The Presence of Intraductal Carcinoma of The Prostate Is Closely Correlated with Poor Prognosis: A Systematic Review and Meta-Analysis

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Abstract

Background

We aimed to confirm the predictive ability of the presence of intraductal carcinoma of the prostate (IDC-P) on prognosis and association between IDC-P and clinicopathological parameters.

Methods

Literatures were identified in PubMed, Cochrane Library, etc. up to December 1st, 2019. Hazard ratio (HR) for survival data and odds ratio (OR) for clinicopathological data with 95% confidence interval (CI) were extracted. Heterogeneity was evaluated by I² value and quality assessment by Newcastle-Ottawa Scale (NOS) criteria.

Result

A total of 4179 patients from 13 studies were included. The results showed IDC-P presence was significantly associated with poor progression-free survival (PFS) (HR = 2.31; 95% CI 1.96 to 2.73), cancer-specific survival (CSS) (HR=1.89; 95% CI 1.28 to 2.77) and overall survival (OS) (HR=2.14; 95% CI 1.53 to 3.01). In subgroup analysis, IDC-P presence was significantly associated with poor PFS in prostate cancer treated by radical prostatectomy (RP) (HR = 2.48; 95% CI 2.05 to 3.00) and those by radiotherapy (RT) (HR=2.83; 95% CI 1.65 to 4.85). For clinicopathological characteristics, IDC-P present patients showed significantly higher tumor clinical stage, Gleason score and probability of lymph node invasive, positive surgical margin and positive extraprostatic extension.

Conclusion

Our meta-analysis indicates presence of IDC-P is closely correlated with poor prognosis and adverse clinicopathological characteristics. Our data support the value and clinical utility of routine detection of IDC-P by pathological examination. These conclusions need further validation and prospective studies are needed to find better treatment modalities for patients with IDC-P other than traditional first-line androgen deprivation therapy.

Background

Due to high heterogeneity in histology, genetics, and clinical outcome, the management of newly diagnosed prostate cancer remains challenging. Currently, the clinical decision is usually made
according to serum PSA level, clinical tumor stage, and Gleason score by biopsy. Although there are several powerful prognosis predictive factors including TNM staging, a stronger one remains lacking so far. IDC-P is one histological variant of prostate cancer which has been identified as a potential prognostic factor. IDC-P is strongly associated with high-grade and high-volume invasive prostate cancer and unfavorable clinical outcomes.[1, 2] The incidence of IDC-P is approximately 20%.[3-5] Moreover, IDC-P has been recognized in the 2014 ISUP and 2016 World Health Organization classifications,[6, 7] and officially recommended being reported by The College of American Pathologists in 2017.[8]

Until now, some clinical studies have reported treatment prognosis of IDC-P with conflicting results.[9] In order to further confirm the predictive ability of IDC-P on treatment outcome, we conducted this systematic review and meta-analysis of relevant studies.

Methods

**Data sources and searches**

A comprehensive literature search was performed of databases including PubMed, Cochrane Library, EMBASE, Web of Science, and SCOPUS to identify relevant studies up to December 1st, 2019. The following terms and their combinations were employed: ("prostate cancer") AND ("intraductal carcinoma") OR ("IDC-P") OR ("intraductal carcinoma of the prostate") OR ("intraductal carcinoma of prostate").

**Study selection**

Every study was independently examined by two reviewers (Guoliang Sun and Yucong Zhang) for comprehensive evaluation according to the following inclusion criteria: (1) Patients were confirmed prostate cancer by pathological examination; (2) IDC-P was identified in prostate cancer tissues and was divided into present and absent categories; (3) studies investigated the association between IDC-P with clinicopathological features or prognosis; (4) studies directly provided HR with corresponding 95% CI, or survival curves of patients to estimate them; (5) studies were published in English. The exclusion criteria were as follows: (1) case reports, letters, reviews, editorials, notes, meeting abstracts, etc.; (2) non-human studies or in vitro studies; (3) duplicated studies with overlapping data;
(4) studies provided information unable to be pooled.

**Data extraction**

Two authors (Chao Wei, Haojie Shang) independently extracted and summarized the data of interest, and disagreement was resolved by discussion. The following basic characteristics were collected: name of the first author, year of publication, country, tumor type, treatment, number of patients, age, Gleason score, tumor stage, nodal status, PSA, follow-up months. For survival data, IDC-P present or absent status with HR and 95% CI for PFS, CSS and OS were collected. The following clinicopathological data were extracted: numbers of IDC-P present and absent patients with (a) PSA values, (b) tumor stage cT1-cT2, (c) tumor stage cT3-cT4, (d) Gleason score≥8, (e) Gleason score <8, (f) lymph node metastasis N0, (g) lymph node metastasis N1, (h) positive surgical margins (i) negative surgical margins (j) positive extraprostatic extension, (k) negative extraprostatic extension.

