The Prognostic Impact of Intraductal Carcinoma of the Prostate: A Systematic Review and Meta-Analysis

Noriyoshi Miura, Keiichiro Mori, Hadi Mostafaei, Fahad Quhal, Reza Sari Motlagh, Benjamin Pradere, Ekaterina Laukhtina, David D'Andrea, Takashi Saika and Shahrokh F. Shariat*

From the Department of Urology (NM, KM, HM, FQ, RSM, BP, EL, DD, SFS), Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria, Department of Urology (NM, TS), Ehime University Graduate School of Medicine, Ehime, Japan, Department of Urology (KM), The Jikei University School of Medicine, Tokyo, Japan, Research Center for Evidence-Based Medicine (HM), Tabriz University of Medical Sciences, Tabriz, Iran, Department of Urology (FQ), King Fahad Specialist Hospital, Dammam, Saudi Arabia, Department of Urology (BP), University Hospital of Tours, Tours, France, Institute for Urology and Reproductive Health (EL, SFS), Sechenov University, Moscow, Russia, Department of Urology (SFS), Weill Cornell Medical College, New York, New York, Department of Urology (SFS), University of Texas Southwestern, Dallas, Texas, Karl Landsteiner Institute of Urology and Andrology (SFS), Vienna, Austria, Department of Urology (SFS), Second Faculty of Medicine, Charles University, Prague, Czech Republic, Department of Urology (SFS), University of Jordan, Amman, Jordan, and European Association of Urology Research Foundation (SFS), Arnhem, The Netherlands

Purpose: This systematic review and meta-analysis aimed to assess the prognostic impact of intraductal carcinoma of the prostate in patients with prostate cancer.

Materials and Methods: A systematic search was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis statement. We searched PubMed®, Web of Science™, the Cochrane Library and Scopus® up to October 2019. The end points were biochemical recurrence-free, cancer specific and overall survival.

Results: We identified 32 studies with 179,766 patients. A total of 31 studies containing 179,721 patients with localized and advanced prostate cancer were eligible for meta-analysis. In localized prostate cancer intraductal disease was associated with adverse outcomes including lower biochemical recurrence-free survival (pooled HR 2.09, 95% CI 1.75–2.50) and cancer specific survival (pooled HR 2.93, 95% CI 2.25–3.81). In advanced prostate cancer overall survival was lower in patients with vs without intraductal disease (pooled HR 1.75, 95% CI 1.43–2.14). Subgroup analysis by specimen type revealed that intraductal carcinoma of the prostate is a significant negative prognostic factor in both biopsies and prostatectomy specimens. Moreover, subgroup analyses based on the histopathological definitions of intraductal carcinoma of the prostate indicated that intraductal disease was significantly associated with lower biochemical recurrence-free, cancer specific and overall survival for almost all definitions.

Conclusions: Intraductal disease is a histopathological feature of biologically and clinically aggressive prostate cancer. It confers worse oncologic outcomes in both localized and advanced prostate cancer, whether assessed in biopsy or prostatectomy specimen. The pathologist should assess for and report on the presence of intraductal disease in all prostate specimens. The urologist and radiation oncologist should consider this adverse feature in their clinical decision making.

Abbreviations and Acronyms

ADT = androgen deprivation therapy
BRFS = biochemical recurrence-free survival
CA = cribriform architecture
CRPC = castration resistant prostate cancer
CSS = cancer specific survival
DTX = docetaxel
IDC-P = intraductal carcinoma of the prostate
OS = overall survival
PCa = prostate cancer
PSA = prostate specific antigen
RP = radical prostatectomy
RT = radiotherapy
WHO = World Health Organization

Key Words: prostatic neoplasms, disease-free survival, progression-free survival

Accepted for publication March 25, 2020.
No direct or indirect commercial, personal, academic, political, religious or ethical incentive is associated with publishing this article.
References 51–71 can be obtained at https://www.jurology.com.

* Correspondence: Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Währinger Gürtel 18-20, 1090, Vienna, Austria (telephone: 4314040026150; FAX: 4314040023320; e-mail: shahrokh.shariat@meduniwien.ac.at).

0022-5347/20/2045-0909/0
THE JOURNAL OF UROLOGY®

https://doi.org/10.1097/JU.0000000000001290
Vol. 204, 909-917, November 2020
Printed in U.S.A.

Intraductal carcinoma of the prostate is characterized by prostate carcinoma cells growing within native prostatic ducts and/or acini.[1,2] These tumors are usually associated with adverse pathological features such as a high Gleason score, a large tumor volume and advanced tumor stage.[3,4] The presence of intraductal disease in radical prostatectomy or biopsy specimens is reportedly associated with early relapse after radical therapies.[4–22] Moreover, intraductal disease is reportedly associated with a decreased response to chemotherapy and/or ADT in advanced prostate cancer.[23–29] This unfavorable impact on survival caused intraductal carcinoma of the prostate to be recognized as a new pathological entity in the 2016 World Health Organization classification.[30]

As the awareness of IDC-P has spread, reports with a large number of cases have increased. Porter et al revealed an unexpectedly high rate of IDC-P, especially in aggressive PCa.[31] However, no meta-analysis has assessed the differential prognostic impact of IDC-P in patients with PCa. Therefore, we performed a systematic review and meta-analysis to summarize the existing data regarding this relationship and to assess the prognostic impact of IDC-P in patients with PCa.

MATERIALS AND METHODS

Search Strategy

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines.[32] We searched PubMed, Web of Science, the Cochrane Library and Scopus to investigate the prognostic value of IDC-P in patients with PCa up to October 2019. We searched articles published in the English language only. There was no restriction regarding the publication period.

After an initial screening based on study titles and abstracts all articles were assessed based on full texts and excluded with reasons when inappropriate. A further check of the appropriateness of the studies based on a full text revision was performed after data extraction. The keywords used in our search strategy were ("intraductal carcinoma" or "intraductal carcinoma of the prostate" or "IDC-P" or "intraductal") and ("survival" or "prognosis" or "outcome" or "mortality" or "progression" or "recurrence") and ("prostate cancer" or "prostate carcinoma" or "prostate neoplasm"). The end points of interest were biochemical recurrence-free, cancer specific and overall survival.

