High GLUT1 membrane expression and low PSMA membrane expression in Ductal Adenocarcinoma and Intraductal Carcinoma of the prostate

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Abstract

BACKGROUND

Both Ductal Adenocarcinoma (DAC) and Intraductal Carcinoma (IDC) of the prostate are generally associated with aggressive clinical behavior and poor prognosis, which were linked with discordant FDG positivity and low Prostate-Specific Membrane Antigen (PSMA) expression. A recent study only cited a DAC patient with low ^{68}Ga-PSMA-11 PET/CT uptake but high ^{18}F-FDG PET/CT uptake, however, there is lack of directly compared articles nor large data sets. Hence, the objective of this study was to investigate the expression of PSMA and GLUT1 in DAC and IDC-P patients.

METHODS

The study was conducted on 87 DAC or/and IDC-P patients without any treatment and 97 PAC patients with a Gleason score ≥ 8 of prostate biopsies and prostatectomy samples between August 2017 and August 2022. We performed immunohistochemical staining and scoring of various cancer component samples from the patients to reflect the protein expression levels of PSMA and GLUT1.

RESULTS

PSMA expression in PAC was significantly higher than in DAC/IDC-P (141.2 vs 78.6, $p < 0.001$). There was no significant difference in PSMA expression between DAC/IDC-P and adjacent PAC (78.6 vs 93.4, $p = 0.166$). GLUT1 expression was higher in DAC/IDC-P than in adjacent PAC (68.6 vs 51.3, $p = 0.007$), but was still lower than that in pure PAC (68.6 vs 93.1, $p = 0.0014$). It is worth noting that GLUT1 membrane expression in DAC/IDC-P was significantly increased than in pure PAC (13.0 vs 6.6, $p = 0.025$), and in PAC adjacent to DAC/IDC-P (13.0 vs 2.0, $p < 0.001$).

CONCLUSIONS

In DAC/IDC-P tissues, PSMA expression is low, while GLUT1 expression, especially GLUT1 membrane expression is high. These findings imply that DAC/IDC-P may have higher glucose metabolic and raise interest in targeting membrane GLUT1 as a novel anticancer strategy for DAC/IDC-P and other prostate cancer with high glucose metabolism.

Introduction

Prostate Cancer (PCa) has become inseparably connected to male's cancer, serving as the second most common and fifth leading cause of death among the male(1). The most prevalent variant histological subtype of PCa, Ductal Adenocarcinoma (DAC), which is only marginally less than Prostatic Acinar

Adenocarcinoma (PAC), could account for 0.1–12.7%(2–4) cases. As a result of its aggressive clinical behavior(5) and poor outcomes(6), about 9.3–67.2%(7) of DAC patients had a grading group (GG) ≥ 4. As a major differential diagnosis for DAC, Intraductal Carcinoma of the prostate (IDC-P), which was initially classified as a new unique entity in the 2016 World Health Organization classification of tumors(8), is also associated with poor prognosis. Although the 2014 International Society of Urological Pathology (ISUP) consensus conference approved reporting IDC-P separately from GG(9), reporting of IDC-P remains contentious between two leading pathological societies(10, 11).

Both DAC and IDC-P are aggressive and potentially lethal(12), requiring urgent attention from global urologists. Radical Prostatectomy (RP) series have demonstrated that over 90% of DACs have greater than or equal to pT3(13–17) disease with 27% of DACs having positive nodal disease(15, 16). Furthermore, Biochemical Recurrence (BCR) can occur in up to 70% of DACs post-surgery(5, 13, 14, 17), with up to 50% of DACs developing metastases post-definitive therapy(18). Before the concept was proposed, the prevalence of IDC-P was grossly underestimated, despite a systematic review revealing that the IDC-P prevalence could even get to 2.1%, 23.1%, 36.7%, and 56.0% in the cohort for low-risk, moderate-risk, high-risk and metastatic or recurrent diseases risk categories. They were also highly prevalent, with 60% in tumors after Androgen Deprivation Therapy (ADT) or chemotherapy(19). Nevertheless, both DAC and IDC-P are difficult to diagnose clinically and histopathologically due to the inaccuracy of standard testing and their unique pathological structure.

Positron emission tomography/computed tomography (PET/CT) is a promising non-invasive diagnostic imaging technology that is often used for PCa diagnosis. With its high sensitivity and specificity, ^{68}Ga-PSMA-11 PET/CT can even change the diagnosis and treatment approach of approximately half of PCa patients(20). Due to the heterogeneity of PCa, ^{18}F-FDG PET/CT, commonly used in the diagnosis of tumors, is not commonly used in PCa compared to ^{68}Ga-PSMA-11 PET/CT. Previous studies found that discordant FDG positivity and low PSMA expression are associated with aggressive clinical behavior and poor prognosis (21–25) in CRPC or NEPC. Additionally, a recent study showed that a DAC patient, with low ^{68}Ga-PSMA-11 PET/CT uptake but high ^{18}F-FDG PET/CT uptake(26). This indicated that DACs might have higher tumor glucose metabolism. Considering that IDC-P is the main differential diagnosis of DAC, thus we hypothesize that both may have the features of lower Prostate-specific membrane antigen (PSMA) expression and higher glucose uptake than ordinary PAC. Nevertheless, there are currently no direct comparative articles or support from larger samples. The Glucose Transporter (GLUT) family is a group of facilitative proteins, that primarily mediate glucose uptake, with GLUT1 being the most widely distributed subtype of the transporter isoforms. Moreover, there is evidence that GLUT1 expression is correlated with ^{18}F-FDG-PET/CT uptake(27). Based on these, we preliminarily examined immunohistochemical expression of PSMA and GLUT1 in DAC/IDC-P and PAC to evaluate whether there would be variations in protein level between these two groups.

