The Significance of Aldehyde Dehydrogenase 1A1 Expression in Benign Prostatic Hyperplasia, Prostatic Intraepithelial Neoplasia and Prostatic Adenocarcinoma

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Abstract:

Background: Prostatic carcinoma contains a small population of cancer stem cells (CSCs) that promote tumor growth, maintenance, and progression. CSC markers could provide a prognostic tool for human malignancies. Therefore, CSCs may have a role in prostatic carcinoma. This study aimed to evaluate the expression patterns and significance of stem cell marker aldehyde dehydrogenase 1A1 (ALDH1A1) in prostatic adenocarcinoma. **Methods**: This is a retrospective study performed upon 60 cases grouped as; 10 cases (16.7%) of benign prostatic hyperplasia (BPH), 6 cases (10%) of high-grade prostatic intraepithelial neoplasia (HGPIN) and 44 cases (73.3%) of prostatic adenocarcinoma (PCa) of different Gleason scores. Immunohistochemistry was applied on formalin-fixed, paraffin-embedded blocks using ALDH1A1. The relation between ALDH1A1 expression and clinicopathologic parameters was assessed. **Results:** Low expression of ALDH1A1 was seen in all cases (100%) of BPH, 5/6 (83.3%) of HGPIN and 12/44 (27.3%) of PCa, while high expression was in 1/6 case (16.7%) of HGPIN and 32/44 (72.2%) of PCa cases. There were significant relations between the expression levels of ALDH1A1 in PCa compared with HGPIN and BPH cases ($P<0.01$). ALDH1A1 expression showed highly significant associations with pre-operative serum PSA level, Gleason score, Gleason Grade Group ($P<0.01$) and was significantly associated with perineural invasion and tumor stage ($P<0.05$). No significant relations were found between ALDH1A1 expression and patients` age, capsular invasion, lymphovascular invasion, depth of invasion (pT) or lymph node metastasis. **Conclusion:** ALDH1A1 is a prostate CSC marker, could be involved in tumorigenesis and progression of prostatic adenocarcinoma

Keywords: ALDH1A1, BPH, HGPIN, prostatic adenocarcinoma.

Introduction:

Prostate cancer ranks as the second most common cancer in men worldwide after cancer lung.[1] Old age, genetic factors, geographical residence and lifestyle are firmly-established risk factors for prostate cancer.[2]

In Egypt, prostatic cancer formed the majority of male genital cancers (60.7%) at the National Cancer Institute in ten years from 2006 to 2016. The median age was 72.8 years.[3] There is strong evidence that many solid tumors like breast, liver, lung, pancreatic, colorectal, brain and prostate cancers arise from cancer stem cell (CSC) population. Cancer stem cells promote more aggressive tumors with high metastatic potential and high risk of recurrence. Moreover, they give rise to tumors that are resistant to conventional therapy.[4] So, identification of specific markers for the CSCs will increase knowledge about tumor biology and progression.[5]

Aldehyde Dehydrogenase-1, family member A1 (ALDH1A1) is a stem cell marker which has a central role in the biology of tumor initiating cells.[6] It is a detoxifying enzyme which has a role in the oxidization of intracellular aldehydes with resistance to alkylating agents. It protects CSCs from oxidative injury and enhances their proliferation and differentiation.[7] ALDH1A1 plays a major role in retinoic acid metabolism and androgen receptor binding which are both considered in prostate development.[8]

In prostate cancer (PCa), high ALDH activity has been associated with increase migratory activity, tumor progression and metastasis. While the role of ALDH1A1 in prostate cancer is still poorly understood .[9]

This study aimed at assessment of immunohistochemical expression of ALDH1A1 in prostatic adenocarcinoma and its association with tumorigenesis and potential prognostic role.

Material and Methods:

This study was performed in Pathology Department and Early Cancer Detection Unit; Benha Faculty of Medicine. Cases were processed during the years from January 2013 to December 2018. The study was approved by the Ethical committee of faculty of Medicine, Benha University.

