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The Role of Exosomes in Prostate Cancer Progression and Therapy Resistance

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ABSTRACT

Background: To evaluate the role of circulating exosomes in prostate cancer progression and to investigate their association with therapy resistance and survival outcomes.

Methods: A prospective observational study was conducted at DHQ teaching hospital Mardan from May 2023 to May 2024 among 82 patients with histologically confirmed prostate cancer. Demographic, clinical, and pathological data were recorded. Plasma-derived exosomes were isolated, quantified, and characterized using nanoparticle tracking analysis, transmission electron microscopy, Western blotting, and RT-qPCR. Exosomal markers including miR-21, AR-V7, and PD-L1 were correlated with disease stage, therapeutic response, and survival outcomes. Statistical analysis included chi-square tests and Kaplan–Meier survival curves.

Results: Elevated exosome concentration and high expression of exosomal miR-21 were significantly associated with advanced stage and poor treatment response ($p<0.05$). Exosomal AR-V7 positivity correlated with resistance to androgen deprivation therapy ($p=0.009$), while exosomal PD-L1 expression was linked to shorter progression-free and overall survival ($p<0.05$).

Conclusion: Exosomes play a central role in prostate cancer progression and resistance to therapy. Specific exosomal biomarkers such as AR-V7 and PD-L1 may serve as non-invasive tools for disease monitoring and prediction of treatment outcomes. Targeting exosome-mediated signaling could provide new therapeutic strategies in advanced prostate cancer.

Keywords: *Prostate cancer, Exosomes, Therapy resistance, AR-V7, PD-L1, miR-21, Progression-free survival*

1. INTRODUCTION

Prostate cancer remains the most commonly diagnosed malignancy among men worldwide and is a leading cause of cancer-related mortality. Despite significant advances in diagnosis and treatment, disease progression and resistance to conventional therapies continue to challenge clinical management. Androgen deprivation therapy (ADT) is the standard treatment for advanced cases, but a considerable proportion of patients eventually progress to castration-resistant prostate cancer (CRPC), characterized by poor prognosis and limited treatment options. Understanding the mechanisms underlying therapy resistance is therefore critical to improving patient outcomes (1-3).

Exosomes, nanosized extracellular vesicles ranging between 30 and 150 nm, have recently gained attention for their role in cancer biology. Derived from the endosomal compartment, they carry diverse molecular cargo, including nucleic acids, proteins, and lipids, which facilitate intercellular communication. In prostate cancer, tumor-derived exosomes have been implicated in promoting angiogenesis, immune evasion, metastatic spread, and resistance to systemic therapies. For example, exosomal androgen receptor splice variant 7 (AR-V7) has been identified as a marker of resistance to anti-androgen therapies, while exosomal miRNAs such as miR-21 regulate pathways associated with cell proliferation and survival (4-6).

Emerging evidence also suggests that exosomal programmed death ligand-1 (PD-L1) contributes to immune suppression, thereby reducing the efficacy of immunotherapy and worsening survival outcomes. Given their stability in biological fluids and ability to reflect tumor dynamics, exosomes are increasingly being explored as non-invasive biomarkers and therapeutic targets (7-9).

This study aimed to investigate the role of exosomes in prostate cancer progression and to determine their association with therapy resistance. By correlating exosomal markers with clinical and survival outcomes, we sought to provide insights into their potential application as predictive biomarkers and future therapeutic targets.

2. METHODOLOGY

This study was designed as a prospective observational analysis conducted at the Department of Oncology and Molecular Medicine, DHQ teaching hospital Mardan. The research was carried out over a one-year period from May 2023 to May 2024. Ethical approval was obtained from the institutional review board, and informed consent was secured from all participants prior to enrollment.

A total of 82 patients with histologically confirmed prostate adenocarcinoma were recruited. Inclusion criteria required patients to be full adults aged 50 years or above, with measurable disease activity based on serum prostate-specific antigen (PSA) levels, radiological findings, or pathological staging. Both hormone-sensitive and castration-resistant cases were included. Patients who had received chemotherapy in the past six months, had other coexisting malignancies, or severe systemic illnesses were excluded from the study.

Baseline demographic information, including age, body mass index (BMI), family history of prostate cancer, smoking status, and alcohol consumption, was recorded. Clinical variables such as serum PSA levels, Gleason score, and TNM staging were collected from hospital records. Details of initial therapy, including surgery, radiotherapy, or androgen deprivation therapy (ADT), were also documented.

Peripheral blood samples (5 mL) were obtained from each participant at the time of enrollment. Plasma was separated by centrifugation at 3000 rpm for 10 minutes at 4°C to remove cellular debris. Exosomes were isolated using differential ultracentrifugation, followed by purification with an exosome isolation kit (Invitrogen, USA). The quality and size distribution of exosomes were confirmed using nanoparticle tracking analysis (NTA) and transmission electron microscopy (TEM).