Materials and methods

Patients characteristics

Patients were selected from all prostate biopsies and prostatectomy samples with comprehensive pathological reports in Xiangya Hospital of Central South University between August 2017 and August 2022. Patients enrolled had to be diagnosed with DAC or/and IDC-P, whereas about the same number of PAC patients were included in the control cohort, from the crowd with a Gleason score ≥ 8. The most important prerequisite was that all patients must not have received any treatment before diagnosis. Furthermore, all samples were pathologically re-evaluation by the pathologist from the Pathology Department of Xiangya Hospital. Patient screening and clinical data collection were done using a simple data management system supported by Chestnut Electronic Data Capture (Chestnut EDC) system (https://empoweredc.com, Solution Inc, Shanghai, China).

Immunohistochemistry

To detect the protein expression, Immunohistochemistry (IHC) staining was performed on slices of Formalin-Fixed Paraffin-Embedded (FFPE) blocks obtained from biopsy and RP samples. Deparaffinization, hydration, epitope antigen retrieval, endogenous peroxidase removal, and serum blocking were all done sequentially. Tissue sections were then incubated for 12 hours at 4°C with primary antibody, anti-PSMA antibody (1:500, ab133579, Abcam), and anti-GLUT1 antibody (1:3000, 21829-1-AP, Proteintech). After incubating the second antibody for 30 minutes at room temperature, sections were stained with DAB horseradish peroxidase chromogenic agent and Haematoxylin, as well as the judgment of the result.

Briefly, the histochemistry score (H-score) was used to evaluate the result of staining intensity(28, 29), calculated from the product of the percentage of area stained at each intensity level multiplied by the weighted intensity (graded as 0, non-staining; 1, weak; 2, median; 3, strong). The range of possible scores was between 0 and 300. Tissue sections were scored by the pathologist from the Pathology Department of Xiangya Hospital.

Statistical analysis

Statistical analyses of the patient age at the corresponding time of biopsy or prostatectomy, initial serum PSA level (< 20 vs ≥ 20), Gleason score (≤ 8 vs 9 vs 10), Grading group (≤ GG4 vs > GG4) and clinical stage (≤ cT2 vs > cT2) were performed using the SPSS version 25.0 (IBMCorp., Armonk, N.Y., USA). GraghPad Prisms 8 (GraghPad Software, Inc., San Diego, CA, USA) was used for IHC analyses. *$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$ indicated statistical significance.

Results

Patient characteristics

A total of 4089 cases of prostate biopsies and RP samples were screened. Our study comprised 87 DAC or/and IDC-P patients (Fig. 1). To compare, 97 PAC patients with Gleason score ≥ 8 were later

incorporated into our study (Fig. 1). The baseline characteristics of the enrolled patients are listed in Table 1. In DAC/IDC-P cohort and PAC cohort, the median age of patients at the corresponding time of biopsy or prostatectomy was 69.0 (65.0–74.0) and 70.0 (64.0-74.5) years, respectively. In total, 29.9% (n = 26) DAC/IDC-P patients had initial serum PSA level < 20 ng/mL, and 56.3% (n = 49) DAC/IDC-P patients ≥ 20 ng/mL, but we didn't get the initial PSA level for 13.8% (n = 12) of DAC/IDC-P patients. The majority of PAC patients (86.6%, n = 84) had PSA levels ≥ 20 ng/mL, with only 13.4% (n = 13) of PAC patients having PSA levels < 20 ng/mL. In total, 51.7% (n = 45) of DAC/IDC-P patients had an initial GG > 4. To match this, 62.9% (n = 61) of PAC patients with an initial GG > 4 were also enrolled in the group. Additionally, 39.1% (n = 34) of DAC/IDC-P patients and 40.2% (n = 39) of PAC patients with clinical stage T3 disease or above were enrolled.