It is a retrospective, controlled, selective study performed upon formalin-fixed, paraffin-embedded blocks of selected 60 cases of Egyptian male patients designated as 10 cases (16.7%) of prostatic chips of benign prostatic hyperplasia, 6 cases (10%) of TRUS guided biopsies of HGPIN and 44 cases (73.7%) of radical prostatectomy specimens of prostatic adenocarcinoma.

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Clinicopathological data were collected from the files of the patients including patients' demographic, clinical and macroscopic data as patient's age, pre-operative PSA serum level, depth of tumor invasion p(T), lymph node metastasis and distant metastasis.

Cases were classified into two groups according to the mean age, <65 years and ≥65 years. According to pre-operative PSA serum level, cases were classified into 3 groups (<4 ng/ml), (4-10 ng/ml) and (>10 ng/ml).

Histopathological study:

Paraffin blocks were collected and two slides of each block of 4 micron thickness were cut, one on plain slide and the other on positively charged slide. The sections were dewaxed at 56^{o} C for 2 hours and one slide was made ready for staining with hematoxylin and eosin. Slides of all cases were reviewed by two observers simultaneously to confirm the diagnosis. The remarkable microscopic features such as tumor grade, capsular invasion, lymphovascular invasion and perineural invasion were noted.

Prostatic adenocarcinoma cases were classified as stated in the WHO classification [10] and were graded according to the Gleason scoring system which was based on the guidelines of The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma.[11]

According to the recent Gleason Grade Group (GGG) system, prostatic adenocarcinoma cases were divided into five categories based on the primary and secondary Gleason patterns: Grade Group I (Gleason score 3 + 3), Grade Group II (3 + 4), Grade Group III (4 + 3), Grade Group IV (4 + 4, 3 + 5, or 5 + 3) and Grade Group V (4 + 5, 5 + 4, or 5 + 5).[12] TNM staging was performed for PCa cases in accordance to AJCC staging system.[13]

Immunohistochemical study:

Slides were immune stained with ALDH1A1 Rabbit polyclonal antibody (Chongqing biopsies co., Cat No YPA1390, China, conc) at a dilution of 1:100, at room temperature overnight. Immunodetection was carried out using a standard labeled streptavidin-biotin system (Genemed, CA 94080, USA, South San Francisco). It was performed based on manufacturer's instructions. Antigen retrieval was done by using 10 mmol/L citrate monohydrate buffer (PH 6.0) and heated for 15 minutes in the microwave. DAB) was used as chromogen. Normal liver tissue was used as external positive control. Negative control was obtained by processing tissue section with omitting the primary antibody and adding Phosphate Buffered Saline (PBS) instead.

Immunostaining evaluation:

Positivity was considered as brownish homogenous cytoplasmic staining of tumor cells. The intensity of the ALDH1A1

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immunostaining was scored on a scale of 0 to 3+, as score of 0=no visible staining, 1=faint staining, 2=moderate staining, and 3=strong staining. Percentage of tumor cells with positive staining was graded as <25%, 25% to 50%, 51% to 75%, and >75% of tumor cells.

To compare all of the available data, an overall Histochemical Score (H-score) was assigned to each case by multiplying the intensity score by the percentage of stained cells, and a final score of 0 to 300 was given.

Cutoff points were chosen to categorize samples as high or low ALDH1A1-expressing samples in terms of the H-score (Cutoff =33). The specimens with H-score ≤33 were regarded as low ALDH1A1-expressing specimens, and the specimens with H-score >33 were regarded as high-ALDH1A1 tissues.[15]

Statistical analysis: Results were analyzed using SPSS (version 16) statistical package for Microsoft windows (SPSS Inc., Chicago, IL, USA). Categorical data were expressed as numbers and percentages.

Numerical data were expressed as mean ± standard deviation. Pearson Chi square test(X^2) and Fisher`s Exact test (FET) were used to assess relations between groups. P-value >0.05 was considered non-significant (NS), <0.05 significant (S), ≤ 0.01 highly significant (HS).

