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REVIEW

Impact of comedonecrosis on prostate cancer outcome: a systematic review

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Impact of comedonecrosis on prostate cancer outcome: a systematic review

Cribriform architecture has been recognised as an independent parameter for prostate cancer outcome. Little is yet known on the added value of individual Gleason 5 growth patterns. Comedonecrosis is assigned Gleason pattern 5 and can occur in both invasive and intraductal carcinoma. The aim of this study is to systematically review the literature for the prognostic value of comedonecrosis in prostate cancer. A systematic literature search of Medline, Web of Science, Cochrane library and Google scholar was performed according to the Preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines. After identification and screening of all relevant studies published up to July 2022, 12 manuscripts were included. Clinicopathological data were extracted and the presence of comedonecrosis in either invasive, intraductal or ductal carcinoma was associated with at least one clinical outcome measure. No meta-analysis was performed. Eight of 11 studies showed that comedonecrosis was significantly associated with biochemical recurrence and two studies with metastasis or death. The only studies using metastasis-free and disease specific-free survival as an endpoint both found comedonecrosis to be an independent prognostic parameter in multivariate analysis. The studies were all retrospective and demonstrated considerable heterogeneity with regard to clinical specimen, tumour type, grade group, correction for confounding factors and endpoints. This systematic review demonstrates weak evidence for comedonecrosis to be associated with adverse prostate cancer outcome. Study heterogeneity and lack of correction for confounding factors prohibit drawing of definitive conclusions.

Keywords: comedonecrosis, cribriform, ductal, intraductal, prostate cancer, review

Introduction

The Gleason grading system is one of the most powerful predictors of outcome in prostate cancer (PCa) patients. PCa growth patterns are categorised into three groups, i.e. Gleason patterns 3, 4 and 5. The most prominent and highest patterns are added to a final Gleason score in biopsies; in radical prostatectomy specimens the Gleason score is composed of the two most common patterns, as long as high-grade tertiary patterns do not exceed 5% of the tumour volume.[1] Clinical outcome measures such as biochemical recurrence-, metastasis- and disease-specific-free survival are all strongly correlated with Gleason score.[2]

Gleason patterns 4 and 5 both encompass tumours with various architectural features. Gleason pattern 4 is assigned to poorly formed, fused, glomeruloid and cribriform glands. During the last decade, many groups have shown that cribriform architecture has independent prognostic value on top of the Gleason score.[3–5] Cribriform growth can occur both in invasive tumour structures as well as in pre-existent

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prostate acini, the latter being referred to as intraductal carcinoma (IDC). Invasive cribriform and intraductal carcinoma often coincide, and both are associated with adverse outcome.[4] Therefore, the International Society of Urological Pathology (ISUP) and Genitourinary Pathology Society (GUPS) both recommend including the presence of invasive cribriform and/or intraductal carcinoma explicitly in pathology reports.[1,6]

Gleason pattern 5 encompasses tumours growing as individual cells, cords, linear arrays and solid nests. Furthermore, presence of comedonecrosis within a solid or cribriform structure is also assigned Gleason pattern 5. Currently, it is unclear whether any of the individual Gleason 5 patterns has added clinical value, such as cribriform architecture among Gleason pattern 4 tumours.

Comedonecrosis has been shown to have a prognostic impact in some genitourinary malignancies, such as renal cell carcinoma and upper tract urothelial carcinoma.[7,8] In renal cell carcinoma, the presence of necrosis is even a component of the Leibovich score, estimating the individual risk of development of metastasis after operation.[9] Little is yet known as to whether comedonecrosis also has independent added prognostic value in PCa (Figure 1). Therefore, in this study we sought to systematically review the literature on comedonecrosis in prostate adenocarcinoma in relation to clinical outcome.

Methods

PROTOCOL AND REGISTRATION

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[10,11] The protocol for this systematic review was registered at the International Prospective Registry of Systematic Reviews (PROSPERO) (registration ID: CRD42022364802) before starting the research, according to the PRISMA guidelines.