Table 1
Characteristics of untreated patients initially diagnosed as DAC/IDC-P versus PAC

	DAC/IDC-P n = 87	Prostactic acinar adenocarcinoma n = 97		*p* value
Subtype				
DAC	n = 29 (33.3%)			
IDC-P	n = 50 (57.5%)	PAC	n = 97 (100%)	
DAC and IDC-P	n = 8 (9.2%)			
Age				0.345
	69.0 (65.0–74.0)		70.0 (64.0-74.5)	
PSA (ng/mL)				0.001
Loss	n = 12 (13.8%)			
< 20	n = 26 (29.9%)		n = 13 (13.4%)	
≥ 20	n = 49 (56.3%)		n = 84 (86.6%)	
Gleason score				0.310
≤ 8	n = 42 (48.3%)		n = 36 (37.1%)	
9	n = 30 (34.5%)		n = 41 (42.3%)	
10	n = 15 (17.2%)		n = 20 (20.6%)	
Grading Groups				0.126
≤ GG4	n = 42 (48.3%)		n = 36 (37.1%)	
≥ GG4	n = 45 (51.7%)		n = 61 (62.9%)	
Clinical staging				0.223
≤ cT2	n = 53 (60.9%)		n = 58 (59.8%)	
> cT2	n = 34 (39.1%)		n = 39 (40.2%)	

Expression of PSMA and GLUT1

We used immunohistochemical staining to monitor the protein expression of PSMA and GLUT1. Approximately 1/3 of patients in each cohort were randomly selected to score different components of the prostate tissue, such as the normal tissue adjacent to cancer, PAC, and DAC or/and IDC-P, while others were scored regardless of the normal tissue adjacent to cancer. Figures 2A-C shows the representative imagines of various weighted intensity of PSMA and GLUT1. Moreover, GLUT1 exhibited heterogeneous expression in both the cell membrane and cytoplasm (Fig. 2A-C). Thus, from a more clinically relevant

perspective, we re-evaluate the GLUT1 membrane expression, which may reflect possible membrane transport.

In patients with pure PAC, PSMA expression in PAC was higher than that in adjacent normal tissue (Fig. 2D, 141.2 vs. 40.6, $p < 0.001$), despite GLUT1 expression not being significantly different from that of adjacent normal tissue (Fig. 2D, 93.1 vs. 81.09, $p = 0.266$). Similarly, membrane GLUT1 expression in PAC and adjacent normal tissue was not significantly different (Fig. 2D, 6.6 vs. 1.8, $p = 0.067$).

In patients with DAC/IDC-P, PSMA expression of DAC/IDC-P was not significantly different from that in adjacent PAC (Fig. 2E, 78.6 vs. 93.4, $p = 0.166$), but both of them were higher than that in adjacent normal tissue (Fig. 2E, 78.6 vs. 31.8, $p = 0.0012$, and 93.4 vs. 31.8, $p < 0.001$). Nonetheless, GLUT1 expression of DAC/IDC-P was higher than that of adjacent PAC (Fig. 2E, 68.6 vs. 51.3, $p = 0.007$) and normal tissue (Fig. 2E, 68.6 vs. 35.2, $p < 0.001$). GLUT1 expression of adjacent PAC was also higher than that of adjacent normal tissue (Fig. 2E, 51.3 vs. 35.2, $p = 0.035$). Additionally, GLUT1 membrane expression of DAC/IDC-P was higher than that of both adjacent PAC and adjacent normal tissue (Fig. 3D, 13.0 vs. 2.0, $p < 0.001$, and 13.0 vs. 0.9, $p = 0.010$). However, there was no significantly different between adjacent PAC and adjacent normal tissue (Fig. 3D, 2.0 vs. 0.9, $p = 0.394$).

PSMA and GLUT1 expression differences between pure PAC and adjacent PAC accompanied with DAC/IDC-P, as well as between pure PAC and DAC/IDC-P

Figure 3A-C illustrates representative imagines of a PAC patient with high PSMA expression and low GLUT1 expression and DAC/IDC-P patients with low PSMA expression and high GLUT1 expression. We further investigated whether there was a difference in PSMA and GLUT1 expression between pure PAC and adjacent PAC alongside DAC/IDC-P, as well as between pure PAC and DAC/IDC-P.

The results showed that PSMA expression of PAC adjacent to DAC/IDC-P was significantly lower than that of pure PAC (Fig. 3D, 93.4 vs. 141.2, $p < 0.001$), with PSMA expression of DAC/IDC-P also lower than that of pure PAC (Fig. 3D, 78.6 vs. 141.2, $p < 0.001$). The GLUT1 expression of PAC adjacent to DAC/IDC-P was significantly lower than that of pure PAC (Fig. 3D, 51.3 vs. 93.1, $p < 0.001$). Similarly, GLUT1 expression of DAC/IDC-P was lower than that of pure PAC (Fig. 3D, 68.6 vs. 93.1, $p = 0.0014$).

On the contrary, while GLUT1 membrane expression of PAC adjacent to DAC/IDC-P was lower than that of pure PAC (Fig. 3D, 2.0 vs. 6.6, $p = 0.008$), GLUT1 membrane expression of DAC/IDC-P was significantly higher than that of pure PAC (Fig. 3D, 13.0 vs. 6.6, $p = 0.025$).

