Prognostic value of intraductal carcinoma for adjuvant radiotherapy candidates after radical prostatectomy

Abstract

Objective: We aimed to investigate the prognostic significance of intraductal carcinoma in radical prostatectomy (RP) specimens and predictive value of IDC-P for biochemical recurrence and adjuvant therapy decision.

Method: Patients who underwent RP between 2000-2014 with final pathological stage pT3a and negative surgical margins (Group 1, n=35) and pT2 with positive surgical margins (Group 2, n=32) were included. RP specimens were re-evaluated for the presence of IDC-P component and other prognostic factors. In both groups, prognostic factors were compared according to the presence of IDC-P and biochemical recurrence status.

Results: In group 1, IDC-P was detected in 5 cases and biochemical recurrence was detected in 3 cases. Patients with IDC-P showed significantly higher biochemical recurrence than those without IDC-P ($p=0.002$). In univariate analysis, IDC-P was found to be significantly associated with worse progression free survival ($p<0.001$). In group 2, IDC-P was detected in 4 cases and biochemical recurrence was detected in 10 cases. Also, tumor volume was significantly higher in patients with IDC-P than those without IDC-P ($p=0.02$). IDC-P was also significantly associated with worse progression free survival in group 2 ($p=0.033$).

Conclusions: In both groups, IDC-P is a prognostic factor for progression free survival and / or biochemical recurrence. Especially in these patients, presence of IDC-P might be helpful for postoperative adjuvant therapy management decision.

Keywords: radical prostatectomy, intraductal carcinoma of prostate (IDC-P), prostate cancer, biochemical recurrence, progression free survival

What's already known about this topic?

IDC-P has been reported as an unfavorable prognostic factor in prostate cancer specimens and associated with higher GS, higher tumor volume and rapid progression of the disease, and there is no consensus for adjuvant RT after RP for patients with negative SM and EPE (pT3a) and also for patients with localised disease (pT2) but SM positivity.

What does this article add?

This article evaluates the prognostic value of the presence of IDC-P for biochemical recurrence and its possible role for decision making in candidates for adjuvant RT in these specific patient subgroups.

Introduction

Prostate cancer (PCa) is one of the most prevalent cancer and cause of mortality among all cancers. Its prevalence increases with aging and the majority is clinically localised prostate cancer (1). Radical prostatectomy (RP) is suggested as the best treatment option for patients with clinically localised prostate cancer and long life expectancy (2). However, biochemical recurrence rates after RP have been reported as up to 30% (3). Biochemical recurrence usually precedes clinical disease recurrence and there are some prognostic factors for prediction of biochemical recurrence. These factors are surgical margin (SM) positivity, lymphovascular invasion (LVI), lymph node involvement, extraprostatic extension (EPE), Gleason score (GS), seminal vesicle invasion (SVI), perineural invasion (PNI) and intraductal carcinoma of the prostate (IDC-P) (4-6). Adjuvant radiotherapy (RT) indications after RP are SM positivity, EPE, and other unfavorable pathological findings mentioned above (7).

IDC-P has been reported as an unfavorable prognostic factor in prostate cancer specimens and associated with higher GS, higher tumor volume and rapid progression of the disease (8-10). Recent reports including high risk patients treated with RP or RT also suggest IDC-P as an important predictive factor for early biochemical recurrence and worse prognosis (11,12).

There is no consensus for adjuvant RT after RP for patients with negative SM and EPE (pT3a) and also for patients with localised disease (pT2) but SM positivity (7,13). Pros and cons of adjuvant RT should be discussed with patients by a multidisciplinary team before decision making in these circumstances as stated above.

We aimed to evaluate the prognostic value of the presence of IDC-P for biochemical recurrence and its possible role for decision making in candidates for adjuvant RT in these specific patient subgroups.

Materials and Methods

Patients and Follow-up

After approval of the local ethics committee (aproval number: 1947-GOA:2015/09-33), patients who admitted to our tertiary referral center and underwent RP due to clinically localised PCa between 2000-2014 were retrospectively evaluated. Patients with organ confined disease (EPE (-), stage pT2) and positive surgical margins and extraprostatic extension (EPE (+), stage pT3a) and surgical margins were included. Patients who underwent adjuvant RT were excluded. In this study, patients were divided into two groups as EPE (+) and SM (-) patients (Group 1) and EPE (-) and SM (+) patients (Group 2).

Patients were followed-up with serial serum PSA measurements (in the first three years after RP every 3 months, then every 6 months) according to the recommendations of EAU guidelines. The PSA value after RP above 0.2 ng / ml in at least two serial measurements was defined as biochemical recurrence.