**Population, Interventions, Comparators, Outcomes and Study Designs (PICOS)**

The population of our study is prostate cancer patients. IDC-P status was assessed in these patients. IDC-P present or absent were compared by the endpoint including PFS, CSS and OS. The associations between IDC-P status and clinicopathological characteristics were evaluated. The study was designed to evaluate the association between IDC-P status and prognosis and clinicopathological characteristics.

**Quality assessment**

Quality assessment was performed by two investigators (Zhuo Liu, Rui Li) independently according to the Newcastle-Ottawa Scale (NOS) criteria. The NOS criteria consists of the following three parameters of quality: (1) selection: 0-4; (2) comparability: 0-2; and (3) exposure/outcome: 0-3. Studies scoring greater than five were considered to be of high quality.

**Data synthesis and analysis**

HR with their 95% CI was used to estimate the association between PFS, CSS and OS and IDC-P status. Patients were dichotomized by tumor stage (cT1-T2 vs. cT3-T4), Gleason score (<8 vs.≥8), lymph node metastasis (N0 vs. N1), surgical margins (positive vs. negative), and extraprostatic extension (positive vs. negative) categories. OR with 95% CI was used to evaluate the correlation.
between IDC-P status and clinicopathological features. We used the Review Manager software version 5.3 to calculate HR and OR with 95% CIs. Heterogeneity was assessed by the Chi-squared test and $I^2$ statistic. Fixed-effect models were employed when P-values of Chi-squared test is more than or equal to 0.05, and random-effect models when less than 0.05. Statistical tests were two-sided and P-values < 0.05 was considered to be statistically significant. Publication bias was assessed by funnel plots if number of included cohorts was over or equal to 10.

Results

Study characteristics

As Fig. 1 shows, 906 records were identified at first and 13 articles were included in the final qualitative and quantitative synthesis. Table 1 shows the characteristics of the included studies.[11-23] These studies were published between 2010 and 2019. A total of 4179 patients from 6 countries including Portland, Canada, Japan, America, China and Norway were enrolled. Of note, the article by Kwast et al offered 2 cohorts, one of which included 2 arms. Among these articles, IDC-P status was detected by immunohistochemistry, with the percentage ranging from 9.4 to 76.5%. According to NOS score, all included studies are high-quality (Additional file 1, Supplementary Table 1).

Quantitative data synthesis

Prognostic value of IDC-P status in prostate cancer

Progression-free survival 9 studies including 11 comparisons reported the relationship between PFS and IDC-P status. The HR for PFS showed that IDC-P present status was significantly associated with poor PFS in prostate cancer. IDC-P present status increased the risk of progression by 131% with fixed effects (HR = 2.31; 95% CI 1.96 to 2.73; p < 0.00001) (Fig. 2a). There was no significant heterogeneity (p = 0.31; $I^2$ = 14%). The publication bias was assessed by funnel plot, which indicates moderate publication bias (Additional file 2, Supplementary Figure 1).

Cancer-specific survival Four studies reported the association between CSS and IDC-P status. The HR showed that IDC-P present status was associated with poor CSS in prostate cancer with statistical significance and it increased the risk of cancer-specific death by 89% (HR = 1.89; 95% CI 1.28 to
2.77; \(p = 0.001\) (Fig. 2b). There was no significant heterogeneity (\(p = 0.38; \, I^2 = 3\%\)), so fixed-effects model was used.

**Overall survival** Three studies discussed the relation between CSS and IDC-P status. An association with statistical significance between IDC-P present status and the increased risk for death was found (fixed effect, HR = 2.14; 95% CI 1.53 to 3.01; \(p < 0.0001\)) (Fig. 2c), without significant heterogeneity (\(p = 0.68; \, I^2 = 0\%\)).

**Prognostic value of IDC-P status in prostate cancer with radical prostatectomy**

**Progression-free survival** Seven studies reported the relationship between PFS and IDC-P status of prostate cancer treated by RP. IDC-P present status was significantly associated with poor PFS in prostate cancer treated by RP with fixed effect (HR = 2.48; 95% CI 2.05 to 3.00; \(p < 0.00001\)) (Fig. 3a).