The initial screening was performed independently by 2 investigators based on the titles and abstracts to check ineligible reports. The reasons for exclusions were recorded. Potentially relevant reports were subjected to a full article review, and the relevance of the report was confirmed after the data extraction process. In case of multiple reports of the same cohort the most complete data aggregated with the longest followup duration were selected. Discrepancies were resolved by consensus or recourse to the senior author.

Inclusion and Exclusion Criteria

Studies were included if they compared patients with intraductal carcinoma of the prostate who had undergone radical prostatectomy, radiotherapy or ADT vs those without IDC-P to assess the prognostic impact of IDC-P on biochemical recurrence-free, cancer specific and overall survival. Included series used multivariate Cox regression analysis in nonrandomized, observational or cohort studies. We excluded articles not in English, reviews, editorials, letters or case reports.

Data Extraction

The information was extracted by 2 investigators independently from the included articles and consisted of author names, disease status, therapy, publication year, period of registration, number of patients, study design, pathological definition of IDC-P, specimen for diagnosis, age, prostate specific antigen, rate of Gleason score greater than 7, number of patients with IDC-P, followup duration, HRs and 95% CIs for the presence of IDC-P in multivariate analysis, and oncologic outcomes. Subsequently the HRs and 95% CIs of the presence of IDC-P associated with each of the outcomes were retrieved. The HRs were extracted from the multivariate analysis. Discrepancies were resolved by consensus or recourse to the senior author.

Quality Assessment

To assess the quality of the included nonrandomized studies, we used the Newcastle-Ottawa Scale (NOS) according to the Cochrane Handbook for Systematic Reviews of Interventions.[33,34] In this meta-analysis the article quality of cohort studies was assessed as low (0-3 points), moderate (4-6 points) or high (7-9 points). The main confounding factors were identified as the important prognostic factors of BRFS, CSS and OS. The articles were reviewed to determine the presence of confounders. Studies with scores above 6 were identified as "high quality" choices.

Statistical Analyses

We performed meta-analyses of studies on localized and advanced PCa. Advanced PCa was defined as PCa with metastases. We separated the studies on localized and advanced disease because the treatment strategies and prognosis were very different between the 2 disease groups. Forest plots were used to assess multivariate HRs and to obtain summary HRs to describe the relationship of intraductal disease with BRFS, CSS and OS. Biochemical recurrence was defined as a PSA level of 0.2 ng/ml or greater assessed at 2 consecutive time points more than 3 months apart after RP[35] or any PSA increase greater than 2 ng/ml higher than the PSA nadir value after RT.[36] Biochemical recurrence-free survival was defined as the time from RP or RT to biochemical recurrence.

Many diagnostic criteria for IDC-P have been proposed based on different concepts. This analysis included the definitions of IDC-P based on McNeal and Yemoto,[4] ICD (International Classification of Diseases) Oncology 0–3 codes,[6] WHO 2016 criteria,[30] Guo and Epstein,[37] and Cohen et al,[38] as well as Pickup, the International Society of Urological Pathology 2014 grading system, SEER (Surveillance, Epidemiology, and End Results) and the combination of published criteria.

To assess the different possibilities for each definition, subgroup analyses were performed subsequently based on references of histopathological definition and specimen types (biopsy or surgery). We also performed subgroup analyses for each treatment type, such as RP and RT, in localized PCa. Heterogeneity among the outcomes of included studies in this meta-analysis was evaluated using the Cochran Q test and I^2 statistics. Significant heterogeneity was indicated by $p < 0.05$ in the Cochran Q tests and a ratio greater than 50% in I^2 statistics. We used fixed effects models for the calculation of pooled HRs for non-heterogeneity results. If there was heterogeneity, we used random effects models.[39–41] Publication bias was assessed with funnel plots. All statistical analyses were performed using Stata®/MP version 14.2, and statistical significance level was set at $p < 0.05$.

RESULTS

Literature Search

Overall, 703 publications were identified in the initial search (218 in PubMed, 264 in Scopus, 221 in Web of Science and 0 in the Cochrane Library). Among these articles 326 were excluded because they were duplicates, nonrelevant articles according to inclusion criteria, books, reviews, editorial comments, case reports, abstracts only or nonEnglish. A full text review was performed for 94 potentially relevant articles. After evaluating the selection criteria we identified 32 articles with 179,766 patients for systematic review and 31 articles with 179,721 patients for meta-analysis. The selection process and list are shown in figure 1.[4–29,42–47]

Study Characteristics

There were 37 cohorts that were evaluated for end points in the 32 included studies. Overall, 4,720 (2.6%) of the 179,766 patients had IDC-P. Of these included cohorts 29 contained patients with localized PCa and 8 contained patients with advanced PCa. The prevalence of IDC-P was 2.3% (4,028 of 177,769 cases) in localized PCa and 34.8% (692 of 1,991) in advanced PCa. According to the NOS, 30 studies were considered high quality and 2 were judged as medium quality (supplementary table 1, https://www.jurology.com).

Meta-Analysis

Association of IDC-P with Biochemical Recurrence-Free and Cancer Specific Survival in Localized PCa. We assessed the association between IDC-P and BRFS in 21 cohorts including 14,465 patients with localized PCa. The forest plot (fig. 2) revealed that the presence of IDC-P was significantly associated with worse BRFS (pooled HR 2.09, 95% CI 1.75–2.50; $z = 8.15$). The Cochran Q test (chi-square 65.97, $p = 0.000$) and I^2 test (69.7%) showed significant heterogeneity. The funnel plot identified 5 cohorts over the pseudo 95% CI. Seven cohorts including

