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Clinical and histopathological characteristics of prostate cancer in Erbil city/ Iraq

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Abstract

Background and objective: Prostate cancer is the third most common cancer in men in Iraq. We aimed to study the epidemiology, clinical and histopathological characteristics of prostate cancer in Erbil city.

Methods: The research was performed retrospectively at Nanakali Teaching Hospital and the Oncology Department of Rizgary Teaching Hospital in Erbil city, covering the period from 2016 to 2021. Comprising 212 people diagnosed with prostate cancer.

Results: The median age of the patients was 71 years. The proportion of patients who present with urinary tract symptoms, no symptoms and other were 81.6%, 4.7% and 13.7% respectively. Two hundred eight prostate cancer patients with available histopathological data had adenocarcinoma and two patients had neuroendocrine carcinoma and one patient had urothelial cancer. The proportion of patients with high grade tumor, intermediate and low grade were 61%, 29% and 10% respectively. While, the percentage of patients with TPSA level > 20 ng/ml, TPSA >100 ng/ml were 80% and 35% respectively. Furthermore, the proportion of patients with stage IV, III, II and I were 62.7%, 17.9%, 17.9% and 1.4% respectively. And, the percentage of high-risk groups, intermediate and low risk were 90.1%, 8% and 1.9% respectively. After correlation of TPSA with stage of disease and grade of tumor there was statistically positive correlation between them.

Conclusion: Patients diagnosed with prostate cancer in our region are more likely to belong to the high-risk category, exhibiting aggressive disease and advanced stage at the time of diagnosis. Nevertheless, they exhibit comparable demography and epidemiology as shown in the recent international literature about the global population and the Middle East region.

Keywords: Prostate cancer; Gleason score; PSA; Erbil city.

Introduction

Prostate cancer is the second most common cancer in men worldwide and the fourth most common cancer in both sexes combined.[1] In Iraq, prostate cancer constitutes the sixth most common cancer in both sexes combined and third most common cancer in men.[2]

The incidence of prostate cancer is increasing rapidly by age with highest incidence being reported in elderly men over 65 years of age.[3] Other common risk factors are race, ethnicity, family history, genetic and environmental factors.[4]

Patients with prostate cancer could present with different clinical features depending on the stage of the disease at the presentation. When cancer is limited to the prostate gland, it is regarded as a localized disease and usually cause no or minimal irritative urinary and or obstructive symptoms. In a locally advanced disease, when the cancer has extended outside of prostate gland to nearby organs, it can cause more pronounced lower urinary tract symptoms. While in metastatic disease

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where the cancer has already spread to distant organs such as the skeleton, patients may present with symptoms secondary to the site of metastasis such as bone pain, fatigue, change in bowel habits, anorexia, or even unexplained weight loss.[5] Serum prostate specific antigen (PSA), a protein produced by the epithelial cell of prostate gland, is regarded as the single most important tumor marker that can be used to aid in the diagnosis, risk stratification, disease monitoring and follow up of prostate cancer patients.[6] Serum total prostate specific antigen (TPSA) elevation can occur in the setting of both benign (prostatitis, benign prostatic hyperplasia (BPH) and malignant prostate diseases and as well as a result of prostate manipulation (prostate massage and prostate biopsy). Therefore, an increased TPSA level is not specific for prostate cancer. Furthermore, not all patients with prostate cancer have elevated serum TPSA levels.[7]

The most common histological subtype of prostate cancer is adenocarcinoma which can be found in about 90% of cases. Other, less common histological subtypes are sarcomatoid carcinoma, squamous and basal cell carcinomas, and neuroendocrine tumors, (specifically small-cell carcinoma).[8]

Diagnosis of prostate cancer starts with clinical suspicion based on the clinical signs and symptoms and is completed by digital rectal examination, TPSA level and imaging. The final diagnosis is usually made by obtaining a tissue biopsy from the prostate using, most commonly, transrectal ultrasound guided prostate biopsy. The choice of therapy and prediction of the outcome of prostate cancer patients is based on histopathological features of tumor, Gleason's score, TPSA level at diagnosis, and stage of the disease as well as presence or absence of comorbid conditions.[9]