**Prognostic value of IDC-P status in prostate cancer with radiotherapy**

**Progression-free survival** IDC-P present status was significantly related to poor PFS in prostate cancer treated by RT and it increased the risk of progression by 183% (HR = 2.83; 95% CI 1.65 to 4.85; \(p = 0.0002\)) (Fig. 3b). There was no significant heterogeneity (\(p = 0.37; \, I^2 = 0\%\)), so fixed-effects model was used.

**Correlation between clinicopathological characteristics and IDC-P status in prostate cancer**

Fig. 4a - f compared the clinicopathological characteristics of IDC-P present and absent patients. There was no significant difference for PSA value in two group (WMD = 1.59, 95% CI -1.62 to 4.79; \(p = 0.003\)). Furthermore, IDC-P present patients seemed to show significantly more clinical stage T3-T4 (OR = 2.20, 95% CI 1.14 to 4.22; \(p = 0.02\)), higher Gleason score (OR = 4.03, 95% CI 2.40 to 6.75; \(p < 0.00001\)), more N1 lymph node status (OR = 3.79, 95% CI 1.97 to 7.28; \(p < 0.0001\)), more positive surgical margin (OR = 1.77; 95% CI 1.26 to 2.48; \(P = 0.0009\)) and more positive extraprostatic extension (OR = 3.49, 95% CI 1.88 to 6.47; \(P < 0.0001\)) than IDC-P absent patients. Significant heterogeneity was detected in the analysis of clinical stage, Gleason score, extraprostatic extension, so random-effect model was used. In other analysis, fixed-effect models were used.
Discussion

IDC-P is defined as growth of tumor cells within benign prostatic ducts and acini.[24] Specifically, it is defined as malignant epithelial cells filling large acini and prostatic ducts, with preservation of basal cells forming either solid or dense cribriform patterns or loose cribriform or micropapillary patterns with marked nuclear atypia (nuclei six times the normal size or larger) or comedonecrosis.[25] IDC-P is usually juxtaposed with invasive adenocarcinoma, and both histopathologies arise from a common tumor clone.[26] Tumors with IDC-P are also enriched for copy number aberrations associated with poor prognosis.[27] Several studies have reported on genetic abnormalities related to CR/IDC-P. Dawkins et al reported frequent losses of 8p22 and 16q23.1 in intraductal carcinoma.[28] Bettendorf et al found that intraductal carcinoma has more frequent loss of TP53, RB1, and PTEN.[29] Using break-point regions to infer phylogenetic relationships, Lindberg et al showed that the clone closely related to the metastases was found in intraductal carcinoma. These are consistent with the reporting of IDC-P in patients with adverse pathological and clinical features.[26]

The incidence of intraductal carcinoma of the prostate was reported to be 36.3% in needle biopsies and 50.5% in radical prostatectomy specimens of high-risk prostate cancer patients, and that the incidence rose to 67% in patients with distant metastasis at initial diagnosis.[11] Though in the TAX327 study, visceral metastasis, performance status, pain, and hemoglobin and alkaline phosphatase levels were proposed as prognostic parameters for overall survival[30, 31], they demonstrated that the presence of intraductal carcinoma of the prostate on needle biopsy was the strongest prognostic parameter for cancer-specific survival and overall survival among previously reported parameters, including clinical parameters, in patients with distant metastasis at initial diagnosis.

However, two studies also discussed the relationship between presence of IDC-P on diagnostic needle biopsy and a high risk of mortality in localized and metastatic prostate cancer patients.[18, 32] Both of them did not demonstrated the presence of IDC-P was a prognostic factor by multivariate analysis, although they showed it was a prognostic factor by univariate analysis. Even so, the detection of IDC-
P in a needle biopsy may still be superior to prostatectomy in predicting high-risk and aggressive prostate cancer. Furthermore, the detection of IDC-P in a needle biopsy can give useful information regarding patients’ outcome prior to radical prostatectomy. Pre- or/and post- surgical therapies may be needed to improve patients’ outcome in patients with IDC-P in needle biopsies.[12] Though some conflicting results were reported, our meta-analysis also demonstrates that IDC-P is related to poor prognosis and adverse pathological and clinical features. Overall, the presence of IDC-P is significantly related to shorter PFS, CSS and OS. Whether receiving RP or RT, patients with IDC-P show higher risk of tumor progression. And no matter high-risk prostate cancer or localized cancer, the presence of IDC-P also shows higher risk of tumor progression. In addition, patients with IDC-P showed significantly higher PSA value, tumor stage, Gleason score and probability of lymph node invasive, positive surgical margin, and positive extraprostatic extension. Therefore, beyond RP and RT, other anti-tumor modalities may be necessary for IDC-P patients.