Finally, we separated DAC and IDC-P and compared them with PAC separately. We found PSMA expression in pure PAC to be significantly higher than both PAC adjacent to DAC and DAC (Fig. 3E, 141.2 vs. 100.2, $p = 0.005$, and 141.2 vs. 79.0, $p < 0.001$, respectively), and PAC adjacent to IDC-P and IDC-P (Fig. 3E, 141.2 vs. 92.2, $p < 0.001$, and 141.2 vs. 78.4, $p < 0.001$, respectively). There was no significant difference between both PAC adjacent to DAC and DAC (Fig. 3E, 100.2 vs. 79.0, $p = 0.230$), and PAC adjacent to IDC-P and IDC-P (Fig. 3E, 92.2 vs. 78.4, $p = 0.312$). GLUT1 expression was also upregulated in

pure PAC relative to both PAC adjacent to DAC and DAC (Fig. 3E, 93.1 vs. 48.8, $p < 0.001$, and 93.1 vs. 63.7, $p = 0.005$, respectively), and PAC adjacent to IDC-P and IDC-P (Fig. 3E, 93.1 vs. 54.8, $p < 0.001$ and 93.1 vs. 71.7, $p = 0.019$, respectively). GLUT1 expression was higher in IDC-P compared to PAC adjacent to IDC-P (Fig. 3E, 71.7 vs. 54.8, $p = 0.043$), while there is no significant difference between DAC and PAC adjacent to DAC (Fig. 3E, 63.7 vs. 48.8, $p = 0.101$). Similarly, membrane GLUT1 expression was higher in PAC compared to PAC adjacent to DAC and PAC adjacent to IDC-P (Fig. 3E, 6.6 vs. 1.2, $p = 0.031$ and 6.6 vs. 1.0, $p = 0.010$, respectively), whereas membrane GLUT1 expression in IDC-P was significantly higher than that in PAC (Fig. 3E, 14.4 vs. 6.6, $p = 0.005$). Membrane GLUT1 level in IDC-P was significantly increased compared to PAC adjacent to IDC-P (Fig. 3E, 14.4 vs. 1.0, $p < 0.001$), whereas there is no significant difference between DAC and PAC adjacent to DAC (Fig. 3E, 5.1 vs. 1.2, $p = 0.056$).

Discussion

At the protein level, we confirmed that the GLUT1 expression, particularly membrane GLUT1 expression in DAC/IDC-P was higher than that in the adjacent PAC structure, with PSMA expression in DAC/IDC-P being possibly lower, especially in IDC-P tissues. PSMA, a type II transmembrane protein with glutamate-carboxypeptidase activity, is significantly over-expressed on prostatic cancer cells, including advanced-stage prostate carcinomas(30, 31), compared to normal prostate tissue. Several studies have reported the expression level of PSMA increases with the stage of PCa(30, 32). Few studies, on the other hand, reported that the upregulation of PSMA expression is not in all PCa cells, especially in the advanced stage of PCa(33). This implies that there is heterogeneity in PSMA expression in PCa cells. In our study, the under-expression of PSMA in DAC/IDC-P may be attributed to the poor differentiation of either DAC or IDC-P.

There is a general assumption that the glucose uptake in tumor cells is high, with the glucose uptake primarily related to GLUT1(34), which is associated with malignant tumors. Similarly, glucose metabolism plays a critical role in the progression of PCa(35). In our study, the high GLUT1 expression, particularly the high membrane GLUT1 expression in DAC/IDC-P, indicates that the glucose metabolism of DAC/IDC-P is higher, demonstrating that the tumor might be more malignant during PCa development. Furthermore, the increased GLUT1 expression of pure PAC in this study could be due to the selection of more malignant patients with a Gleason score ≥ 8. However, more importantly, membrane GLUT1 might play a more important role in DAC/IDC-P in membrane transport, which may also play a hint role in the subsequent control of the progression of invasive PCa, especially DAC/IDC-P, as well as the study of subsequent therapeutic targets.

Although there is a widespread hypothesis that ^{18}F-FDG PET/CT may not be useful in PCa, there was relatively limited evidence suggesting that this imaging method can be used to non-invasively assess the degree of metastatic disease(36). In addition, a DAC patient exhibited higher ^{18}F-FDG PET/CT uptake and a lower ^{68}Ga-PSMA-11 PET/CT uptake based on the existing case report(26). GLUT1 expression was shown to correlate with ^{18}F-FDG PET/CT uptake(27). Moreover, low PSMA expression, as well as discordant FDG positivity is hypothesized to be closely associated with aggressive clinical behavior and

poor prognosis(21–25). In line with this, our results indicated that DAC/IDC-P patients had increased GLUT1 expression by IHC, which could explain the higher ^{18}F-FDG PET/CT uptake. However, none of the patients in our study cohort had undergone both ^{68}Ga-PSMA-11 PET/CT and ^{18}F-FDG PET/CT before receiving any treatment. Hence, we were not able to conduct additional clinical imaging verification. Based on recent research, the positive rate of ^{18}F-FDG PET/CT uptake was also found higher in patients with high-risk prostate cancer, even as high as 90%(25). Therefore, from the clinical aspect, our study suggests that DAC/IDC-P patients may be at high-risk and have a poor prognosis or oncological outcomes, consistent with other studies(37).