Active surveillance appears to be safe and has become the preferred approach for men with less-aggressive early-stage prostate cancer, particularly those with low risks stratification factors. Surgery and radiotherapy continue to be the only curative options for localized disease. However, for locally advanced disease combination therapy such as hormonal therapy followed by surgery/ radiotherapy have a better disease outcome and significantly increase the overall survival.[10] While the treatment for advanced prostate cancer includes hormonal therapies, chemotherapies, immunotherapies, and bone microenvironment-target agents. Most patients require a combination of more than one treatment modality, and they may have to be adjusted from time to time.[11]

The 5-year survival rate for the localized or regional disease is about 100% in the developed countries, while men with advanced stages have a 5-year survival rate of about 31%.[12]

Being such a common cancer in men, and due to the lack of local data on this cancer in our region, this study was designed to study the epidemiology, clinical and pathological characteristics of prostate cancer in Erbil city and compare our data to the already published international data.

Methods

Study population

This retrospective study was conducted in both Nanakali Hospital for Blood Diseases and Cancer and in Oncology Department of Rizgary Teaching Hospital in Erbil city, Kurdistan region, Iraq, for the period from 2016 to 2021.

The study included a total of 212 patients, 208 of them diagnosed with histopathology confirmed prostate cancer and four cases have been diagnosed based on TPSA level (over 100 ng/ml). All the cases were retrospectively retrieved from archived patient's medical file at the registry unit in both hospitals. For this study, a written official permission had been obtained from Nanakali Oncology Center, and Rizgary Oncology Center as the main centers for study samples collection.

The following data were collected from the

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patient's medical records: age, serum TPSA level at time of diagnosis, histopathology subtypes, and grade and Gleason Score, and the disease stage at time of diagnosis. Clinical presentation had been taken from patients directly either via phone calls or by face-to-face meeting.

Data collection

Data collections included age at diagnosis and had been divided into four groups (<50, 51-60, 61-70, and ≥70). Clinical presentation of patient which included no symptoms (whom diagnosed through PSA screening), urinary tract symptoms, and others like fatigue, bone pain, anorexia and unexplained weight loss, histopathological characters include (histopathological subtypes, lympho-vascular invasion, perineural invasion, and seminal vesical invasion). In adenocarcinoma histological subtype, Gleason Score range from 2 to 10, had been grouped into (GS <7, 7, and 8-10). Tumor grading according to national comprehensive cancer network (NCCN) grading group (version 2022),[13] into Grad I (well differentiated), Grade II and III (moderate differentiated), Grade IV and V (poor differentiated). Serum TPSA levels (ng/ml) at diagnosis had been grouped into (<10, 10-20, 21-50, 51-100, and above 100). Stages of disease were grouped into localized (stage I), locally advanced (stage II and III), and advanced (stage IV). The patients were divided into three risk categories based on D'Amico risk classification:[14] Low risk group includes T1_T2a, GS≤6, and/or TPSA<10; intermediate risk group includes T2b, GS=7, and/or TPSA 10-20; while high risk group includes >T2c, GS=8-10, and/or TPSA >20.

Ethical Consideration

This study adhered to the Helsinki Declaration of medical ethics in human research and received approval from the Ethical Committee of the College of Medicine, Hawler Medical University.

Statistical analysis

The data was analyzed using a Statistical Package for the Social Sciences Version 25 (SPSS, IBM Company, Chicago, USA). Descriptive analysis was carried out using calculations of proportions for qualitative variables (frequency, percentage) and means (standard deviation) for the continuous variables. Spearman correlation coefficient was used to study the correlation among the variables. A *P* value of < 0.05 was regarded as statistically significant.