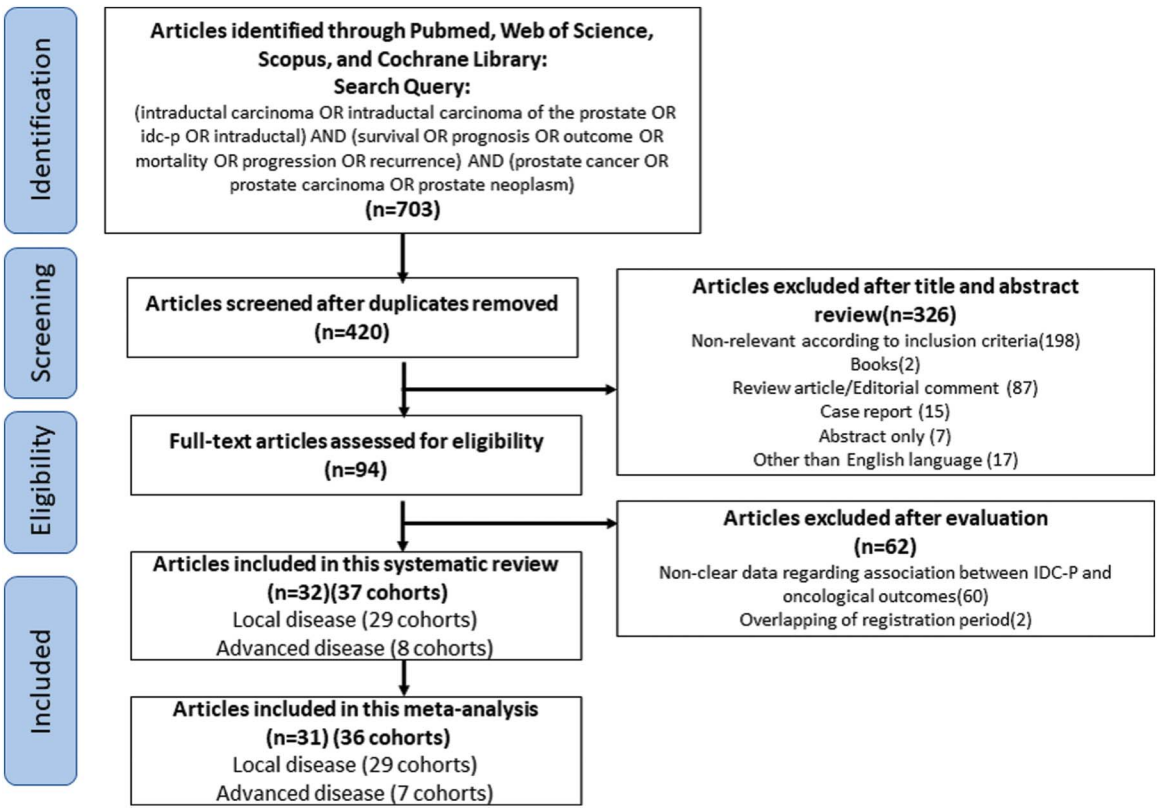

Figure 1. Literature search, screening and selection for inclusion in review

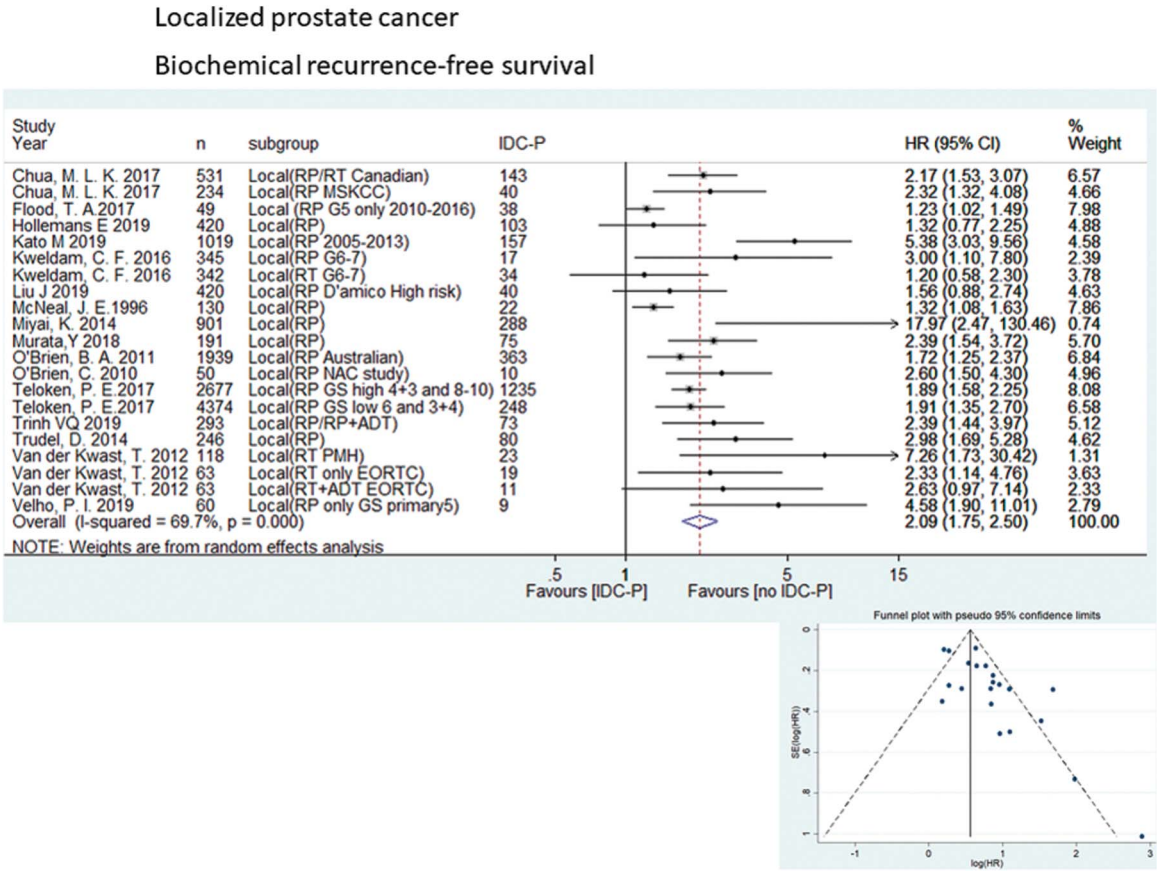

Figure 2. Biochemical recurrence-free survival in patients with localized prostate cancer

163,100 patients had data available on the association of IDC-P with CSS in localized PCa. The forest plot (fig. 3) indicated that the presence of IDC-P was significantly associated with worse CSS (pooled HR 2.93, 95% CI 2.25–3.81; z=8.01). The Cochran Q test (chi-square 10.20, p=0.117) and I^2 test (41.2%) suggested no significant heterogeneity. The funnel plot identified 1 cohort over the pseudo 95% CI.