SEARCH STRATEGY AND REVIEW

A computerised literature search of Embase, Medline, Web of Science, the Cochrane library and Google Scholar was conducted for all peer-reviewed studies that reported on comedonecrosis and PCa. The search strategy was devised in collaboration with a trained librarian and comprised a combination of the following keywords: 'comedonecrosis', 'prostate' and 'cancer', including all relevant variations. Details of the search strategy are provided in Supporting information, Appendix S1. We searched the database from inception until 30 June 2022. References of selected studies were searched for additional records that were not identified through the database search. Two reviewers (K.A., L.K.) independently screened the title and abstract of each record using EndNote.[12] Articles included for full text evaluation by only one of the reviewers were discussed at a consensus meeting with a third reviewer (G.v.L.). Subsequently, full text evaluations of selected records were performed by K.A. and L.K., and appropriate studies were identified by prespecified inclusion and exclusion criteria.

ELIGIBILITY CRITERIA

Manuscripts were eligible for inclusion if comedonecrosis was described in the context of acinar adenocarcinoma, ductal adenocarcinoma or intraductal carcinoma of the prostate and at least one prognostic outcome measurement was reported, such as tumour stage, biochemical recurrence, metastasis or death. Reports on geographical necrosis, treatment-related necrosis or other types of necrosis were excluded. Other exclusion criteria were: reviews and meta-

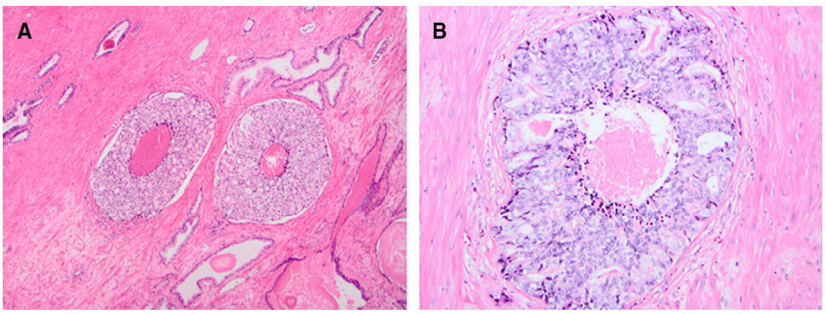

Figure 1. Comedonecrosis in prostate adenocarcinoma.

analyses containing no original data, case reports, non-human studies and non-English reports. Conference abstracts published within the last 3 years were included. Conference abstracts published more than 3 years ago were considered to be either published or of insufficient quality to be accepted for publication, and therefore excluded from the search.

DATA EXTRACTION AND PROCESSING

The following information was extracted from each record: authors, publication date, journal, diagnosis*, number of patients*, number of patients with comedonecrosis*, number of patients in the control group*, control group definition*, prognostic outcome measurements*, definition of the prognostic outcome measurement, how prognostic outcome was measured and reported, diagnostic criteria and guidelines, definition of comedonecrosis, whole slides or tissue micro-array, specimen type* (e.g. biopsy or radical prostatectomy), profession of the reviewer of the histological slides, if the study was blinded, inclusion dates, inclusion and exclusion criteria, time of follow-up and statistical approach; data marked by * were extracted by two reviewers (K.A., L.K.) independently.

RISK OF BIAS ASSESSMENT

Risk of bias was assessed using the quality in prognostic studies (QUIPS) tool.[13] Manuscripts were considered to have low, intermediate or high risk of bias on each of the following subcategories: study participation, prognostic factor measurement, outcome measurement, study confounding and statistical approach and analysis.

STATISTICAL APPROACH

Data are presented descriptively. The small number and heterogeneity of studies prohibited meta-analysis. Data sharing is not applicable to this article, as no new data were created or analysed in this study.