Results

Out of the total 212 prostate cancer patients included in this study, the median age at time of diagnosis was 71 years, with the youngest being 43 years and the oldest 91 years. Most 111 of the patients (52.4%) at the time of diagnosis were above 71 years, while only three patients (1.4%) were below the age of 50 years (Table 1).

Table 1 Age of Patients at Diagnosis

Age group (years)	Number (%)
≤50	3 (1.4)
51-60	28 (13.2)
61-70	70 (33.0)
>70	111 (52.4)
Total	212 (100)

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The clinical presentation at the time of diagnosis is shown in Figure 1. Most of the patients (81.6%) had lower urinary tract symptoms at initial presentation which included irritative voiding symptoms and urinary retention, followed by less commonly reported symptoms (13.7%) such as bone pain, fatigue, and weight loss. While only the minority (4.7%) were asymptomatic at diagnosis.

The histopathological diagnoses were available for 206 patients, of which 124 (60.2%) were established by ultrasound guided multi core biopsy, followed by trans urethral prostatectomy 65 (31.5%) and Radical prostatectomy 17 (8.3%). Only six cases have been diagnosed based on TPSA level which was more than 100 ng/ml. The predominant histopathological subtype was adenocarcinoma which was reported in about 98% of the cases. Only two cases had neuroendocrine carcinoma and one had urothelial cancer. Lymphovascular invasions (LVI) and perineural invasions (PNI) were found in 71 (34.5%) and 100 (48.5%) of cases, respectively. Seminal vesical invasion (SVI) was detected in 35 (17%) of the cases (Table 2).

Table 2 Methods of biopsy and histopathological characteristics

Biopsy type/ histopathological characteristics	No. (%)
Histopathology sub types:	
Adenocarcinomas	203 (95.8%)
Others: NET and urothelial cancer	3 (1.4%)
Biopsy (core biopsy)	124 (60.2%)
TURP (trans- urethral prostatectomy)	65 (31.5%)
Radical prostatectomy	17 (8.3%)
LVI (lymphovascular invasions)	71 (34.5%)
PNI (perineural invasions)	100 (48.5%)
SVI (seminal vesical invasions)	35 (17%)
Total	206 (100%)

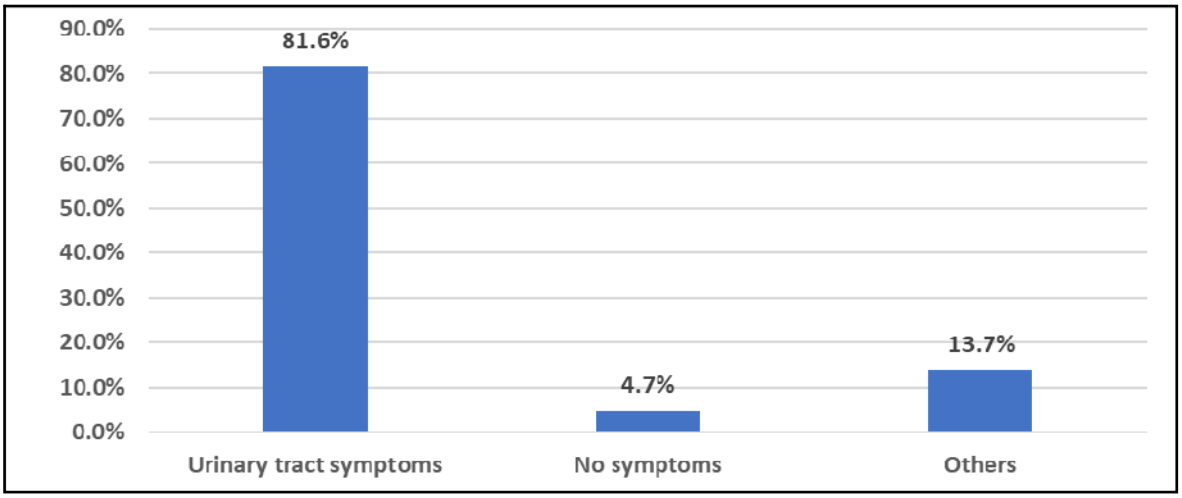

Figure 1 Clinical presentation at diagnosis

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The level of TPSA at time of diagnosis was categorized into five groups. About 35% of the patients had pre- treatment TPSA of more than 100 ng/ml, while the minority (9%) had TPSA less than 10 ng/ml (Figure 2).