Results:

Clinico-pathological features:

The examined 60 cases were 10 cases of benign prostatic hyperplasia, 6 cases of high grade prostatic intraepithelial neoplasia and 44 cases of prostatic adenocarcinoma including: 12 cases (27.3%) of Gleason grade I, 11 cases (25%) of grade II, 7 cases (15.9%) of grade III, 6 cases (13.6%) of grade IV and 8 cases (18.2%) of Gleason grade V.

The relation between Gleason Grade Groups of PCa cases and different clinicopathological data were summarized in table (1). The results revealed statistically significant associations between Gleason Grade Groups (GGG)s of prostatic adenocarcinoma and patient`s age, pre-operative PSA serum level, lymphovascular invasion and perineural invasion (P-value <0.05|). There were highly significant statistical associations between GGGs and tumor depth of invasion p(T) and tumor stage (P-value <0.01). However, no significant statistical relation was found between Gleason Grade Groups and capsular invasion or lymph node metastasis.

Immunohistochemical results:

The percentage and intensity of ALDH1A1 in different study groups were studied and H-score was calculated. All BPH cases (100%) had low H-score, while (72.7%) of PCa cases (72.7%) had high H-score. There was a highly significant statistical associations between studied

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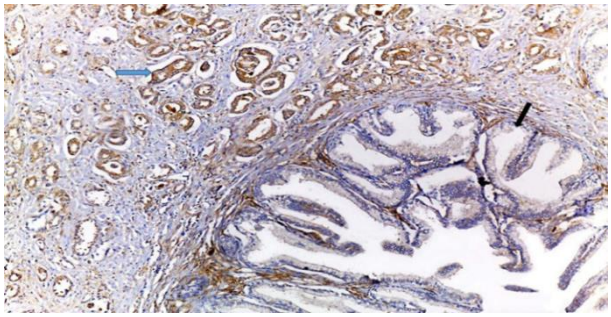
groups and ALDH1A1 expression (table 2).ALDH1A1 expression was related with different clinicopathological findings and this was summarized in table(3). ALDH1A1 expression showed highly significant associations with pre-operative serum PSA level, Gleason score and Gleason Grade Groups (P<0.01) (Figures 1,2,3), and was significantly associated with perineural invasion and tumor stage (P<0.05 for each). No significant relations were found between ALDH1A1 expression and patients` age, capsular invasion, lymphovascular invasion, tumor depth of invasion (pT) or lymph node metastasis.



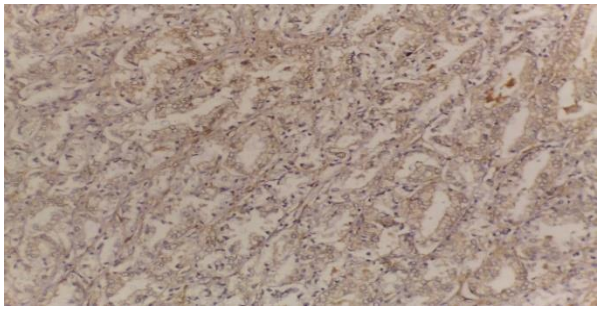
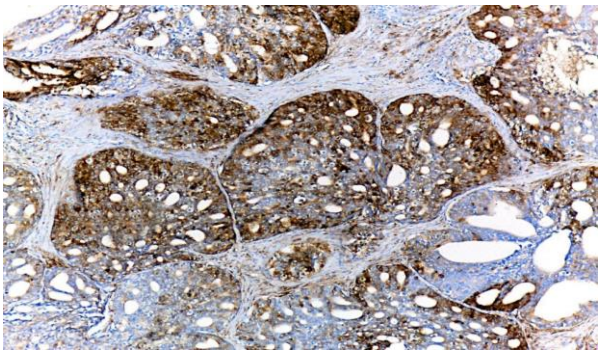


Figure (1A): Prostatic adenocarcinoma Gleason Grade Group I showing moderate positive cytoplasmic expression of ALDH1A1 (blue arrow), with negative adjacent benign glands (black arrow) (IHC, ABC x100). Figure (1B): prostatic adenocarcinoma Gleason Grade Group I illustrated by high power to show moderate positive cytoplasmic expression (IHCX400).