The CHAARTED study and the STAMPEDE trial demonstrated that upfront chemotherapy combined with androgen-deprivation therapy could improve survival in high-volume hormone-sensitive metastatic prostate cancer.[33-35] van Soest et al [36] reported that docetaxel had the most pronounced survival benefit in patients with poorly differentiated tumors (Gleason score 7–10). Therefore, patients with metastatic prostate cancer with intraductal carcinoma of the prostate detected in biopsy specimens are highly likely to obtain the greatest benefit from chemotherapy as a first-line treatment instead of androgen-deprivation therapy.[11] Prospective studies are necessary to verify this.

Our meta-analysis has the following limitations that must be taken into consideration. The quality of the present meta-analysis was limited by several factors which might contribute to seemingly contrary results reported in included studies. First, among 13 included studies, most studies are retrospective studies without randomized controlled studies. Hence, confounding factors cannot be eliminated, which introduced bias to result. Second, small sample size of some studies may lead to completely opposite results caused by publication bias. Third, the adjunctive therapy for RT or RP weren’t fully described in most studies, which may also bring bias to the results. Fourth, as described
above, the presence of IDC-P is often related to poor clinicopathological characteristics, which might account for some part of the poor outcome. It remains unclear to deal with this important confounding factor, even in a randomized setting. Without multi-factor analysis, IDC-P may not be considered as an independent predictive factor of prognosis. Fifth, OS and CSS were only reported in few articles (articles without extractable HR were excluded). Long-term prognosis has not been adequately assessed. Sixth, studies without extractable HR data were excluded, resulting in ignorance of results from those studies. Several vital measures were made to reduce these limitations. Firstly, we conducted a systematic, comprehensive search across multiple online databases. Second, we strictly stipulated the inclusion criteria, eliminating the bias caused by some potential confounding factors and data were extracted by two reviewers. Third, we conducted a subgroup analysis of different treatment modalities and clinicopathological characteristics.

Conclusions
In conclusion, our meta-analysis indicates that presence of IDC-P is closely correlated with poor prognosis. It should be considered to recommend chemotherapy to patients with IDC-P as a treatment option. Our data support the value and clinical utility of routine detection of IDC-P by pathological examination.

Abbreviations
IDC-P: intraductal carcinoma of the prostate; HR: hazard ratio; OR: odds ratio; CI: confidence interval; NOS: Newcastle-Ottawa Scale; PFS: progression-free survival; CSS: cancer-specific survival; OS: overall survival; RP: radical prostatectomy; RT: radiotherapy; PICOS: Population, Interventions, Comparators, Outcomes and Study Designs.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
Not applicable.

**Competing Interests**

The authors declare that they have no competing interests.

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**Authors' contributions**

GS, YZ and XL contributed to the conception. SW and JL performed the literature search. ZL and RL contributed to studies examination and quality assessment. HS and TW did the data analysis. GS and DM drafted the work and CW revised it. All authors read and approved the final manuscript.