The grading of prostate cancer was based on (NCCN) grading group and assessed by the pathologists using the Gleason score. Regarding the Gleason score, most of the patients (61.3%) had a G/S > 7 defined as high tumor grade (poorly differentiated,) and only 9.8% had a G/S < 7 of low tumor grade (well differentiated) (Figure 3).

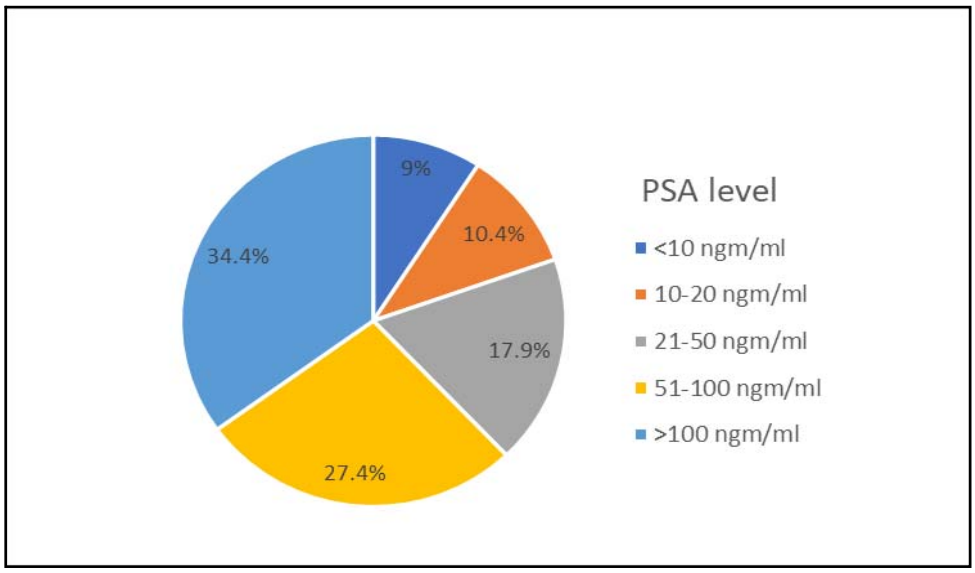

Figure 2 TPSA level groups at time of diagnosis

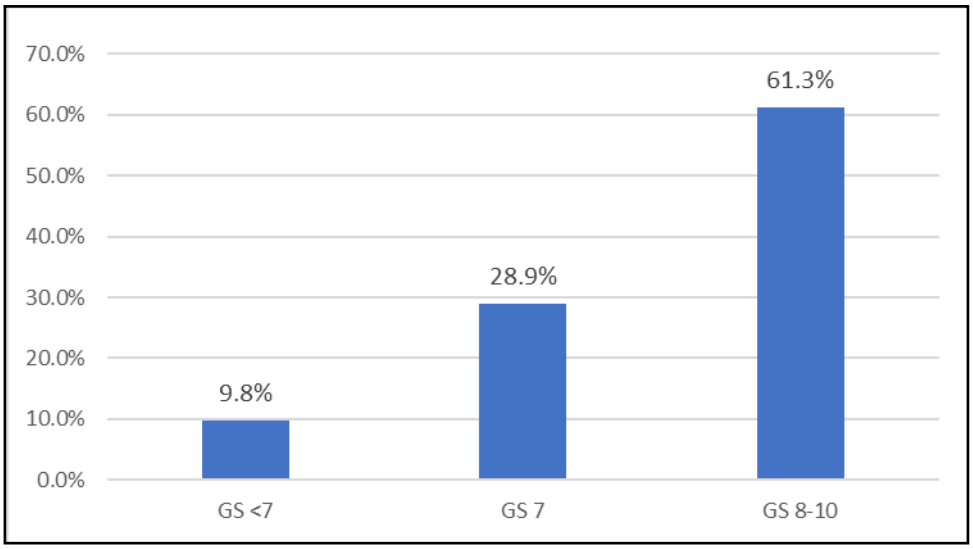

Figure 3 Gleason score of patients

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Based on NCCN grading group, approximately 35.3% of the patients had grade IV (G/S = 8) disease, followed by grade V (G/S = 9 or 10) seen in 26%, then grade II (G/S = 3+4) and III (G/S = 4+3) reported in 14.7% and 14.2% of the cases, respectively, while only 9.8% had grade I (G/S ≤6) disease (Figure 4).

A variety of pre- treatment risk stratification systems of prostate cancer in localized disease globally have been reported and are based on initial TPSA level at diagnosis, G/S and clinically tumor size (T). D'Amico classification system is one of the frequently used by many international guidelines based on this classification, over 90.1% of the patients included in this study were categorized as high-risk group, while intermediate and low risk groups were 8% and 1.9%, respectively (Figure 5).