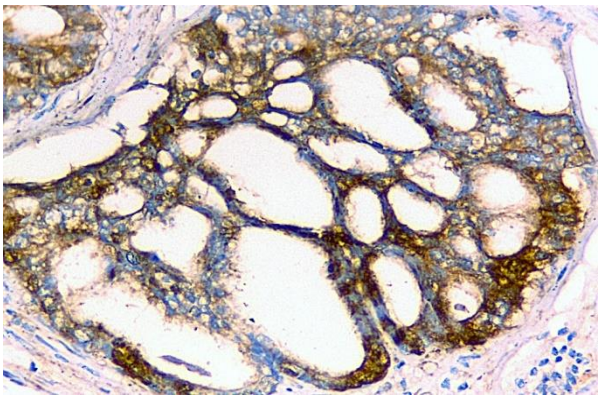


Figure (2A): Cribriform pattern of prostatic adenocarcinoma (Gleason Grade Group IV) showing strong positive ALDH1A1 cytoplasmic expression (IHC, ABC x100). Figure (2B): Prostatic adenocarcinoma with cribriform pattern illustrated by high power to show strong positive cytoplasmic expression (IHC, ABCX400).

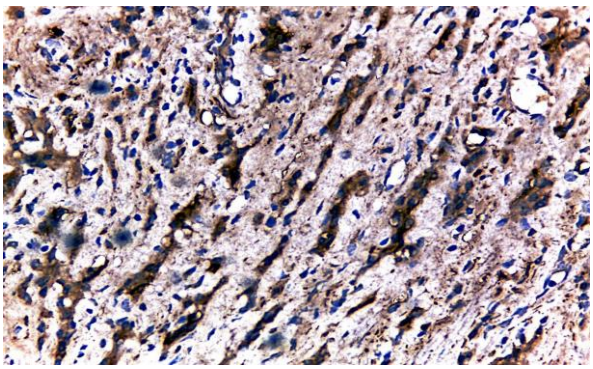


Figure (3): Prostatic adenocarcinoma Gleason Grade Group V showing cords of malignant cells with strong positive ALDH1A1 cytoplasmic expression (IHC, ABC x400).

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Table (1): Relation between Gleason grade group and other Clinico-pathological parameters

Clinico-pathological Parameters	Gleason grade group					P value
	grade I *(12 cases)*	*grade II (11 cases)*	*grade III* *(7 cases)*	*grade IV* *(6 cases)*	*grade V* *(8 cases)*	
Patient`s age						
• <65	8 (66.7%)	9 (81.8%)	5 (71.4%)	3 (50%)	1 (12.5%)	
• ≥65y	4 (33.3%)	2 (18.2%)	2 (28.6%)	3 (50%)	7 (87.5%)	**<0.05***
Preoperative PSA serum level						
• 4-10 ng/ml	8 (66.7%)	7 (63.6%)	2 (28.6%)	2 (33.3%)	0 (0%)	**<0.05***
• >10 ng/ml	4 (33.3%)	4 (36.4%)	5 (71.4%)	4 (66.7%)	8 (100%)	
Capsular invasion						
• Present	1 (8.3%)	2 (18.2%)	3 (42.9%)	3 (50%)	4 (50%)	
• Absent	11 (91.7%)	9 (81.8%)	4 (57.1%)	3 (50%)	4 (50%)	>0.05
Lymphovascular invasion						
• Present	0 (0%)	1 (9.1%)	2 (28.6%)	0 (0%)	4 (50%)	
• Absent	12 (100%)	10 (90.9%)	5 (71.4%)	6 (100%)	4 (50%)	**<0.05***
Perineural invasion						
❖ Present	2 (16.7%)	2 (18.2%)	4 (57.1%)	4 (66.7%)	6 (75%)	
❖ Absent	10 (83.3%)	9 (81.8%)	3 (42.9%)	2 (33.3%)	2 (25%)	**<0.05***
Tumor depth of invasion (pT)						
❖ T2	12 (100%)	11 (100%)	5 (71.4%)	2 (33.3%)	1 (12.5%)	**<0.01****
❖ T3	0 (0%)	0 (0%)	2 (28.6%)	4 (66.7%)	7 (87.5%)	
LN metastasis						
❖ Present	0 (0%)	1 (9.1%)	2 (28.6%)	2 (33.3%)	1 (12.5%)	
❖ Absent	12 (100%)	10 (90.9%)	5 (71.4%)	4 (66.7%)	7 (87.5%)	>0.05
Tumor stage						
❖ Stage I	4 (33.3%)	1 (9.1%)	0 (0%)	0 (0%)	0 (0%)	
❖ Stage II	8 (66.7%)	8 (72.7%)	3 (42.9%)	2 (33.3%)	1 (12.5%)	
❖ Stage III	0 (0%)	1 (9.1%)	2 (28.6%)	2 (33.3%)	6 (75%)	**<0.01****
❖ Stage IV	0 (0%)	1 (9.1%)	2 (28.6%)	2 (33.3%)	1 (12.5%)	