Association of IDC-P with Overall Survival in Advanced PCa. We assessed the association between IDC-P and OS using 7 cohorts including 1,946 patients with advanced PCa. The forest plot (fig. 4) revealed that the presence of IDC-P was significantly associated with worse OS (pooled HR 1.75, 95% CI 1.43–2.14; z=5.43). The Cochran Q test (chi-square 8.17, p=0.226) and I^2 test (26.6%) indicated no significant heterogeneity. The funnel plot identified 1 cohort over the pseudo 95% CI.

Subgroup Analyses. To confirm the influence of the diagnostic methods of IDC-P, subgroup analyses were performed subsequently based on the histopathological definition and specimen types (supplementary tables 1a to 2b, https://www.jurology.com). In localized PCa 11 cohorts were based on biopsy, 16 on RP, and 2 on both biopsy and RP specimens. In advanced PCa IDC-P status in all the cohorts was diagnosed on biopsy specimens. Subgroup analysis based on the specimen type showed that the presence of IDC-P was a significant prognostic factor in both biopsy specimens (supplementary fig. 1A, https://www.jurology.com) and RP specimens (supplementary fig. 1B, https://www.jurology.com).

Subgroup analyses based on histopathological IDC-P definition revealed that cases with vs without IDC-P were significantly associated with worse biochemical recurrence-free, cancer specific and overall survival for the definitions defined by McNeal and Yemoto (pooled HR 2.58, 95% CI 1.60–4.14 for overall survival),[4] Guo and Epstein (pooled HR 1.86, 95% CI 1.25–2.76 for biochemical recurrence-free survival; pooled HR 2.60, 95% CI 1.74–3.88 for cancer specific survival; pooled HR 1.61, 95% CI 1.28–2.01 for overall survival),[37] Cohen et al (pooled HR 1.86, 95% CI 1.61–2.14 for biochemical recurrence-free survival),[38] WHO 2016 criteria (pooled HR 5.78, 95% CI 1.73–19.31 for cancer specific survival)[30] and combination based on the published criteria (pooled HR 2.50, 95% CI 2.06–3.03 for biochemical recurrence-free survival; supplementary figs. 2A to 2C, https://www.jurology.com). Only 1 analysis of BRFS referred from the definition by McNeal and Yemoto was not

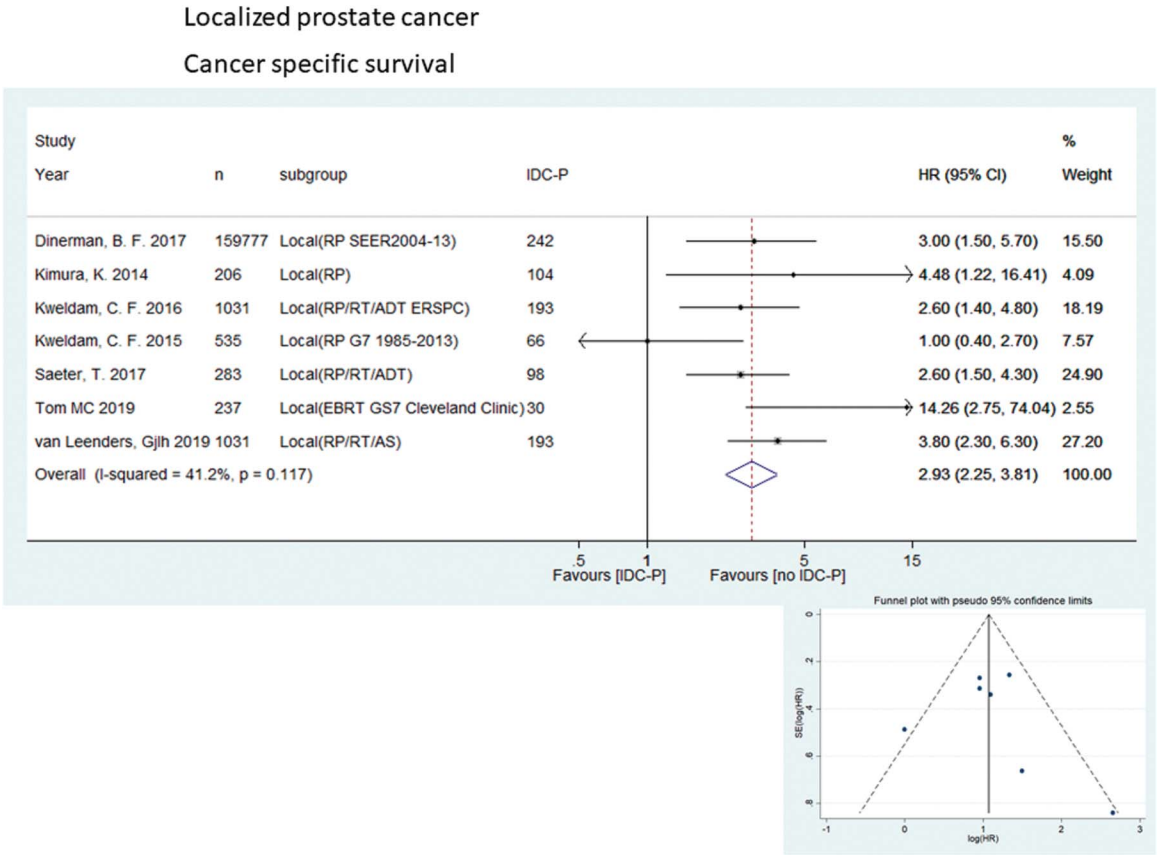

Figure 3. Cancer specific survival in patients with localized prostate cancer

significant (pooled HR 2.60, 95% CI 0.66−10.27). This analysis had high heterogeneity (95.1%) and its sample size was small.