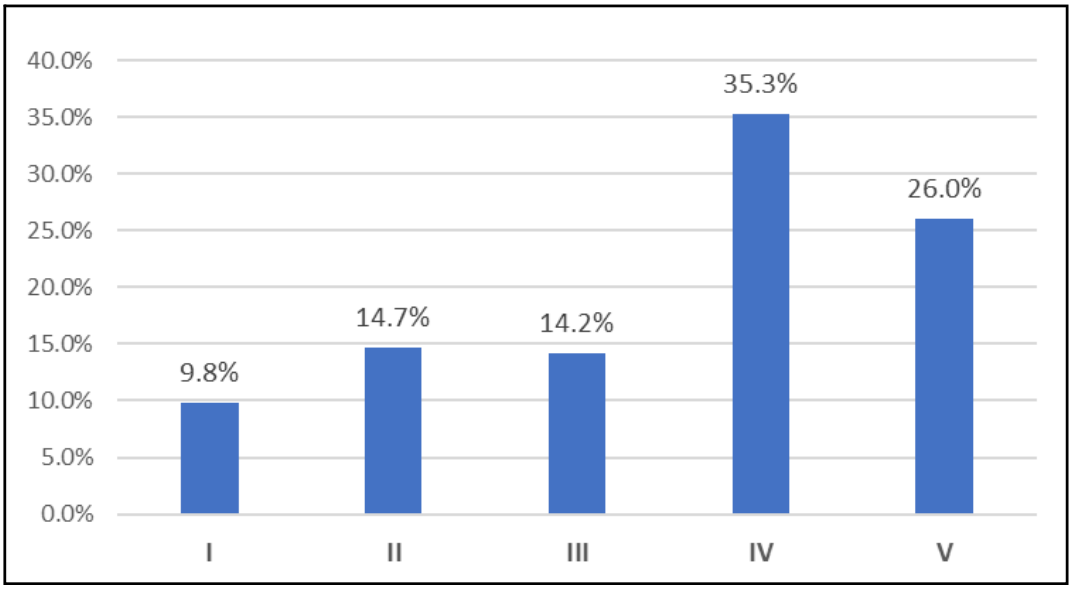

Figure 4 NCCN grade groups of patients

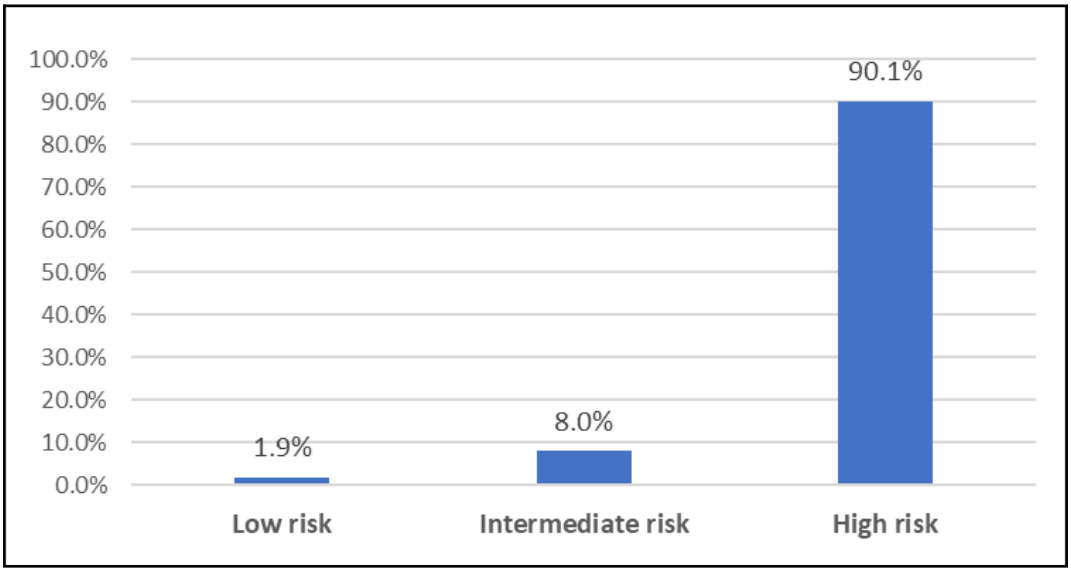

Figure 5 Distribution of subjects by D'Amico classification of risk groups

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Staging of prostate cancer patients was based on AJCC (Edition 8) which depends on the tumor size (T), the regional lymph nodes (N) invasion and presences or absence of distant metastasis (M). Most of the patients 1333(62.7%) had stage IV disease at presentation. Both stage II and III constituted the same proportion 38 (17.9%), while stage I was the least common and only seen in 3 (1.4%) of the patients (Figure 6).

The correlation between stage of the disease at time of diagnosis, PSA level and Gleason Scoring as well as between the TPSA level and Gleason Score, was evaluated and showed a statistically significant positive correlation between the stage of disease and each of TPSA level and the Gleason score. Likewise, a significant positive correlation between TPSA level with Gleason score was observed (Table 3).

Table 3 Correlation between stage of disease with TPSA level and GS grading and TPSA level with GS grading

Variables	Spearman Correlation	*P*- value
Stage vs PSA	0.506	<0.001
Stage vs G/S	0.468	<0.001
PSA vs G/S	0.430	<0.001