Abbreviations: PSA= Prostatic Specific Antigen, T= depth of invasion, LN= Lymph NodeValues: >0.05= non significant, <0.05= significant, <0.01= highly significant

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Table (2): Expression of ALDH1A1 in different studied groups

H-score	BPH	HGPIN	PCa	Total	P-value
Low (≤33)	10 (100%)	5 (83.3%)	12 (27.3%)	27 (45%)	**<0.01****
High (>33)	0	1 (16.7%)	32 (72.7%)	33 (55%)	
Total	10	6	44	60	

Abbreviations: BPH= Benign Prostatic Hyperplasia, HGPIN= High Grade Prostatic Intra-epithelial Neoplasia, PCa= Prostatic adenocarcinoma. Values: >0.05= non significant, <0.05= significant, <0.01= highly significant

Table (3): Relations between ALDH1A1 expression and other clinico-pathological parameters

Clinico-Pathological parameters	Score of ALDH1A1 expression: Low H-score (≤33) No (%)	High H-score (>33) No (%)	P value
Studied Groups			
• BPH	10 (100%)	0 (0%)	
• HGPIN	5 (83.3%)	1 (16.7%)	**<0.01****
• Pca	12 (27.3%)	32 (72.2%)	
Patient`s age			
❖ <65y	15 (44.1%)	19 (55.9%)	>0.05
❖ ≥ 65y	12 (46.2%)	14 (53.8%)	
Pre-operative serum PSA level			
❖ <4 ng/ml	3 (100%)	0 (0%)	**<0.01****
❖ 4-10 ng/ml	18 (62%)	11 (38%)	
❖ >10 ng/ml	6 (21.4%)	22 (78.6%)	
Gleason score			
❖ Score 6	10 (83.3%)	2 (16.7%)	**<0.01****
❖ Score 7	1 (5.6%)	17 (94.4%)	
❖ Score 8	0 (0%)	6 (100%)	
❖ Score 9	1 (12.5%)	7 (87.5%)	
Gleason Grade Groups			
❖ Grade I	10 (83.3%)	2 (16.7%)	**<0.01****
❖ Grade II	0 (0%)	11 (100%)	
❖ Grade III	1 (14.3%)	6 (85.7%)	
❖ Grade IV	0 (0%)	6 (100%)	
❖ Grade V	1 (12.5%)	7 (87.5%)	
Capsular invasion			