In localized PCa RP or RT was performed as a curative treatment. Subgroup analyses based on the treatment type revealed that cases with vs without IDC-P were significantly associated with worse outcomes for both the RP (pooled HR 2.08, 95% CI 1.71−2.55 for biochemical recurrence-free survival; pooled HR 2.30, 95% CI 1.01−5.22 for cancer specific survival) and RT groups (pooled HR 2.05, 95% CI 1.34−3.13 for biochemical recurrence-free survival; supplementary figs. 3A and 3B, https://www.jurology.com).

DISCUSSION

We performed this review and meta-analysis to investigate the impact of IDC-P on PCa prognosis. To our knowledge, this is the first meta-analysis reported on the prognosis of IDC-P. These analyses were divided into 2 groups, localized and advanced PCa, because the treatment strategies and prognosis are very different between the 2 disease states.

Porter et al reported that the incidence of IDC-P varied from 2.1% to 56% in different stages of disease, and that compared with localized PCa, IDC-P prevalence in patients with metastatic and CRPC was relatively higher.[31] Similarly our results showed that IDC-P prevalence in patients with advanced PCa (34.8%) was higher than in patients with localized disease (2.3%). This meta-analysis indicated that the presence of IDC-P was a significant poor prognostic factor in both groups. However, some careful considerations are required to evaluate IDC-P. The most important consideration is that various different diagnostic criteria for IDC-P have been proposed and used. Different criteria may influence IDC-P incidence and prognosis. Kimura et al reported that the incidence of IDC-P with the criteria of either McNeal and Yemoto[4] or Guo and Epstein[37] was different in RP cases.[10] Therefore, we thought that it was necessary to perform subgroup analyses based on the histopathological definition and specimen types.

The diagnostic criteria and clinical significance of IDC-P have been discussed for many decades. In 1985 Kovi et al described IDC-P as a distinct entity in which prostate carcinoma cells are dispersed within lumen spanning preexisting prostate ducts and/or acini.[2] In this report IDC-P was present in 48% of 139 PCa cases in the series, consisting mainly of transurethral resection specimens. McNeal et al described IDC-P in more detail in 1986.[3] Furthermore, McNeal and Yemoto investigated 130 RP

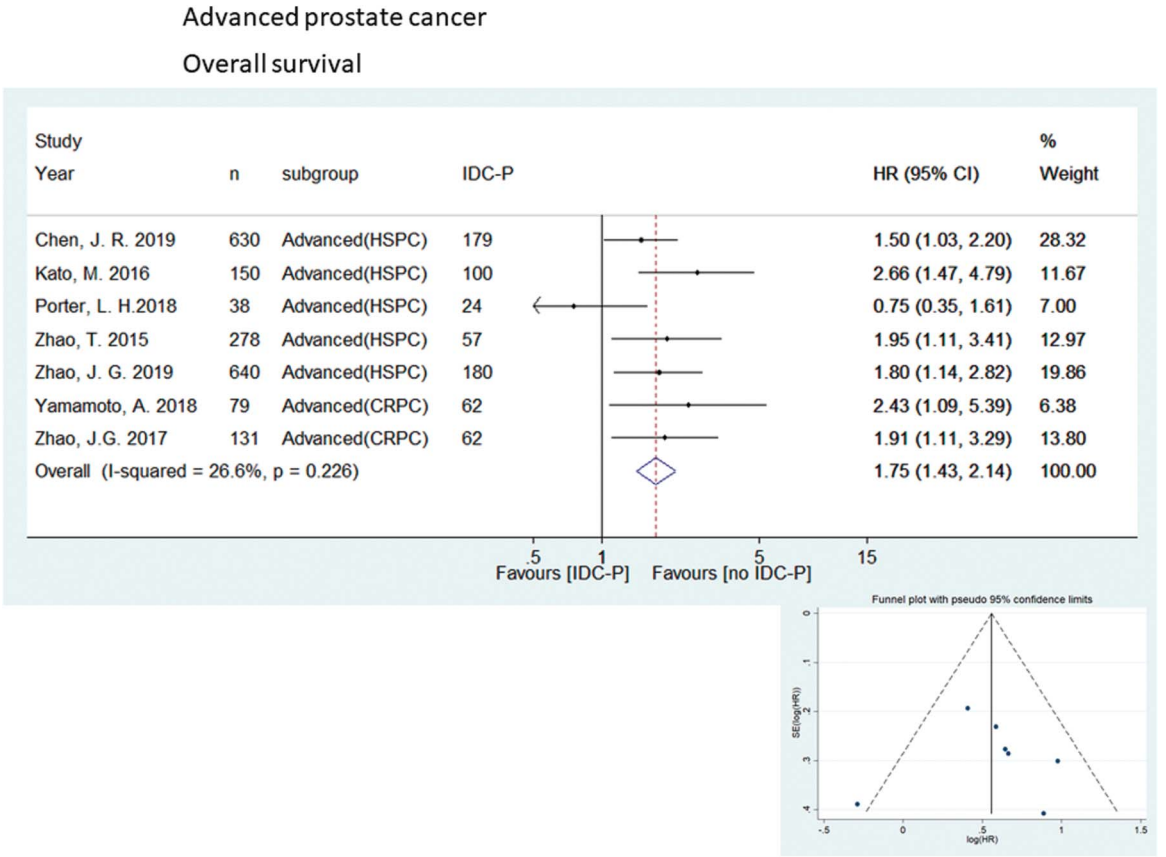

Figure 4. Overall survival in patients with advanced prostate cancer

specimens and described key morphological criteria for the diagnosis of IDC-P in 1996.[4] In 2006 Guo and Epstein also described the histological features to identify IDC-P in needle biopsy.[37] Since then, many definitions of IDC-P have been described, including those by Cohen et al,[38] Pickup, as reported by Shah et al,[48] Herawi, as reported by Tsuzuki,[49] and Tavora, as reported by Varma et al.[50] Moreover, there were many reports of clinical results using definitions that combine various criteria.