Results

GENERAL CHARACTERISTICS AND DATA DISTRIBUTION

Our search strategy yielded 4446 records, reduced to 2709 after de-duplication. After screening titles and abstracts, 2671 articles were excluded. Thirty-eight articles were eligible for full text evaluation. Twenty-six articles were excluded, while 12 were included in this review (Figure 2). Patients were recruited between 1983 and 2019. The 2016 World Health Organisation (WHO), 2014 and 2019 ISUP recommendations were used in all manuscripts on acinar adenocarcinoma, one on ductal adenocarcinoma and one on intraductal carcinoma ($n = 8$).[14–21] The remaining four manuscripts used either Epstein's ($n = 2$)[22,23] or McNeal's ($n = 1$)[24] criteria for IDC, while one report on comedonecrosis in ductal adenocarcinoma[25] did not specify formal diagnostic criteria. One study explicitly provided a definition of comedonecrosis, i.e. a group of cells with clear karyorrhexis, pyknosis, cytoplasmic condensation, and accompanying eosinophilic necrotic debris present in cribriform or solid invasive adenocarcinoma.[15] Nine studies were on radical prostatectomy specimens,[14–16,18,20–22,24,25] two on biopsies,[19,23] and one on both specimen types.[17] Ten studies explicitly stated they used whole slides for review.[14–19,22–25] In nine studies, slides were reviewed by at least one pathologist[14,15,18–24] who was explicitly blinded for clinical outcome in seven studies.[14,18–22,24]

In total, 4059 patients were included in the 12 studies, 410 of whom were reported to have comedonecrosis (Table 1). The mean patients' ages ranged from 59 to 72 years. Six reports focused upon comedonecrosis in acinar adenocarcinoma, four in IDC and two in ductal carcinoma. Biochemical recurrence (BCR) was included as an endpoint in 10 manuscripts and was defined as two consecutive postoperative serum prostate-specific antigen (PSA) values of ≥ 0.2 ng/ml,[18,20,25] one postoperative PSA level ≥ 0.2 ng/ml,[14–17,21,22] and one postoperative PSA ≥ 0.4 ng/ml.[24] Metastasis-free survival,[18] PCa-specific mortality,[19] overall and castration-resistant PCa-free survival[23] were each investigated by one study. Other clinical outcome measures were evaluated in four manuscripts, including pathological stage, tumour volume, extraprostatic extension, seminal vesicle involvement, lymph node involvement or surgical margin status.[15,17,21,24] Median time of follow-up was ≥ 12 months for eight studies and not specifically recorded for the other four.[14,18,19,21]

STUDY DETAILS

In a series of 49 grade group 5 radical prostatectomies, Flood *et al.*[14] found comedonecrosis in 26 cases (53%). Of 28 patients treated by radical prostatectomy as monotherapy, 18 (64%) suffered from BCR. Comedonecrosis was found in 11 of 18 men (61%) with BCR and none of those without ($P = 0.002$). Cribriform glands were identified in all except one patient. Sheets, small solid cylinders, IDC and ductal