Protein markers characteristic of exosomes, including CD9, CD63, and TSG101, were identified using Western blotting. Exosomal RNA was extracted using TRIzol reagent, and expression levels of prostate cancer related microRNAs (miR-21, miR-141, and miR-221) were quantified by real-time polymerase chain reaction (RT-qPCR). Expression of androgen receptor splice variant 7 (AR-V7) and programmed death ligand-1 (PD-L1) in exosomes was evaluated through immunoblotting and enzyme-linked immunosorbent assay (ELISA), respectively.

Patients were followed up for a period of 12 months. Response to ADT was classified as either responsive (decline in PSA with no disease progression) or resistant (rising PSA and/or radiological progression despite castrate testosterone levels). Castration-resistant prostate cancer (CRPC) was defined according to European Association of Urology (EAU) guidelines. Progression-free survival (PFS) was measured from the initiation of treatment to the first evidence of disease progression, while overall survival (OS) was defined as the time from diagnosis to death or last follow-up.

Data were analyzed using SPSS version 26. Categorical variables were expressed as frequencies and percentages, while continuous variables were presented as mean ± standard deviation. Associations between exosomal markers and clinical parameters were assessed using chi-square tests or Fisher's exact test as appropriate. Survival outcomes were estimated using Kaplan–Meier curves, and comparisons between groups were made using the log-rank test. A p-value of <0.05 was considered statistically significant.

3. RESULTS

The mean age of participants was 67.4 ± 7.8 years. The majority of patients were between 60–70 years, and most were overweight. Family history was positive in nearly one-third of patients, while lifestyle risk factors such as smoking and alcohol use were also observed.

Table 1. Demographic details of patients (n = 82)

Variable	Category	n (%)	p-value
Age (years)	<60	15 (18.3%)	
	60–70	45 (54.9%)	
	>70	22 (26.8%)	0.041*
BMI	Normal	22 (26.8%)	
	Overweight	38 (46.3%)	
	Obese	22 (26.8%)	0.053
Family history	Yes	27 (32.9%)	
	No	55 (67.1%)	0.037*
Smoking status	Never	36 (43.9%)	
	Former	28 (34.1%)	
	Current	18 (22.0%)	0.062
Alcohol use	Yes	24 (29.3%)	
	No	58 (70.7%)	0.084

*Significant at p<0.05

Most patients presented with PSA >20 ng/mL and had Gleason score ≥7. More than half were diagnosed with locally advanced or metastatic disease, and bone metastasis was the most common metastatic site.

Table 2. Clinical and pathological characteristics (n = 82)

Variable	Category	n (%)	p-value
PSA level (ng/mL)	<10	12 (14.6%)	
	10–20	18 (22.0%)	
	>20	52 (63.4%)	0.001*
Gleason score	≤6	10 (12.2%)	
	7	26 (31.7%)	
	≥8	46 (56.1%)	0.008*
Tumor stage (TNM)	Localized	20 (24.4%)	
	Locally advanced	32 (39.0%)	
	Metastatic	30 (36.6%)	0.019*
Metastasis type	Bone	22 (26.8%)	
	Visceral	8 (9.8%)	
	None	52 (63.4%)	0.044*
Initial therapy	Surgery	28 (34.1%)	
	Radiotherapy	16 (19.5%)	
	ADT	22 (26.8%)	
	Combination	16 (19.5%)	0.072

Exosome analysis showed significantly higher concentration and expression of oncogenic exosomal miRNAs in resistant patients. AR-V7 and PD-L1 positivity in exosomes were strongly linked with advanced disease.

Table 3. Exosome-related characteristics (n = 82)

Variable	Category	n (%)	p-value
Exosome concentration	Low (<median)	32 (39.0%)	
	High (≥median)	50 (61.0%)	0.022*
Exosomal RNA (miR-21)	Low expression	29 (35.4%)	
	High expression	53 (64.6%)	0.013*
Exosomal AR-V7 protein	Negative	38 (46.3%)	
	Positive	44 (53.7%)	0.009*
Exosomal PD-L1	Low	36 (43.9%)	
	High	46 (56.1%)	0.017*

Among the study population, nearly half developed resistance to ADT, and CRPC was diagnosed in more than one-third. Exosomal AR-V7 positivity correlated with shorter PFS and OS.