The key features of the overall consensus on the diagnosis of IDC-P are prevention of the basal cell layer at least partially, and the malignant cells extending and expanding into preexisting normal prostate ducts and acini. Meanwhile, there are some differences in the proposed criteria in various settings. The definition of McNeal and Yemoto was based on prostatectomy specimens, particularly those with a volume between 4 and 10 ml.[4] All cases of IDC-P defined by them were associated with invasive prostate carcinoma. In contrast, the definition of Guo and Epstein was based on needle biopsy specimens.[37] In addition to the aforementioned key features, diagnosis of IDC-P requires the presence of a solid or dense cribriform pattern. Furthermore, they proposed strict criteria to diagnose IDC-P without invasive prostate carcinoma. These criteria were proposed to include only cases in which the possibility of high grade prostatic intraepithelial neoplasia could be definitively excluded.[37] However, some pathologists consider the interpretation of this definition (nucleus size) as inconsistent, and the incidence of IDC-P without invasive prostate carcinoma is extremely rare. Hence some of them consider that the management of IDC-P without invasive prostate carcinoma on needle biopsies should be carefully done.[49,50]

According to the definition of Cohen et al, the lumen size must be at least twice as large as the benign size but the size of the nucleus is not emphasized.[38] Recently the morphological criteria described by Guo and Epstein[37] have been most frequently used to identify IDC-P in all types of prostate specimens.[51] IDC-P was formally approved as a biologically distinct entity in the WHO 2016 prostate tumor classification.[30] Notably although the WHO 2016 classification suggests several criteria for IDC-P and characterizes IDC-P, there is no definition in the chapter on classification. Thus, uniform IDC-P criteria are needed. This systematic review and meta-analysis included several definitions of IDC-P. The most common single definition was the one proposed by Guo and Epstein.[37] However, 9 cohorts used a combination of published criteria. Interestingly subgroup analyses based on the histopathological IDC-P definition revealed that

compared with no IDC-P, IDC-P was significantly associated with worse biochemical recurrence-free, cancer specific and overall survival in both major definitions and combination definitions. Moreover, subgroup analysis by specimen type showed that the presence of IDC-P was a significant prognostic factor in both biopsies and surgical specimens. Despite some differences in the proposed criteria in different settings, IDC-P was consistently a poor prognostic factor.

IDC-P includes 2 biologically distinct diseases that need to be considered separately. IDC-P associated with invasive carcinoma generally represents a growth pattern of aggressive invasive carcinoma. Taylor et al reported that IDC-P and invasive adenocarcinoma arise from the same ancestral clone in subclonal evolution analysis.[52] These data suggest a common ancestral origin for IDC-P and invasive adenocarcinoma and may indicate the increased clinical aggressiveness of prostate cancers with IDC-P. Although pure IDC-P is a precursor lesion similar to HGPIN and rarely encountered, most cases of pure IDC-P in prostate needle biopsies represent IDC-P with an unsampled invasive component.[50] The management of patients with pure IDC-P in needle biopsies is controversial. Some experts recommend radical therapy immediately,[37,38] whereas others recommend repeat biopsy, as some patients may have only pure IDC-P.[50,53] Further investigations are needed to clarify the management of the patients with pure IDC-P.

Our data suggest the need to identify new treatment strategies for patients with intraductal carcinoma of the prostate. In localized PCa RP or RT is usually performed as a curative treatment. Some experts recommended prompt radical therapy for localized PCa with IDC-P even in the absence of an invasive feature because such patients have high grade, locally advanced or metastatic PCa.[37,38] In a subanalysis by treatment type the presence of IDC-P was a poor prognostic factor for patients treated with RP as well as RT. The best management of patients diagnosed with IDC-P has not yet been determined. Even a small amount of IDC-P identified on a prostate biopsy may reportedly be aggressive even in the absence of high grade carcinoma.[54] Therefore, the presence of IDC-P on prostate biopsy has been proposed as an exclusion criterion for active surveillance.

Similarly in advanced PCa, patients with IDC-P also had a worse prognosis than those without IDC-P. Recently several trials have demonstrated the efficacy of up-front administration of docetaxel or abiraterone combined with ADT in patients with metastatic hormone sensitive PCa and high tumor burden.[55–59] To our knowledge, there are no reports investigating the association between IDC-P and hormone sensitive PCa in patients who received up-front treatment with abiraterone or DTX. In this systematic review 2 studies evaluated the association of IDC-P with prognosis of patients with CRPC. Both studies showed that patients with IDC-P had worse OS than those without IDC-P.[26,28] Interestingly Zhao et al suggested that IDC-P, particularly the nonpure cribriform pattern, seemed to be associated with much worse response to DTX than abiraterone in patients with metastatic CRPC.[28]

Some reports on the molecular characteristics of IDC-P have been published. Loss of heterozygosity of common tumor suppressor genes was reportedly found in 60% of IDC-P cases.[60] Bettendorf et al observed particularly high rates of loss of heterozygosity in PTEN, TP53 and RB.[61] Additionally TMPRSS2-ERG gene fusions were reportedly observed in 75% cases of IDC-P.[62] Lotan et al confirmed that cytoplasmic PTEN loss and ERG expression were common in IDC-P.[63] Thus, PTEN and ERG could potentially be diagnostic markers of IDC-P.[49]

Furthermore, TMPRSS2-ERG fusion was reportedly not associated with PCa recurrence or PCa specific death.[64] However, detection of TMPRSS2-ERG predicts resistance to DTX by evaluating TMPRSS2-ERG expression using peripheral blood mononuclear cells and tissue from patients with metastatic CRPC treated with taxanes.[65] Conversely TMPRSS2-ERG status reportedly was not associated with response to abiraterone treatment.[66] Thus, abiraterone, instead of DTX, might theoretically be more suitable in this patient group. Risbridger et al observed that intraductal growth was significantly more prevalent in xenografts from *BRCA2* mutated cases than in sporadic cases.[67] *BRCA2* mutant PCa harboring IDC-P was reported by Taylor et al to be related to genomic and epigenetic dysregulation of the MED12L/MED12 axis, which has been implicated in cell proliferation and neuroendocrine differentiation.[68] Furthermore, they reported newly diagnosed BRCA-2 mutant tumors had molecular and genomic features that were more similar to those present in CRPC tumors and commonly showed concurrent presence of IDC-P.[52] These tumors may be responsive to treatment with PARP inhibitors. The latest National Comprehensive Cancer Network® guideline recommends genetic tests for patients with IDC-P in needle biopsy.[69] Future studies will be required to clarify the molecular information about IDC-P and to identify effective managements for patients with intraductal carcinoma of the prostate.