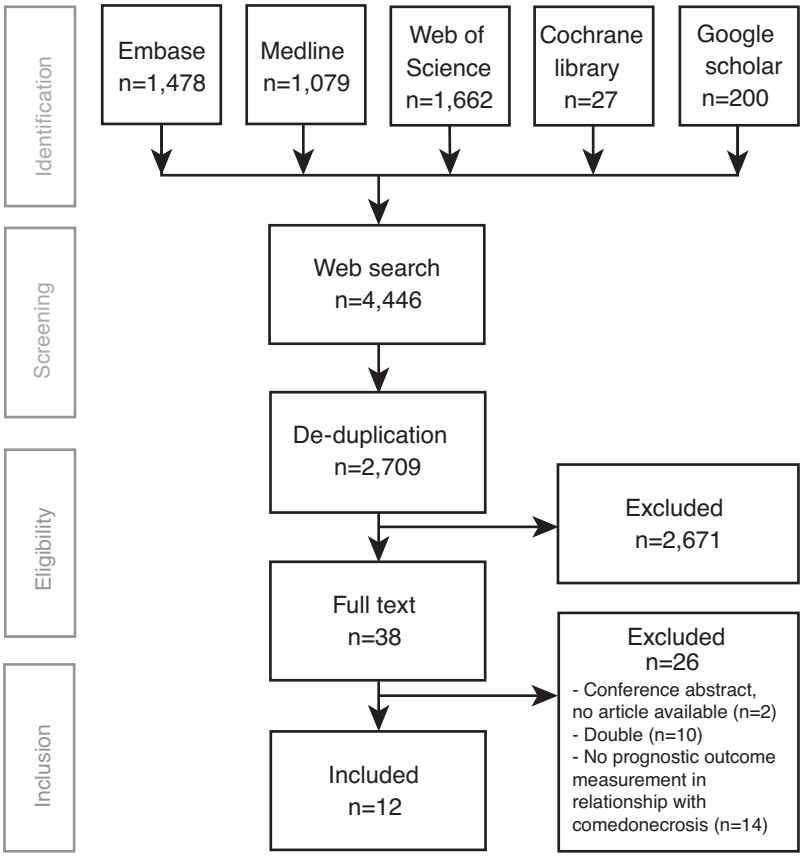

Figure 2. Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flowchart.

morphology were all significantly enriched in men with BCR compared to those without. It was not explicitly stated whether comedonecrosis was assessed in invasive cribriform, solid and/or intraductal carcinoma. Multivariable analysis was not performed.

Acosta *et al.*[15] investigated the clinicopathological features of 56 PCa patients with primary or secondary Gleason pattern 5, selected originally from a cohort of 344 consecutive radical prostatectomies. The authors found comedonecrosis within invasive tumour glands in 18 of 56 (32%) cases. Gleason pattern 5 with comedonecrosis was associated with significantly higher tumour volume ($P < 0.0001$), pT-stage ($P = 0.004$) and seminal vesicle invasion ($P = 0.02$), and showed a trend towards more frequent lymph node metastasis ($P = 0.07$). Biochemical recurrence occurred in 11 of 18 (61%) men with comedonecrosis and in 10 of 38 (26%) of those without ($P = 0.006$). No multivariate analysis was performed.

In a series of 163 grade groups 1–5 radical prostatectomies, Dere *et al.*[16] identified nine (5.5%) cases with comedonecrosis. Biochemical recurrence occurred more frequently ($P = 0.008$) in patients with comedonecrosis. No subgroup or multivariate analysis were performed.

In a cohort of 646 grade group 5 biopsies, Franklin *et al.*[17] observed comedonecrosis in 119 (18%) cases without distinguishing its occurrence in invasive and intraductal carcinoma. In a subset of 472 men who had undergone operation, comedonecrosis at biopsy was predictive for high tumour volume (> 3 cm^3) at radical prostatectomy ($P = 0.023$) and weakly, albeit not statistically significant, associated with extraprostatic extension ($P = 0.056$). No association was found between biopsy comedonecrosis and seminal vesicle ($P = 0.133$) or lymph node involvement ($P = 0.319$). In 338 patients with a median follow-up of 12 months, 112 (33%) developed BCR. Comedonecrosis was not associated with biochemical recurrence-free survival ($P = 0.366$).

Hansum *et al.*[18] studied 1064 patients with grade groups 1–5 PCa at radical prostatectomy, 32 of whom (3%) had comedonecrosis in invasive carcinoma. In the subgroup of grade group 5 tumours, 17 (14%) had comedonecrosis within invasive cribriform or solid

Table 1. Detailed overview of studies included in the systematic review on comedonecrosis