Our study has some limitations. First, we cannot directly compare the protein expression of PSMA and GLUT1 to reflect the uptake value at the imaging level since the uptake value may depend on the comprehensive expression of the GLUT family or other protein families. Furthermore, IHC is a semi-quantitative approach for detecting protein expression, and the H-score is subjective as well. Moreover, our DAC patients were few, which could explain why the expression difference in DAC was not as apparent as that in IDC-P. Finally, because our PAC patients were selected from a Gleason score of 8–10, the malignant degree of the control group may be high, and hence the glucose metabolism of the control group is higher, thus GLUT1 expression might be high.

Conclusions

GLUT1 expression is high in DAC/IDC-P, while PSMA expression is low, implying that we can combine IHC of GLUT1 with ^{18}F-FDG PET/CT in daily clinical practice. On the contrary, just like DAC/IDC-P, it is helpful for early diagnosis of PCa with poor prognosis. It can also assist in the diagnosis of high glucose metabolic PCa with the high malignant degree. Meanwhile, it also suggests that membrane GLUT1 could be a potential target for the treatment of aggressive PCa, especially DAC/IDC-P. Additionally, the research and development of membrane GLUT1 inhibitors have clinical prospects and usefulness.

Declarations

Author contributions: Xingming Wang, Li Zhou and Xiaomei Gao analyzed the data, interpreted the results, prepared the figures and tables, and wrote the manuscript. Li Zhou, Xiaomei Gao and Hongling Yin analyzed the histopathologic and immunohistochemical data. Ye Zhang performed the IHC staining assay and analyzed the data. Yi Cai, Yu Gan and Lin Qi designed the experiment and reviewed the manuscript.

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Ethics approval: The study protocol was approved by the Ethics Committee of Xiangya Hospital.

Consent to participate: All patients provided written informed consent.