Several limitations exist in the current study. First, all included series had a retrospective design, which increases selection bias. It is also possible that negative results were not published. Second, heterogeneity was detected for BRFS analysis, limiting the value of these results. One possible cause is the different definitions of recurrence between

prostatectomy and radiation therapy, and another possible cause is the coexistence of old and new reports. Random effect models considered the heterogeneity among studies but the conclusions should be interpreted with caution. Third, each study included different independent variables in the multivariable analysis, which may have caused confounders.

In addition, in this review some reports have treated IDC-P and carcinoma with cribriform architecture together when assessing the prognostic impact.[5,18,20] One reason suggested is the difficulty in distinguishing invasive CA from IDC-P without basal cell immunohistochemistry.[49,70] There are some reports assessing the impact of the distinction between CA and IDC-P but there is still no consensus regarding its clinical impact.[18,20,44] Therefore, whether the distinction between CA and IDC-P is clinically relevant remains unclear. Future studies including assessment of genomic alterations are required to clarify the benefit of subtyping CA and IDC-P. Finally, pathological specimens were evaluated at each institution. These factors could have influenced the misinterpretation of pathological reports and may have had various effects on oncologic outcomes. Varma et al surveyed 23 expert uropathologists and reported that there were significant variations in the diagnostic criteria and rules to report IDC-P.[71] Therefore, well designed, prospective studies are required to validate the prognostic impact of IDC-P in the clinical setting.

CONCLUSIONS

This meta-analysis demonstrated that biochemical recurrence-free and cancer specific survival were significantly worse in patients with localized PCa, and overall survival was worse in patients with advanced PCa among those with vs without IDC-P. In subgroup analyses IDC-P was consistently a poor prognostic factor regardless of the histopathological IDC-P definition or the specimen type. Therefore, even when the specimen is based on biopsy or RP, it is better that the pathologists describe the presence of IDC-P and that urologists use this information as a prognostic factor to determine treatment strategies.

REFERENCES

1. Rhamy RK, Buchanan RD and Spalding MJ: Intraductal carcinoma of the prostate gland. J Urol 1973; **109:** 457.
2. Kovi J, Jackson MA and Heshmat MY: Ductal spread in prostatic carcinoma. Cancer 1985; **56:** 1566.
3. McNeal JE, Reese JH, Redwine EA et al: Cribriform adenocarcinoma of the prostate. Cancer 1986; **58:** 1714.
4. McNeal JE and Yemoto CE: Spread of adenocarcinoma within prostatic ducts and acini. Morphologic and clinical correlations. Am J Surg Pathol 1996; **20:** 802.
5. Chua MLK, Lo W, Pintilie M et al: A prostate cancer "nimbosus": genomic instability and SChLAP1 dysregulation underpin aggression of intraductal and cribriform subpathologies. Eur Urol 2017; **72:** 665.
6. Dinerman BF, Khani F, Golan R et al: Population-based study of the incidence and survival for intraductal carcinoma of the prostate. Urol Oncol 2017; **35:** 673.e9.
7. Flood TA, Schieda N, Sim J et al: Evaluation of tumor morphologies and association with biochemical recurrence after radical prostatectomy in grade group 5 prostate cancer. Virchows Arch 2018; **472:** 205.
8. Kato M, Hirakawa A, Kobayashi Y et al: The influence of the presence of intraductal carcinoma of the prostate on the grade group system's prognostic performance. Prostate 2019; **79:** 1065.
9. Kato M, Kimura K, Hirakawa A et al: Prognostic parameter for high risk prostate cancer patients at initial presentation. Prostate 2018; **78:** 11.
10. Kimura K, Tsuzuki T, Kato M et al: Prognostic value of intraductal carcinoma of the prostate in radical prostatectomy specimens. Prostate 2014; **74:** 680.
11. Kweldam CF, Kummerlin IP, Nieboer D et al: Prostate cancer outcomes of men with biopsy Gleason score 6 and 7 without cribriform or intraductal carcinoma. Eur J Cancer 2016; **66:** 26.
12. Miyai K, Divatia MK, Shen SS et al: Clinicopathological analysis of intraductal proliferative lesions of prostate: intraductal carcinoma of prostate, high-grade prostatic intraepithelial neoplasia, and atypical cribriform lesion. Hum Pathol 2014; **45:** 1572.
13. Murata Y, Tatsugami K, Yoshikawa M et al: Predictive factors of biochemical recurrence after radical prostatectomy for high-risk prostate cancer. Int J Urol 2018; **25:** 284.
14. O'Brien BA, Cohen RJ, Wheeler TM et al: A post-radical-prostatectomy nomogram incorporating new pathological variables and interaction terms for improved prognosis. BJU Int 2011; **107:** 389.
15. O'Brien C, True LD, Higano CS et al: Histologic changes associated with neoadjuvant chemotherapy are predictive of nodal metastases in patients with high-risk prostate cancer. Am J Clin Pathol 2010; **133:** 654.
16. Sæter T, Vlatkovic L, Waaler G et al: Intraductal carcinoma of the prostate on diagnostic needle biopsy predicts prostate cancer mortality: a population-based study. Prostate 2017; **77:** 859.
17. Teloken PE, Li J, Woods CG et al: The impact of prostate cancer zonal origin on pathological parameters at radical prostatectomy and subsequent biochemical failure. J Urol 2017; **198:** 1316.
18. Tom MC, Nguyen JK, Luciano R et al: Impact of cribriform pattern and intraductal carcinoma on Gleason 7 prostate cancer treated with external beam radiotherapy. J Urol 2019; **202:** 710.
19. Trinh VQ, Benzerdjeb N, Chagnon-Monarque S et al: Retrospective study on the benefit of adjuvant radiotherapy in men with intraductal carcinoma of prostate. Radiat Oncol 2019; **14:** 60.
20. Trudel D, Downes MR, Sykes J et al: Prognostic impact of intraductal carcinoma and large cribriform carcinoma architecture after prostatectomy in a contemporary cohort. Eur J Cancer 2014; **50:** 1610.
21. Van Der Kwast T, Al Daoud N, Collette L et al: Biopsy diagnosis of intraductal carcinoma is prognostic in intermediate and high risk prostate cancer patients treated by radiotherapy. Eur J Cancer 2012; **48:** 1318.