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Table

**Table 1** - Characteristics of studies included in the meta-analysis.

| Author/Year | Study Design | Country | Tumor Type | Treatment | Case, N | Positive Rate (%) | Median Age, year (range) (Positive vs Negative) | Gleason Score, n (%) | Tumor Stage, n (%) | Nodal Status, n (%) | Median PSA, ng/ml (range) (Positive vs Negative) | Follow-up, months (range) |
|-------------|--------------|---------|------------|-----------|---------|-------------------|-------------------------------------------------|----------------------|-------------------|-------------------|------------------------------------------------|------------------------|
| O’Brien 2010| Prospective  | Portland | High, localized PCA | RP (100%); neoadjuvant chemotherapy (100%) | 10 40 | 20.0 63 (52-74) | 6: 5 (10); 7: 19 (38); 8: 13 (26); 9: 12 (24); 10: 1 (2) | pT1: 0 (0); pT2: 24 (48); pT3: 24 (48); pT4: 2 (4) | NA | NA | 12.0 (1.4-58.6) | 65.1 |
| Kwast 2012 PMH cohort | Retrospective | Canada | Intermediate risk PCA | RT (100%); neoadjuvant ADT (22%) | 23 93 | 19.8 71 (55-82) | ≤6: 38 (32); 7: 80 (68); 8: 0 (0); 9: 0 (0) | cT1: 51 (43); cT2: 67 (57); cT3: 0 (0); cT4: 0 (0) | NA | NA | 7.9 (1.3-19.3) | 78 (9.6-124.8) |
| Kwast 2012 EORTC cohort | Retrospective | Canada | High risk PCA | RT arm: RT (100%); RT plus LTAD arm: RT plus LTAD (100%) | 30 102 | 22.7 70 (51-79) | ≤6: 12 (9); 7: 75 (58); 8: 30 (23); 9: 13 (10); U: 5 (4) | cT1: 0 (0); cT2: 6 (4); cT3: 116 (86); cT4: 13 (10) | NA | NA | NA | NA |
| Kimura 2014 | Retrospective | Japan | High, localized PCA | RP (100%); Neoadjuvant hormone therapy (38.8%); Adjuvant hormone therapy (11.2%); Neoadjuvant and adjuvant therapies (26.7%) | 104 102 | 50.5 68 (46-80) | ≤6: 11 (53); 7: 42 (20); ≥8: 153 (74) | cT1: 35 (17); cT2: 85 (41); cT3: 86 (42); cT4: 0 (0) | N0: 176 (85); N1: 30 (15) | N0: 176 (85); N1: 30 (15) | 25.0 (2.4-296) | 82.8 (3.6-237.6) |
| Miyai 2014 | Retrospective | America | PCa | RP (100%) | 613 288 | 68.0 61 (41-79) vs 59 (42-84) | ≤7: 751 (83); ≥8: 150 (17) | ≤pT2: 759 (84); ≥pT3: 142 (16) | N0: 176 (85); N1: 30 (15) | N0: 176 (85); N1: 30 (15) | 25.0 (2.4-296) | 82.8 (3.6-237.6) |
| Kato 2016 | Retrospective | Japan | Metastatic PCa | ADT (100%); chemotherapy | 100 50 | 66.7 73 (50-90) | 7: 15 (10); 8: 18 (12); 9: 108 (72); 10: 9 (6) | cT2: 26 (17); cT3: 71 (48); cT4: 53 (35) | NA | NA | 328 (4.18-10992) | 38 (0.67-141.1) |
| Zhao 2017 | Retrospective | China | Metastatic PCa progressed to | MAB (100%); Standard first-line therapies (abiraterone or | 62 69 | 47.3 72 (64-75) | ≤7: 21 (16); ≥8: 110 (84) | NA | NA | 65.7 (23.3-172.7) | 59 |
| Year   | Study Type | Country/City | Stage | Treatment | Method | Median PSA (IQR) | Median Age (IQR) | Median PSA (IQR) | Median Age (IQR) |
|--------|------------|--------------|-------|-----------|--------|-----------------|-----------------|-----------------|-----------------|
| 2017   | Retrospective | Norway | M0 or Mx PCa | mCRPC (docetaxel) (73%) | Radical prostatectomy (RP) (14%); RT (12%); Endocrine treatment (34%); Watchful waiting (39%); Other (1%) | 73% | 98 | 185 | 34.6 / 71 (66-78) # |
| 2018   | Retrospective | Japan | High risk PCa | RP (100%) | | 100% | 76 | 116 | 39.3 / 70 (41-78) # |
| 2018   | Retrospective | Japan | High risk, localized PCa | RP (100%) | | | 74 | 130 | 36.3 / 68 (46-80) |
| 2018   | Retrospective | Canada | Localized PCa | RP (100%); Adjuvant RT (16%) | | | 65 | 20 | 76.5 / 62.0 ± 5.5^& |
| 2019   | Retrospective | Japan | Localized PCa | RP (100%) | | | 157 | 862 | 15.4 / 67 (45-80) |
| 2019   | Retrospective | China | High risk PCa | RP (100%) | | | 36 | 382 | 9.4 / 69 (64-73) # |

PSA, prostate-specific antigen; PCa, prostate cancer; RP, radical prostatectomy; NA, not available; RT, radiotherapy; ADT, androgen deprivation therapy; LTAD, long-term androgen deprivation; U, unknown; MAB, maximal androgen blockade; mCRPC, metastatic castration-resistant prostate cancer.

# IQR

^& Mean ± SD

Figures
Figure 1

Study selection process.
Figure 2

Forest plots assessing the association between IDC-P status and (A) PFS, (B) CSS, (C) OS in patients with prostate cancer. Bars indicate the 95% CI.
Figure 3

Forest plots assessing the association between IDC-P status and PFS in patients with prostate cancer treated by (A) RP, (B) RT. Bars indicate the 95% CI.
Forest plots assessing the association between IDC-P status and clinicopathological characteristics: (A) PSA, (B) tumor clinical stage, (C) Gleason score, (D) lymph node status, (E) surgical margin, (F) extraprostatic extension. Bars indicate the 95% CI.

**Supplementary Files**

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