2551 PCa patients. In the Hopkins study, BCR was detected in only 0.5 % of organ-confined GS 6 cancers within 5 years after RP [42]. For the heterogeneous group of GS 7 PCa, PSA recurrence rates were shown to be mainly dependent on the extent of the Gleason 4 pattern [14, 15]. The five-year actuarial risk of BCR in GS 7a and GS 7b carcinomas was reported with 19 % and 47 %, respectively [43]. Additionally, the Gleason 4 component was associated with cancer-related mortality [16, 42]: five years after RP, BCR-free survival rates were reported with 88.1 % for GS 7a, 69.7 % for GS 7b, 63.7 % for GS 8, and 34.5 % for GS 9-10 carcinomas [43, 44]. Intermediate grade cancers (GS 6/2b and GS 7a/2b) with stages pT2b and pT2c correspond with the former group of GS 6 with low DoD rates, whereas the current group of GS 7b PCa is comparable with the former GS 7 group. No differences between the previous and modified GS were seen for high grade cancers (GS 8-10), although the number of PCa after RP certainly was very limited.

Insignificant, low Grade Prostate Cancer In our study, not a single patient with organ-confined or low grade PCa (GS 6/2a) died of his disease within 5–10 years after RP. This observation is supported by results from the Hopkins study [42], in which BCR-free survival improved incrementally with well-differentiated PCa, ranging between 95 % and 99 % (Table 6) [44]. If PSA values remained below 10 ng/ml during the first 10–15 years, the mortality rate was further shown to be <3 %

Table 6 Gleason grading and survival in literature

Grading-Staging	Survival 5–10- 15 Yrs	Death	Ref.
Low grade GS 6 (2a) pT2a	95–99 % (96.6 %)	1.0 %	Pierorazio 2013, Isbarn 2010 [44, 45]
Low-intermediate grade GS 6 (2b) - GS 7a pT2 (pT3a)	83–88 % (88.1 %)		Chun 2006, Ward 2005 [52, 53]
Intermediate - high grade GS 7b pT2-pT3a	70–80 % (69.7 %)		Pierorazio 2013 [44]
High grade GS 8 GS 9-10 ≥pT2-pT3-pT4	(63.7 %) 20–30 % (34.5 %)		Andreoiu 2010, Chun 2006, Ward 2005, Pierorazio 2010, Pierorazio 2013, Isbarn 2013 [49, 52, 53, 54, 44, 47]

in organ-confined GS 6 carcinomas, irrespective of whether patients were treated or not [45]. In fact, the discussion is recently ongoing as to whether these tumors should be treated or even be labelled "cancer" at all [25, 38, 41].

Concerning this matter, combigrading may provide additional information essential for therapeutic decision making. Our results have shown that in contrast to GS 6/2a carcinomas with a bland nuclear morphology, GS 6/2b cancers with prominent nucleoli show a biological behavior resembling GS 7a PCa [35]. These findings are in agreement with results published by the Scandinavian prostate cancer group and observations by Isbarn and Huland, who studied the outcome of patients with GS 6 carcinomas [45, 46]. Hence, GS 6 cancers with cytological atypia might need to be excluded from AS. Therefore, awaiting the results from the German PREFERE study would imply a particular risk, as this trial studies AS in patients with intermediate grade carcinomas [40].

Intermediate and High Risk Prostate Cancer According to the literature, the 10-year survival rate of patients with intermediate grade carcinomas (GS 6/2b and GS 7a) accounts for 88 %, not significantly differing between organ-confined (pT2) and more advanced PCa (pT3). For GS 7b carcinomas and high grade cancers, decreasing ten-year survival rates of 70 % and 63–20 % have been reported (Table 6). Fortunately, the results for high grade PCa have been more promising in recent studies, demonstrating a cancer-specific 10-year survival of 98 % (pT3a), 87 % (pT3b), and 77 % (pT4) [47]. In our present study, cancer-related death only occurred in high grade PCa (Fig. 2).

Conclusion

Based on our studies, we conclude that GS 6 carcinomas without cytological atypia, less than 50 % tumor infiltration within one lobe, and a distribution in no more than two adjacently located biopsy specimens (for a total of 10 or 12 biopsies) meet the criteria of low grade PCa [8, 48]. These tumors correspond with stage pT2a cancers (<5 mm tumor diameter) with tumor-free surgical margins and without metastases in RP specimens. With the exclusion of clinical sampling error, these patients will not develop PSA recurrence [8, 46, 47, 49], and therefore AS remains the therapy of choice for this patient group [27]. The question as to whether intermediate grade PCa might also be eligible for AS ultimately needs to be ascertained by future clinical trials such as the German cancer study PREFERE [40]. However, adding combigrading to the modified GS allowed for a more accurate distinction between low and intermediate grade PCa in the present study, therefore offering a valuable tool for the prognostically relevant discrimination of PCa correlating with the study of Montironi et al. [50, 51].

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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