22. van Leenders G, Kweldam CF, Hollemans E et al: Improved prostate cancer biopsy grading by incorporation of invasive cribriform and intraductal carcinoma in the 2014 grade groups. Eur Urol 2020; **77:** 191.

23. Chen JR, Zhao JG, Zhu S et al: Clinical and oncologic findings of extraprostatic extension on needle biopsy in de novo metastatic prostate cancer. Asian J Androl 2020; **22:** 427.

24. Chen Z, Chen N, Shen P et al: The presence and clinical implication of intraductal carcinoma of prostate in metastatic castration resistant prostate cancer. Prostate 2015; **75:** 1247.

25. Kato M, Tsuzuki T, Kimura K et al: The presence of intraductal carcinoma of the prostate in needle biopsy is a significant prognostic factor for prostate cancer patients with distant metastasis at initial presentation. Mod Pathol 2016; **29:** 166.

26. Yamamoto A, Kato M, Matsui H et al: Efficacy of docetaxel in castration-resistant prostate cancer patients with intraductal carcinoma of the prostate. Int J Clin Oncol 2018; **23:** 584.

27. Zhao J, Liu J, Sun G et al: The prognostic value of the proportion and architectural patterns of intraductal carcinoma of the prostate in patients with de novo metastatic prostate cancer. J Urol 2019; **201:** 759.

28. Zhao J, Shen P, Sun G et al: The prognostic implication of intraductal carcinoma of the prostate in metastatic castration-resistant prostate cancer and its potential predictive value in those treated with docetaxel or abiraterone as first-line therapy. Oncotarget 2017; **8:** 55374.

29. Zhao T, Liao B, Yao J et al: Is there any prognostic impact of intraductal carcinoma of prostate in initial diagnosed aggressively metastatic prostate cancer? Prostate 2015; **75:** 225.

30. Humphrey PA, Moch H, Cubilla AL et al: The 2016 WHO classification of tumours of the urinary system and male genital organs—part B: prostate and bladder tumours. Eur Urol 2016; **70:** 106.

31. Porter LH, Lawrence MG, Ilic D et al: Systematic review links the prevalence of intraductal carcinoma of the prostate to prostate cancer risk categories. Eur Urol 2017; **72:** 492.

32. Liberati A, Altman DG, Tetzlaff J et al: The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009; **6:** e1000100.

33. Stang A: Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010; **25:** 603.

34. Deeks JJ, Dinnes J, D'Amico R et al: Evaluating non-randomised intervention studies. Health Technol Assess 2003; **7:** 1.

35. 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.

36. Roach M III, Hanks G, Thames H Jr et al: Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 2006; **65:** 965.

37. Guo CC and Epstein JI: Intraductal carcinoma of the prostate on needle biopsy: histologic features and clinical significance. Mod Pathol 2006; **19:** 1528.

38. Cohen RJ, Wheeler TM, Bonkhoff H et al: A proposal on the identification, histologic reporting, and implications of intraductal prostatic carcinoma. Arch Pathol Lab Med 2007; **131:** 1103.

39. DerSimonian R and Kacker R: Random-effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials 2007; **28:** 105.

40. DerSimonian R and Laird N: Meta-analysis in clinical trials. Control Clin Trials 1986; **7:** 177.

41. Higgins JP, Thompson SG, Deeks JJ et al: Measuring inconsistency in meta-analyses. BMJ 2003; **327:** 557.

42. Hollemans E, Verhoef EI, Bangma CH et al: Large cribriform growth pattern identifies ISUP grade 2 prostate cancer at high risk for recurrence and metastasis. Mod Pathol 2019; **32:** 139.

43. Kweldam CF, Kummerlin IP, Nieboer D et al: Disease-specific survival of patients with invasive cribriform and intraductal prostate cancer at diagnostic biopsy. Mod Pathol 2016; **29:** 630.

44. Kweldam CF, Wildhagen MF, Steyerberg EW et al: Cribriform growth is highly predictive for postoperative metastasis and disease-specific death in Gleason score 7 prostate cancer. Mod Pathol 2015; **28:** 457.

45. Liu J, Zhao J, Zhang M et al: The validation of the 2014 International Society of Urological Pathology (ISUP) grading system for patients with high-risk prostate cancer: a single-center retrospective study. Cancer Manag Res 2019; **11:** 6521.

46. Porter LH, Hashimoto K, Lawrence MG et al: Intraductal carcinoma of the prostate can evade androgen deprivation, with emergence of castrate-tolerant cells. BJU Int 2018; **121:** 971.

47. Velho PI, Lim D, Wang H et al: Molecular characterization and clinical outcomes of primary Gleason pattern 5 prostate cancer after radical prostatectomy. JCO Precis Oncol 2019; doi: 10.1200/PO.19.00081.

48. Shah RB, Magi-Galluzzi C, Han B et al: Atypical cribriform lesions of the prostate: relationship to prostatic carcinoma and implication for diagnosis in prostate biopsies. Am J Surg Pathol 2010; **34:** 470.

49. Tsuzuki T: Intraductal carcinoma of the prostate: a comprehensive and updated review. Int J Urol 2015; **22:** 140.

50. Varma M, Delahunt B, Egevad L et al: Intraductal carcinoma of the prostate: a critical re-appraisal. Virchows Arch 2019; **474:** 525.