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Figures

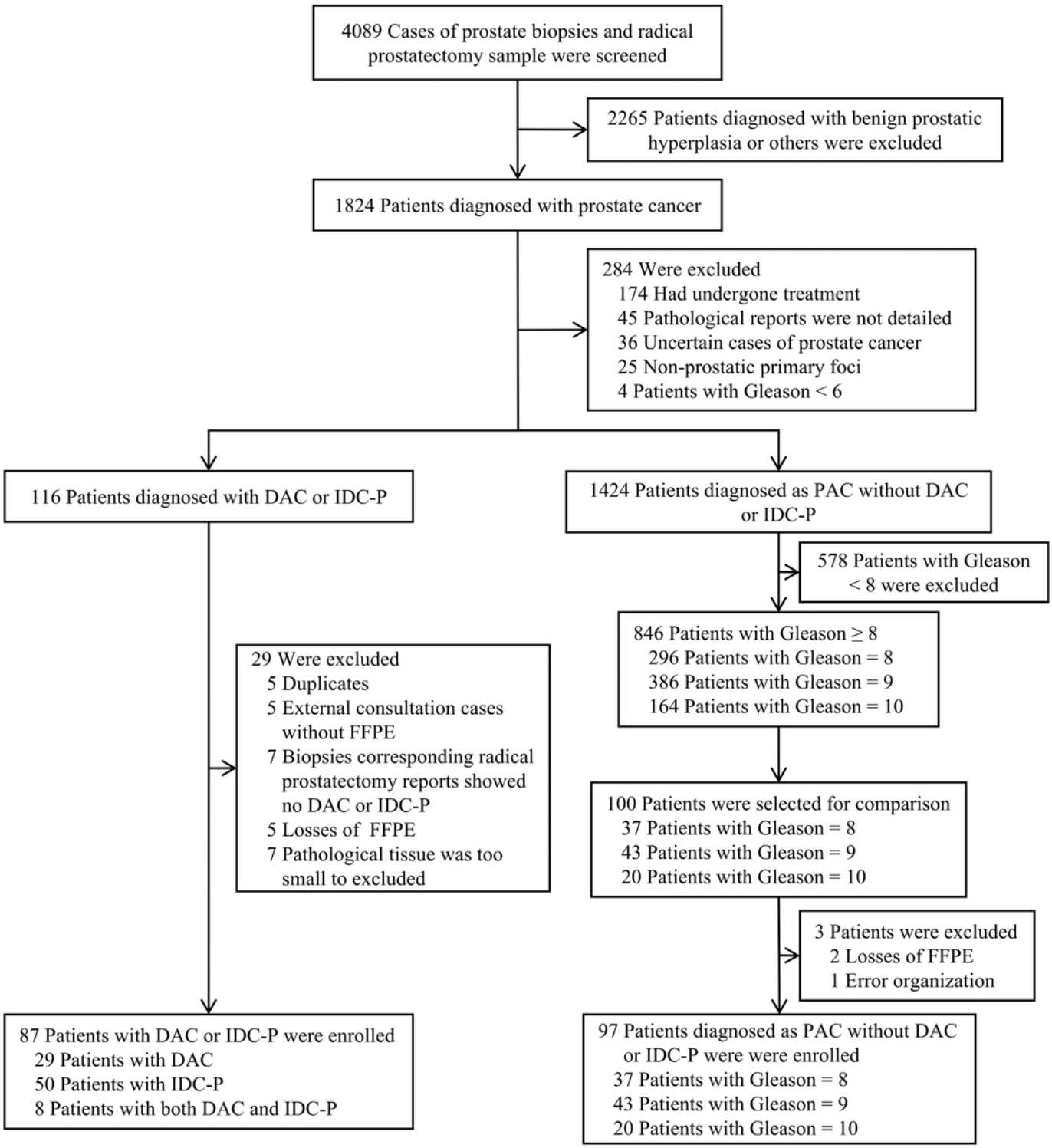

Figure 1

Screening flow diagram.

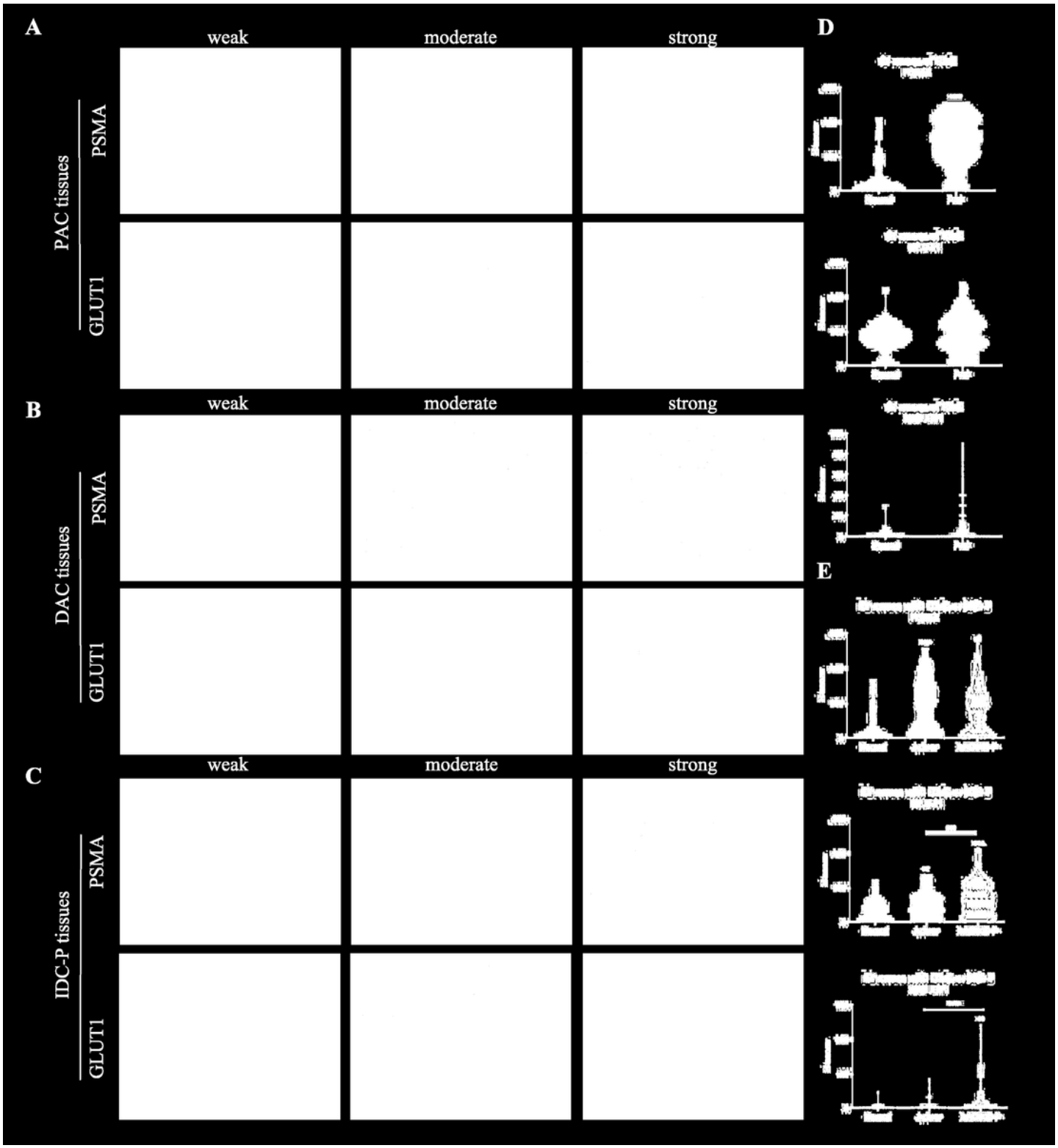

Figure 2

IHC expression level of PSMA and GLUT1 in PAC, DAC, and IDC-P. Representative images of PSMA and GLUT1 staining in different types of prostate cancer tissues with weak, moderate, and strong staining. Analysis of PSMA and GLUT1 protein level in FFPE of clinical prostate tissue. **A**Representative image of PSMA and GLUT1 in PAC tissues with weak, moderate, and strong staining. The scale bar is 100 μm. **B**Representative image of PSMA and GLUT1 in DAC tissues with weak, moderate, and strong staining.