Pathological Evaluation and Definition of IDC-P

All RP specimens were fixed with 10% formaldehyde, totally processed, and paraffin embedded. Tumor volume was calculated with stereological analysis. Sections from RP materials stained with hematoxylin- Eosin (HE) were reevaluated by both two experienced uropathologists blinded to the clinical data of the patients. When necessary, basal cell marker immunohistochemistry (p63 and high molecular weight cytokeratin) and racemase was performed. GS, SM status, EPE, PNI, LVI and also the presence of IDC-P were reassessed for each patient. GS was reassessed according to the 2005 International Society of Urological Pathology (ISUP) grading system. IDC-P was defined according to Epstein criteria that are

preserved basal membrane and filling large acinus and prostatic ducts completely with malignant epithelial cells with nuclear atypia (14).

Statistical Analysis

Prognostic and demographic characteristics of patients with and without IDC-P and biochemical recurrence were analysed using Mann-Whitney U Test and Chi-square Test in both group 1 and 2. Kaplan-Meier survival analysis was performed to investigate the effect of IDC-P on progression-free survival in both Group 1 and Group 2. Statistical analysis was performed by the using of SPSS version 22.0 (SPSS, Chicago, IL, USA). The p value was taken as $p < 0.05$ for significance.

Results

A total of 67 patients out of 501 patients were included in the study where, 35 patients were in Group 1 and 32 patients in Group 2. IDC-P was detected in 5 (14.2%) and 4 (12.5%) patients in Group 1 and Group 2, respectively.

Mean follow-up was 48±35.1 months (min 3- max 131 months) for Group 1. Presence of IDC-P was significantly associated with higher biochemical recurrence rates whereas no statistically significant difference were noted for age, GS, tumor volume, PNI and PSA value between patients with and without IDC-P (Table 1). Factors related to biochemical recurrence were found as both tumor volume and presence of IDC-P in group 1 (Table 2, $p=0.002$).

Mean-progression free survival was 51.8 months in patients who with IDC-P, no biochemical recurrence was observed in the absence of IDC-P (Figure 1, $p<0.001$).

Mean follow-up time was 63±43.6 (min 4 - max 131) months for Group 2. There were not any statistical significance found for age, GS, PNI, LVI, PSA and biochemical recurrence between the patients with and without IDC-P. However, tumor volume was significantly higher in patients with IDC-P compared to patients without IDC-P (6.4±3.9 cc vs 2.4 ±2.7 cc, $p=0.02$). There was no parameter related to biochemical recurrence found for patients in Group 2 (Table 4). Progression-free survival was 28.3 months in patients whit IDC-P, and 88.9 months in patients without IDC-P for Group 2. Also, one-year progression-free survival rates were 50% and 83% in patients with and without IDC-P, respectively (Figure 1, $p=0.033$).

Discussion

Although the best treatment modality of clinically localised PCa is RP in patients with a long life expectancy, tumor recurrence detected by serial PSA measurements can be occured after RP and it can cause death (2). A few clinical and pathological factors have been defined to predict PSA recurrence. One of the pathological factors is IDC-P which has been emphasized in last years. Many studies have shown that the presence of IDC-P is a prognostic factor in PSA recurrence after RP (9,10,15,16). IDC-P usually coexists with adenocarcinoma.

Unlike localized prostate cancer, locally advanced prostate cancer is associated with unfavorable pathological features such as higher GS, higher tumor volume and higher positive SM (17). Many retrospective studies reported in recent years have highlighted that IDC-P worsely affected the prognosis, biochemical recurrence and cancer specific survival in locally advanced PCa (12,18).

In our study, IDC-P status were separately evaluated on the disease prognosis in patients groups who were in Group 1 consisted of locally advanced prostate cancer with negative surgical margin and Group 2 consisted of localized prostate cancer with positive surgical margin, separately. It was determined that the rate of biochemical recurrence was higher in Group 1 patients with positive IDC-P in accordance with the literature. However, in this group, there was not any differences in terms of GS and tumor volume between patients with and without IDC-P in contrast with the literature. On the other hand, biochemical recurrence was found to be associated with high tumor volume in Group 1 patients. In addition, the presence of IDC-P was found to be a prognostic factor for progression free survival. According to the summary of these results, we think that IDC-P is an important prognostic factor in predicting the biochemical recurrence and it can be helpful for us in decision of postoperative adjuvant therapy in pT3a and SM negative patients.

When we look at the Group 2 patients, It was found that the presence of IDC-P had no effect on biochemical recurrence. One of the possible reasons for this may be the limited number of patients. Another possible reason is that the positive surgical margin characteristics of these cases (focal or extensive SM positivity, in multiple or single location and neglected GS at the SM) were missed (19-22). In accordance with the literature, it was observed that the tumor volume was higher in patients with IDC-P than IDC-P negative patients in this group. However, it was detected that biochemical recurrence was not associated with high GS, high tumor volume and high PSA value. The presence of IDC-P was also found to be a prognostic factor for progression free survival in this group.