First author	References	Publication year	Tumour type	Specimen type	Grade group	Number of patients	Comedonecrosis	Comedonecrosis in invCR or IDC	Outcome measure	Significant relation with outcome	Uni-/ multivariate analysis	Correction for grade group	Correction for invasive cribriform/ intraductal ca
Flood	14	2018	Acinar	RP	GG 5	49	26	NS	BCR	Yes	Univariate	GG 5 only	No
Acosta	15	2018	Acinar	RP	GG 4 and 5	56	18	invCR	pT stage, SVI, TV, BCR	Yes	Univariate	No	No
									EPE, PSM, LNI	no			
Dere	16	2018	Acinar	RP	GG 1–5	163	9	NS	BCR	Yes	Univariate	No	No
Franklin	17	2021	Acinar	PBx	GG 5	646	119	invCR and IDC	TV	Yes	Uni/ multivariate	GG 5 only	No
									EPE, SVI, LNI, BCRFS	No	Univariate		
Hansum	18	2021	Acinar	RP	GG 1–5	1064	32	invCR	BCRFS, MFS	Yes	Multivariate	Yes	Yes
Zelic	19	2022	Acinar	PBx	GG 1–5	738	29	NS	PCSM	Yes	Multivariate	Yes	No
Wilcox	24	1998	Acinar	RP	GG 1–5	252	12	IDC	SVI, TV	No	Univariate	No	No
									BCRFS	Yes			
Zhao	23	2015	Acinar	PBx	GG 1–5	278	36	IDC	overall survival	Yes	Univariate	No	No
									CRPCFS	No			
Diop	22	2021	Acinar	RP	GG 1–5	108	23	IDC	early BCR	Yes	Univariate	No	No
									BCRFS	No			
Wang	21	2022	Acinar	RP	GG 2–5	558	46	IDC	GG, pT3, TV, pN1, BCRFS	Yes	Uni/ multivariate	Yes	Yes
Seipel	25	2013	Ductal	RP	GG 2–5	86	27	Ductal	BCRFS	No	Univariate	No	No
Jeong	20	2017	Ductal	RP	GG 2–5	61	17	Ductal	BCRFS	Yes	Univariate	Yes	No
										No	Multivariate		

EPE, extraprostatic extension; PSM, Positive surgical margin; LNI, lymph node invasion; BCRFS, biochemical recurrence-free survival; MFS, metastasis-free survival; PCSM, prostate cancer-specific mortality; CRPCFS, castration-resistant prostate cancer-free survival; RP, radical prostatectomy; PBx, prostate biopsy; GG, grade group; NS, not specified; invCR, invasive cribriform pattern; IDC, intraductal carcinoma; BCR, biochemical recurrence; PSA, prostate-specific antigen; SVI, seminal vesicle involvement; TV, tumour volume.

sheets. After a median follow-up of 64 months for the entire cohort (n = 1064), 342 (32%) men had biochemical recurrence and 136 (13%) developed postoperative or distant metastasis. In multivariate analysis adjusted for PSA, pT-stage, grade group, surgical margin status, lymph node metastasis at time of operation, cribriform architecture and medium to large solid sheets, comedonecrosis was significantly associated with biochemical recurrence-free survival [hazard ratio (HR) = 2.1, 95% confidence interval (CI) = 1.3–3.2, P = 0.001] and metastasis-free survival (HR = 2.1, 95% CI = 1.2–3.7, P = 0.01). While cribriform architecture was also significantly associated with both outcome measures, small solid nests and medium to large solid fields were not.

In a nested case–control study including 738 men with grade groups 1–5 PCa, Zelic *et al.*[19] found that comedonecrosis was present in 29 (4%) of biopsies. Comedonecrosis was present in 27 of 369 (7%) men who died of disease and 0.5% of controls. In a multivariate model including grade group, cT-stage, age and PSA, comedonecrosis was an independent parameter [odds ratio (OR) = 5.1, 95% CI = 1.2–21] for PCa-specific death.

In a study of 252 grade groups 1–5 radical prostatectomies from 1998, Wilcox *et al.*[24] was the first to report on the impact of IDC morphological subpatterns. In that study, 108 (43%) men had IDC, 12 of whom (11%) with comedonecrosis. Patients having IDC with solid pattern or comedonecrosis had higher Gleason score (P < 0.0001) and shorter biochemical recurrence-free survival (P < 0.001) than those with cribriform IDC only (P < 0.0001). While IDC was an independent parameter for biochemical recurrence-free survival in multivariate analysis, comedonecrosis was not included as a separate variable.