The scale bar is 100 μm. **C**Representative image of PSMA and GLUT1 in IDC-P tissues with weak, moderate, and strong staining. The scale bar is 100 μm. **D** IHC analysis of PSMA and GLUT1 protein in 97 PAC patients. The H-score method was used to score each section. PSMA is upregulated in PAC tissue compared to normal prostate tissue (unpaired t-test, $p < 0.001$), while there is no significant difference in GLUT1 (unpaired t-test, $p = 0.266$). mGLUT1 in PAC tissue and normal prostate tissue is not significantly different (unpaired t-test, $p = 0.007$). **E** IHC analysis of PSMA and GLUT1 protein in 87 DAC/IDC-P patients. H-score method was used to score each section. PSMA is upregulated in DAC/IDC-P tissue and adjacent acinar adenocarcinoma tissue compared to normal prostate tissue (unpaired t-test, $p = 0.0012$ and $p < 0.001$, respectively). There is no significant difference between DAC/IDC-P and adjacent acinar adenocarcinoma (unpaired t-test, $p = 0.166$). GLUT1 protein is significantly higher in DAC/IDC-P tissue and adjacent acinar adenocarcinoma tissue than in normal prostate tissue (unpaired t-test, $p < 0.001$ and $p = 0.035$, respectively). GLUT1 expression is also higher in DAC/IDC-P tissue than in adjacent acinar adenocarcinoma tissue (unpaired t-test, $p = 0.007$). mGLUT1 protein is significantly increased in DAC/IDC-P tissue compared to adjacent acinar adenocarcinoma tissue and adjacent normal prostate tissue (unpaired t-test, $p < 0.001$ and $p = 0.010$, respectively), but there is no significant difference between adjacent acinar adenocarcinoma tissue and adjacent normal prostate tissue (unpaired t-test, $p = 0.394$).