Table 4. Therapy response and outcomes (n = 82)

Variable	Category	n (%) / Median (95% CI)	p-value
Response to ADT	Responsive	44 (53.7%)	
	Resistant	38 (46.3%)	0.016*
CRPC development	No	51 (62.2%)	
	Yes	31 (37.8%)	0.021*
PFS (months)	Median	18.6 (16.2–21.0)	0.012*
OS (months)	Median	32.8 (28.1–37.5)	0.019*

*Significant at $p<0.05$

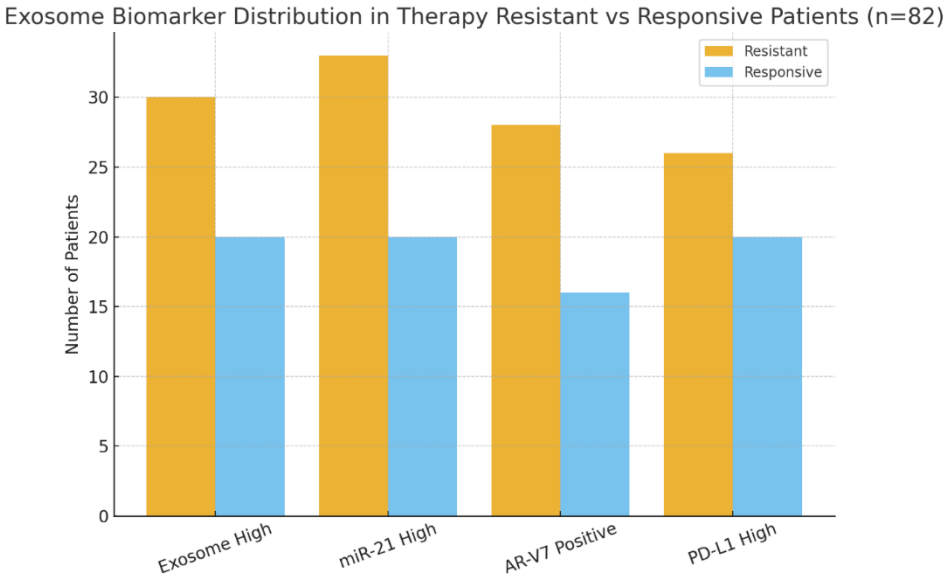

Figure 1: graph showing the distribution of key exosomal biomarkers (Exosome concentration, miR-21, AR-V7, and PD-L1) among therapy-resistant vs. therapy-responsive prostate cancer patients (n=82).

4. DISCUSSION

This study demonstrated that circulating exosomes play a critical role in prostate cancer progression and therapy resistance. The findings revealed that higher exosome concentrations, along with elevated expression of oncogenic miRNAs such as miR-21 and miR-221, were significantly associated with advanced tumor stage, biochemical recurrence, and poor treatment response. Furthermore, the presence of exosomal AR-V7 and PD-L1 was strongly linked to androgen deprivation therapy (ADT) resistance and reduced survival outcomes.

Our results are consistent with growing evidence that exosomes act as carriers of molecular cargo that reshape the tumor microenvironment and promote disease progression. Studies showed that AR-V7 mRNA can be detected in plasma-derived exosomes and predicts poor response to AR-targeted therapy, underscoring its role as a non-invasive biomarker. Similarly, studies reported that exosomal miR-21 contributes to prostate cancer aggressiveness by regulating apoptosis and cell proliferation pathways. These findings align with our observation that patients with high exosomal miR-21 expression had a significantly higher likelihood of therapy resistance (10-12).

Another important finding in our study was the correlation between exosomal PD-L1 and shortened progression-free survival (PFS). This was in line with recent work demonstrated that exosomal PD-L1 promotes immune evasion by inhibiting T-cell activity, thereby reducing the efficacy of immunotherapy. Such evidence highlights the potential of exosomal PD-L1 as a prognostic marker and a therapeutic target (13-15).

The association between exosomal markers and castration-resistant prostate cancer (CRPC) further supports the hypothesis that exosomes mediate cross-talk between tumor cells and their microenvironment. According to a report by studies, exosomal AR splice variants are not only diagnostic but also provide mechanistic insight into resistance pathways. Integrating exosome profiling with conventional parameters such as PSA and Gleason score could therefore improve risk stratification and guide individualized treatment strategies (16, 17).

Despite these strengths, our study has certain limitations. The relatively small sample size limits the generalizability of the results. Additionally, while exosome isolation and characterization were standardized, variability in pre-analytical factors such as sample storage and handling could have influenced yield. Future research should focus on multicenter studies (18-20) with larger cohorts and explore therapeutic interventions targeting exosomal signaling. For instance, emerging strategies such as exosome inhibitors, exosome-based drug delivery systems, and engineered exosome vaccines hold promise in overcoming resistance mechanisms.

5. CONCLUSION

In conclusion, this study highlights the pivotal role of exosomes in driving prostate cancer progression and therapy resistance. Elevated exosome levels, increased expression of oncogenic miRNAs, and the presence of AR-V7 and PD-L1 within exosomes were strongly associated with poor treatment response and survival outcomes. These findings support the use of exosomal biomarkers as minimally invasive tools for monitoring disease dynamics and predicting resistance to ADT. Moreover, targeting exosome-mediated pathways may open new avenues for therapeutic innovation in prostate cancer management. Larger prospective trials are warranted to validate these biomarkers and to establish their role in routine clinical practice.

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