In an analysis of 278 prostate biopsies from men diagnosed with metastatic PCa, Zhao *et al.*[23] identified 57 cases with IDC, 36 of whom with solid/comedonecrosis pattern (13%) and 21 (8%) with cribriform pattern. Men with solid/comedonecrosis IDC had significantly (P < 0.05) shorter overall survival than those with cribriform IDC. They also had a shorter time to castration-resistant disease, but this was not statistically significant (20 versus 27 months; P = 0.13). No multivariate analysis was performed.

Diop *et al.*[22] included 108 grade groups 1–5 patients, who all had IDC at radical prostatectomy, and distinguished a test (n = 39) and validation (n = 69) cohort for IDC features associated with adverse outcome. Comedonecrosis was present in IDC in 11 of 39 (28%) men of the test cohort, and was significantly associated with early biochemical recurrence within 18 months. In the validation cohort (n = 69), with a median follow-up of 67 months in which 12 (17%) men had comedonecrosis, 31 (45%) patients experienced BCR. Comedonecrosis was not predictive for biochemical recurrence-free survival (P = 0.117) in the validation cohort.

Wang *et al.*[21] included 558 grade group > 1 radical prostatectomy specimen, 213 of which had IDC (38%), and investigated the impact of comedonecrosis (46 of 213, 22%) in IDC. Men with IDC with comedonecrosis more frequently had grade group ≥ 3 (P < 0.001), pT3 stage (P = 0.009), higher tumour volume (P < 0.001) and lymph node metastasis (P = 0.02) at time of operation than IDC cases without comedonecrosis. Furthermore, they had significantly shorter biochemical recurrence-free survival (P < 0.001). In multivariate analysis including grade group, pT-stage, surgical margin status and lymph node metastasis, IDC patients with comedonecrosis had significantly shorter biochemical recurrence-free survival.

In a cohort of 1051 grade groups 1–5 radical prostatectomies, Seipel *et al.*[25] identified a ductal adenocarcinoma component in 86 cases (8%), 27 of which (31%) had comedonecrosis. Biochemical recurrence-free survival of ductal carcinoma patients with and without comedonecrosis was not statistically significant (P = 0.90).

Jeong *et al.*[20] investigated a series of 61 grade groups 2–5 radical prostatectomies with ductal adenocarcinoma, 17 of which (28%) had comedonecrosis. While comedonecrosis was associated with shorter biochemical recurrence-free survival (HR = 2.6; 95% CI = 1.2–5.7; P = 0.015) in univariate analysis, it was not statistically significant in multivariate analysis.

QUALITY ASSESSMENT

The studies included in this review were all retrospective, and demonstrated large methodological and statistical heterogeneity. They were performed on radical prostatectomy and biopsy specimens, investigated comedonecrosis in invasive acinar, ductal and intraductal carcinoma and used biochemical recurrence, overall survival, metastasis and pathological factors as outcome measurements. Of the nine studies showing an association of comedonecrosis with biochemical recurrence- or disease-free survival, four also included multivariate analysis with potentially confounding factors. Quality assessment indicated moderate to high risk of bias in 10 of 12 studies due to lack of multivariate analysis or lack of

inclusion of relevant confounding factors in multivariate analysis.

Discussion

Since the first report by Iczkowski *et al.*[3] on the independent prognostic value of cribriform pattern in PCa patients, many studies have addressed the clinical impact and molecular background of individual growth patterns. The aim of the current study was to systematically review scientific literature on the prognostic impact of comedonecrosis in PCa. Twelve studies fulfilling the eligibility criteria showed that comedonecrosis is relatively rare, occurring in < 5% of unselected consecutive PCa samples. It can occur in invasive acinar, ductal and intraductal carcinoma. Eight of 12 studies showed that comedonecrosis was significantly associated with BCR. Two of these also found comedonecrosis to be prognostic in multivariate analysis, while five had not performed multivariate analysis and one did not show significance. The only studies using metastasis-free and disease-specific-free survival as an endpoint both found comedonecrosis to be an independent prognostic parameter in multivariate analysis. Due to the significant heterogeneity and lack of multivariate analysis including all potentially relevant confounding factors, there is only weak evidence that comedonecrosis is associated with adverse outcome.