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❖ Present	1 (7.7%)	12 (92.3%)	>0.05
❖ Absent	11 (35.5%)	20 (64.5%)	
Lymphovascular invasion			
❖ Present	0 (0%)	7 (100%)	>0.05
❖ Absent	12 (32.4%)	25 (67.6%)	
Perineural invasion			
❖ Present	2 (11.1%)	16 (88.9%)	**<0.05***
❖ Absent	10 (38.5%)	16 (61.5%)	
Tumor depth of invasion pT			
❖ T2	11 (35.5%)	20 (64.5%)	>0.05
❖ T3	1 (7.7%)	12 (92.3%)	
LN metastasis			
❖ Present	0 (0%)	6 (100%)	>0.05
❖ Absent	12 (31.6%)	26 (68.4%)	
Tumor stage			
❖ Stage I	3 (60%)	2 (40%)	**<0.05***
❖ Stage II	8 (36.4%)	14 (63.6%)	
❖ Stage III	1 (9.1%)	10 (90.9%)	
❖ Stage IV	0 (0%)	6 (100%)	

Abbreviations: ALDH1A1= Aldehyde Dehydrogenase 1A1, No= Number, BPH= Benign Prostatic Hyperplasia, HGPIN= High Grade Prostatic Intra-epithelial Neoplasia, PCa= Prostatic adenocarcinoma, PSA= Prostatic Specific Antigen, T= depth of invasion, LN= Lymph Node. Values: >0.05= non significant, <0.05= significant, <0.01= highly significant

Discussion:

Determination and isolation of prostate CSCs has a central role in understanding the tumorogenesis, progression, drug resistance and metastasis of the tumor.[5] ALDH superfamily is one of the proteins in CSCs especially in solid tumors .[14] Overexpression of ALDH1A1 has a role in tumor progression in several malignancies and it may has a diagnostic and therapeutic role for cancer prostate.[15]

In this study, all cases of BPH (100%) and (83%) cases of HGPIN showed low expression of ALDH1A1, while 72% of prostatic adenocarcinoma cases showed high ALDH1A1 expression. There was a highly significant statistical association between ALDH1A1 expression and studied groups (p value <0.01). These results were in agreement with Van den et al., [8], Abdelmoneim et al., [4] and Kalantari et al.,)[15] who found that almost all BPH and HGPIN cases had no detectable staining while there was high expression of ALDH1A1 in prostatic adenocarcinoma and there was a statistically significant correlation. Elevated enzymatic reactivity of cytosolic ALDH1A1 in CSCs proves the

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oncogenic role of ALDH1A1 in prostate carcinogenesis.[14]

As regard pre-operative PSA serum level, there was a highly significant statistical association between PSA level and ALDH1A1 expression (p value <0.01). Kalantari et al., [15] agreed with these results. This is not surprising as cases in this study with PSA level <4 ng/ml were BPH and HGPIN which showed low expression of ALDH1A1.

Additionally, there was a highly significant statistical association between the expression of ALDH1A1 and Gleason score and Gleason Grade Groups (p value <0.01). These findings were in agreement with previous studies carried out by Li et al., [5], Abdelmoneim et al.,)[4] and Nastały et al., [16] who noticed that there was an increase in ALDH1A1 immunoreactivity is association with the pathologic grade (Gleason score) in cases of prostatic adenocarcinoma .

In harmony with these results, van den et al.,)[8] and kalantari et al., [15] found that high aldehyde dehydrogenase activity identifies tumor-initiating cells in prostate cancer and increased expression in higher tumor grades may have a role in tumor progression.

In contrast, Matsika et al., [17] in his study on prostate cancer found no significant relation between ALDH1 expression and Gleason score. This may be due to different interpretation of ALDH1A1 expression and different number of PCa cases of each Gleason score.

Other studies performed by Penumatsa et al., [18] on cancer ovary, Kahlert et al., [19] on pancreatic carcinoma and Tanaka et al., [20] on hepatocellular carcinoma revealed that well differentiated tumors showed higher expression of ALDH1A1 compared to poorly differentiated malignancies. These variabilities of ALDH1A1 expressions among studies may be due to different tissues with different molecular signature.or different tissue specificity.

In the present study, although 92% of prostatic adenocarcinoma cases with positive capsular invaion and all cases of prostatic adenocarcinoma with positive lymphovascular invasion showed high ALDH1A1 expression, this didn`t give statistical significance may be due to limited number of positive cases.