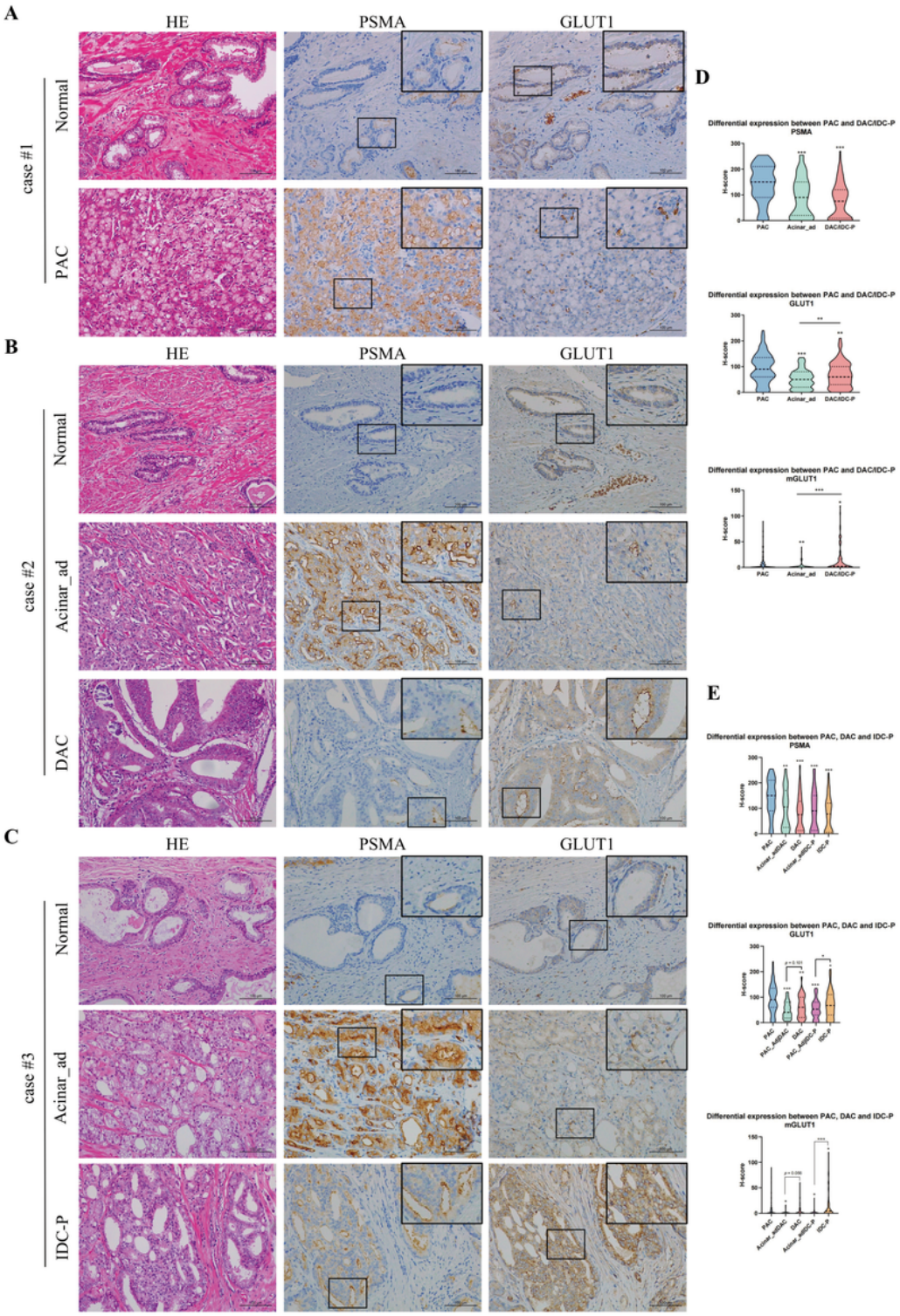

Figure 3

Representative image and IHC expression differences of PSMA and GLUT1 in PAC, DAC, and IDC-P. Representative image of HE and two different IHC markers in 3 patients with various types of prostate cancer. Analysis of PSMA, GLUT1, and mGLUT1 protein levels in FFPE of clinical prostate tissue. **A**Representative image of a PAC patient with strong PSMA expression and weak GLUT1 expression. The scale bar is 100 μm. **B**Representative image of a DAC patient with strong PSMA expression and weak

GLUT1 expression in adjacent acinar adenocarcinoma structures, and a strong GLUT1 expression and weak PSMA expression in DAC structure. The scale bar is 100 μm. **C** Representative image of an IDC-P patient with strong PSMA expression and weak GLUT1 expression in adjacent acinar adenocarcinoma structure, and a strong GLUT1 expression and weak PSMA expression in IDC-P structure. The scale bar is 100 μm. **D** Analysis of various PSMA and GLUT1 expressions between cancers. H-score method was used to score each section. PSMA is upregulated in PAC tissue than in acinar adenocarcinoma tissue adjacent to DAC/IDC-P (unpaired t-test, $p < 0.001$). PSMA is upregulated in PAC tissue compared with DAC/IDC-P tissue (unpaired t-test, $p < 0.001$). GLUT1 is upregulated in DAC/IDC-P tissue and PAC tissue than in acinar adenocarcinoma tissue adjacent to DAC/IDC-P (unpaired t-test, $p = 0.007$ and $p < 0.001$, respectively). GLUT1 is upregulated in PAC tissue compared with DAC/IDC-P tissue (unpaired t-test, $p = 0.0014$). mGLUT1 is increased in DAC/IDC-P tissue than in PAC tissue (unpaired t-test, $p = 0.025$), while mGLUT1 is upregulated in PAC tissue than in acinar adenocarcinoma tissue adjacent to DAC/IDC-P (unpaired t-test, $p < 0.001$). **E** IHC analysis of PSMA, GLUT1, and mGLUT1 in PAC, DAC, and IDC-P. Each section was scored using the H-score method. PSMA is significantly upregulated in PAC tissue compared with acinar adenocarcinoma adjacent to DAC, DAC, acinar adenocarcinoma adjacent to IDC-P, and IDC-P tissue (unpaired t-test, $p = 0.005$, $p < 0.001$, $p < 0.001$ and $p < 0.001$, respectively). GLUT1 is upregulated in PAC tissue relative to acinar adenocarcinoma adjacent to DAC, DAC, acinar adenocarcinoma adjacent to IDC-P and IDC-P tissue (unpaired t-test, $p < 0.001$, $p = 0.005$, $p < 0.001$ and $p = 0.019$, respectively). GLUT1 is increased in IDC-P tissue than in acinar adenocarcinoma adjacent to IDC-P (unpaired t-test, $p = 0.043$), whereas there is no significant difference between DAC and acinar adenocarcinoma adjacent to DAC (unpaired t-test, $p = 0.101$). mGLUT1 is upregulated in PAC tissue relative to acinar adenocarcinoma adjacent to DAC and acinar adenocarcinoma adjacent to IDC-P (unpaired t-test, $p = 0.031$ and $p = 0.010$, respectively), while mGLUT1 expression in IDC-P is significantly higher than that in PAC (unpaired t-test, $p = 0.0049$). mGLUT1 is significantly increased in IDC-P tissue compared with acinar adenocarcinoma adjacent to IDC-P (unpaired t-test, $p < 0.001$), while there is no significant difference between DAC and acinar adenocarcinoma adjacent to DAC (unpaired t-test, $p = 0.056$).