When we look at previous studies, Van der Kwast et al. showed that the presence of IDC affected early biochemical recurrence in patients received radiotherapy (11). In another study reported by Kimura et al, the presence of IDC-P has been shown to be associated with advanced stage PCa, PSA recurrence and poor prognosis. In addition, it has been also detected that there was a resistance to neoadjuvant hormonal therapy in these patients (12). In a study reported by Lotan et al, PTEN alterations were found to be more frequent in IDC-P than other invasive prostate cancers (22). This finding shows us that IDC-P has a different genetic structure than other invasive prostate cancers and this may be the main reason underlying hormonal resistant disease (12). Then, this finding has been supported by a study of Zhao et al and the prognostic significance of IDC-P has been detected to be in patients with metastatic prostate cancer who transformed to the castration-resistant prostate cancer after the receiving long-term androgen deprivation therapy (ADT). Therefore, they stated that reporting of IDC-P would be beneficial to predict the progression of the disease in the first biopsy, and the treatment protocol may change due to ADT resistance in these patients (23). In the study of Chen et al., they showed that the rate of IDC-P significantly increased in the second biopsy after development of castration resistant prostate cancer under the treatment of ADT

compared to the first biopsy of metastatic prostate cancer diagnosis. Based on this, they accepted that IDC-P is an important risk factor in ADT resistance (24). In addition, in patients who switched to docetaxel chemotherapy after developing castration resistance, while the PSA response rate has been detected to be 66.7% in the absence of IDC-P, the PSA response has been significantly observed to decreased up to 20% in the presence of IDC-P. Thus, they thought that the presence of IDC-P could be an important risk factor for docetaxel resistance (25). Some recent studies have also showed that the loss of PTEN and alterations of ERG and bcl-2 family members may be associated with docetaxel resistance (25-27). Considering the studies conducted, the poor prognostic effect of IDC-P is mentioned in almost all patient groups. However, there is no clear information regarding the treatment protocol. It is obvious that in order to understand the aggressive nature of the IDC-P, more researches are needed in this area.

In contrast to the literature, we aim to evaluate two isolated patient groups in the current study. However, there are several limitations to be considered in the study. One of the limitation is that small number of patients who were evaluated in the study. However, although the number of patients is not striking, the results are remarkable. Another limitation is difficulty in evaluating IDC-P with H-E staining. However, sections from RP materials stained with H-E were reevaluated by both two experienced uropathologists, when necessary, basal cell marker immunohistochemistry (p63 and high molecular weight cytokeratin) and racemase was also performed for our population. In parallel, a study reported by Robinson et al, it was stated that the diagnosis of IDC-P is quite difficult with H-E staining alone and P63, AMACR and high molecular weight cytokeratin containing immune staining are necessary for the diagnosis (28).

In the different series, different detection rate of IDC-P have been given. Kimura et al detected it in 50.5% of high-risk prostate cancers in RP specimens (12). Cohen et al found

that 16.9% of prostate biopsies included IDC-P for localized prostate cancers (17). In a prospective study, Watts et al detected that the rate of IDC-P were 2.8% in all prostate biopsies and 10.6% in PCa diagnosed with prostate biopsies (29). In addition, Guo and Epstein determined the rate of isolated IDC-P unrelated to invasive prostate cancer as 0.06% (14). They stated that, when immunohistochemical staining is not used, IDC-P will been undoubtedly less diagnosed and it may been misclassified as intraductal spread of HGPIN, invasive high-grade prostate carcinoma, ductal adenocarcinoma or urothelial carcinoma. Therefore, in this study, more or less IDC-P could have been diagnosed than normal. However, there is insufficient data about the incidence of IDC-P in our population. Therefore, we think that our results will help update the data on the incidence of IDC-P for the future studies carring out in our country.

Conclusions

It is emphasized in recent years that IDC-P has a negative prognostic effect on biochemical recurrence, survival and response of treatments. Therefore, reporting of the IDC-P in the pathology report of prostate biopsy and RP may be helpful in predicting the poor outcomes that the clinician may encounter. The prognostic effect of the presence of IDC-P was evaluated in highly selected patient groups (pT3a, SM- and pT2 and SM+ groups), and it can be assumed that IDC-P may be used as a predictive factor for the decision of adjuvant therapy in these patient groups according to our results. However, it is obvious that further studies are needed for the optimal treatment option in patients with IDC-P.

Conflict of interest: There are no conflict of interest in connection with this paper.

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