A recent study carried out by Wang et al., [21] by quantitative PCR assay results were in agreement with these results and explained that cancer cells with higher migration potential had increased expression of the ALDH1A1. This elevated expression of the putative cancer stem cell marker ALDH1A1

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suggests the relationship between stem cells and tumor invasion.

In this study, about 90% of cases with positive perineural invasion showed high expression of ALDH1A1. There was a statistically significant association between ALDH1A1 expression and perineural invasion (p value <0.05). This may be because most cases with positive perineural invasion were of higher grade which highly express ALDH1A1.

Similarly ,Nour El Hoda et al., [22] who found a statistically significant positive relation between ALDH1A1 expression and nerve invasion in cancer bladder cases.

In opposition to these findings, Xu et al.,)[23] found no statistically significant relation between ALDH1A1 expression in x cholangiocarcinoma cases and nerve invasion. These variations may be due to different tissue and also different geographic and genetic variability between races because it was performed on Chinese patients.

Concerning tumor depth of invasion p(T), most PCa cases with pT2 (65%) and pT3 (92%) showed high expression of ALDH1A1. However, it didn`t reach a statistical significance value (p value >0.05). These results were consistent with studies performed by Li et al., [5] and Matsika et al., [17] on prostate cancer.

This can be explained by the role of ALDH1A1 in increasing tumor growth and cancer stem cell proliferation. ALDH1A1 oxidizes aldehydes and reduces NAD+ to NADH using glutathione (GSH) and dihydrolipoic acid (DHLA) as electron donors. This activity of ALDH1A1 was found to promote tumor growth .[24]

In the current study, all cases of prostatic adenocarcinoma with positive lymph node metastasis showed high expression of ALDH1A1 although not statistically significant due to limited number of Pca cases with positive nodal metastasis (only 6 cases (13.5%) out of 44).

ALDH1A1 was found to provoke tumor invasion and LN metastasis via the Wnt/β-catenin signaling pathway [25] The association between Wnt/β-catenin signaling pathway and the retinoic acid signaling pathway has been reported .[26]

As regard TNM stage, high expression of ALDH1A1 was more frequently seen in PCa tumors with advanced tumor stage (about 90% of stage III and 100% of stage IV PCa cases showed high expression). There was a statistically significant association between TNM stage and ALDH1A1 expression (P value <0.05).

Many studies on ALDH1A1 expression were in agreement with these results indicating the role of ALDH1A1 positive CSCs in tumor

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progression and advanced stage. These studies were carried out by Li et al., [27] on cancer lung, Li et al.,)[28] on gastric cancer, Xing et al.,)[29] on papillary thyroid carcinoma, Yang et al., (2014)[30] on cancer esophagus and Zhou et al.,)[31] on colorectal carcinoma.

Aldehyde dehydrogenase 1A1 promotes epithelial mesenchymal transition (EMT) which is important for tumor metastasis. Koren et al.,[32] revealed a significant association between ALDH1A1 expression and (EMT)-inducing transcription factor Bmi1 which indicated its major role in EMT and tumor invasion.

Another mechanism of tumor spread is pathological angiogenesis. ALDH1A1 expression was found to be correlated with activation of angiogenic factors, particularly hypoxia inducible factor-1α (HIF-1α) and proangiogenic factors, such as vascular endothelial growth factor (VEGF) [33] This proves the important role of ALDH1A1 in tumor metastasis.

In disagreement with our results, other studies showed no significant relation between ALDH1A1 expression and TNM stage including Kahlert et al.,[19] on pancreatic cancer, XU et al.,[23] on cholangiocarcinoma, Khalifa et al.,[7] on epithelial ovarian tumors, Yang et al.,[25] on colorectal carcinoma and Ye et al.,[34] on gastric neuroendocrine carcinoma.

These disparities in ALDH1A1 expression between studies could arise from variations in the tissue specificity, stage distribution, use of different clones of antibodies and different means of interpretation

Conclusion:

ALDH1A1 is a prostate CSC marker, could be involved in tumorgenesis and progression of prostatic adenocarcinoma

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