Comedonecrosis is generally assigned Gleason pattern 5 and occurs in cribriform or solid glands. Therefore, it is essential that comedonecrosis is studied in a homogeneous grade group or that analyses are corrected for grade as confounding factor, which was performed in two and four studies, respectively. Many groups have shown that invasive cribriform and intraductal carcinoma are independent predictive factors for PCa outcome.[3–5] As comedonecrosis generally occurs in invasive cribriform, solid or intraductal carcinoma, it is important to take these patterns into account and determine whether comedonecrosis has added prognostic value after correction for the adverse clinical patterns, which was only performed by Hansum *et al.* and Wang *et al.*[18,21]

After three-dimensional imaging of clinical PCa samples, Verhoef *et al.*[26] distinguished essentially two families of growth patterns. The first group consisted of structures in which tumour cells contacted adjacent stroma, including Gleason pattern 3 tubules, poorly formed and fused Gleason pattern 4 glands and Gleason pattern 5 cords. These structures were spatially continuous, with decreasing lumen size and increasing branching. The second family consisted of cribriform Gleason pattern 4 and solid Gleason pattern 5, either with or without comedonecrosis, in which the majority of tumour cells did not have stromal contact. In this model, the occurrence of comedonecrosis in cribriform or solid glands was considered as an endstage of tumour derangement, which is supported by the findings of Hansum *et al.* and Wang *et al.*,[18,21] who both found independent prognostic value after correction for presence of cribriform growth in invasive and intraductal carcinoma, respectively. In a molecular analysis, Chua *et al.*[27] observed that invasive cribriform and intraductal carcinoma were associated with genomic instability and were characterised by a hypoxic signature. It is tempting to speculate that the occurrence of comedonecrosis in invasive cribriform and intraductal carcinoma is therefore the ultimate result of molecular derangement and chronic hypoxia in these structures.

Detailed basal cell immunohistochemistry studies have shown that comedonecrosis occurs more frequently in intraductal than invasive adenocarcinoma. In a series of 125 high-grade PCa at radical prostatectomy, Fine *et al.*[28] found 19 cases (15%) with comedonecrosis. Comedonecrosis occurred exclusively in IDC in 12 cases (63%), in both invasive carcinoma and IDC in six (32%) and in invasive areas in only one case (5%). These rates are in line with those reported by Madan *et al.*,[29] who found comedonecrosis in 24 (60%), seven (18%) and nine (23%) of 40 radical prostatectomy samples, respectively. Whether IDC with comedonecrosis adjacent to invasive carcinoma should be assigned Gleason pattern 5 or should not be graded at all is a matter of debate. According to the latest ISUP meeting, it was agreed that IDC with comedonecrosis should be graded pattern 5, while GUPS recommended not to grade this pattern.[1,6] Due to the rarity of comedonecrosis, definitive scientific evidence for either of the recommendations will be extremely difficult, not to say impossible, to gain. As comedonecrosis is found mainly in high-grade PCa and IDC already is an aggressive lesion by itself, the grading practice adhered to will not change risk stratification or therapeutic approach in the vast majority of patients.

As far as we are aware, this is the first systematic review on the clinical impact of comedonecrosis on PCa outcome. All studies were retrospective. An important limitation of the current systematic review is that the overall quality and heterogeneity of the eligible studies prohibit performance of a meta-analysis and drawing of robust conclusions. An assessment of publication bias was not performed. We

have pointed out significant confounding factors that need to be taken into account to draw strong conclusions with low risk of bias in future studies on this subject.

Conclusion

This systematic review summarises the evidence to date regarding the prognostic value of comedonecrosis in prostate cancer. There is weak evidence that comedonecrosis has added adverse prognostic value on prostate cancer outcome, but study heterogeneity and lack of correction for confounding factors prohibit drawing definitive conclusions.

Acknowledgements

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Conflicts of interest

There are no conflicts of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Supplementary material.