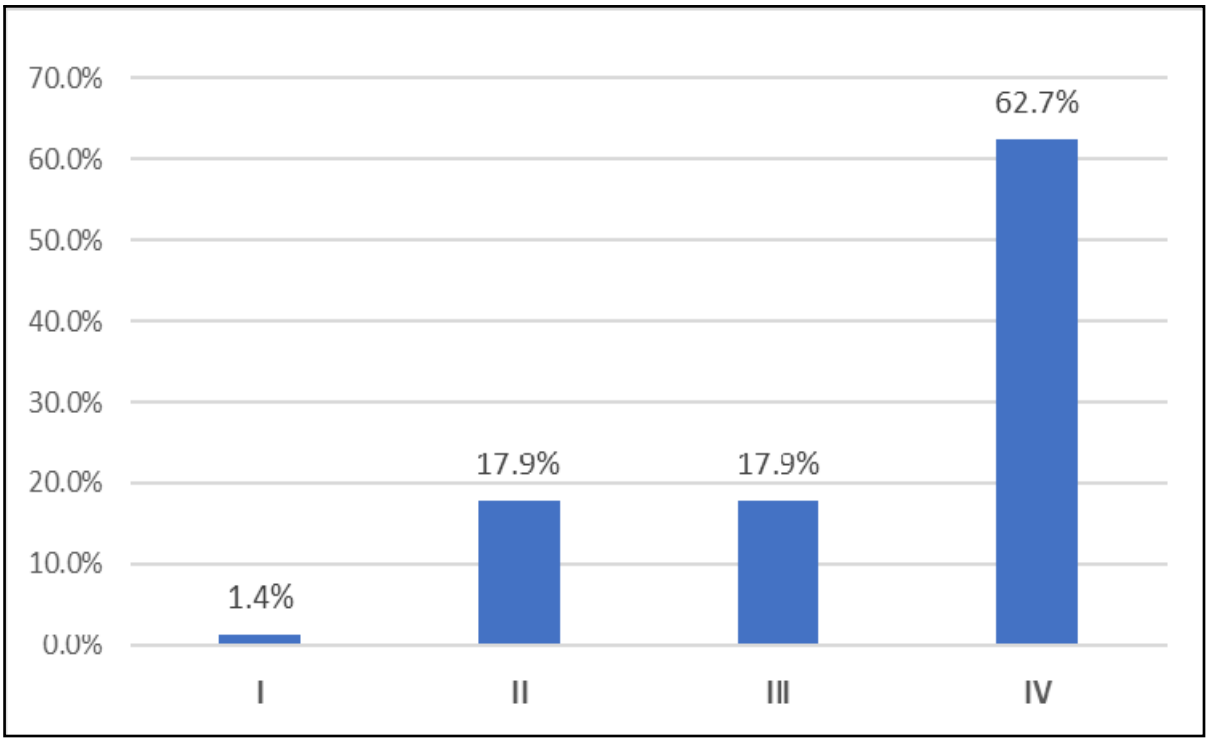

Figure 6 AJCC staging of the patients

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Discussion

Prostate cancer is one of the commonest cancers in men globally and the third most common male cancer in Iraq.[1] The current lifetime risk of developing prostate cancer is 12.5% (one in eight men). Prostate cancer usually has an indolent course and it is one of the cancers that has an excellent prognosis in the early stage with at 5-year survival rate reaching about 100% in the developed countries. However, metastatic prostate cancer is still incurable and eventually lead to the death of the patient with at 5-years survival rate about 31%.[12] To the best of our knowledge, this is the first comprehensive retrospective study conducted in Erbil city describing the clinical and pathological characters of prostate cancer patients.

Age is the most common established risk factor for prostate cancer.[15] Published studies from Middle East, United states and Sweden have reported a median age at diagnosis of 68, 70 and 71 years old, respectively.[16-18] In this study, the median age at the diagnosis was 71 years keeping in line with reported median age from other published international data on prostate cancer. This data further supports that even in our locality prostate cancer is a disease of elderly.

The clinical presentation of prostate cancer could be heterogeneous depending on the stage of disease ranging from asymptomatic to severe urinary symptoms or even signs and symptoms of metastases such as bone ache and or pathological fractures.[19] The commonest clinical complaints reported by about 81% of the patients in this study was, in general, urinary tract symptoms. Similar presentation was shown in studies from India and Egypt.[20, 21] Among all the study cases only 4% of patients have been diagnosed through routine medical check-up. Diagnosis of prostate cancer in the asymptomatic phase has varied widely among the countries and over the years. This is mainly attributed to the regional variations in offering PSA as screening and partly to the medical awareness of the community and how much they are willing to come forward and ask for a medical checkup. Although the major international guidelines recommend against PSA screening, yet this test has been widely offered for elderly patients during routine medical checkup as screening in many parts of the world and specially in the developed countries with a better health care system.[22] This could partly reflects difference between our study and other published studies in regard to the TPSA level at time of diagnosis. Approximately 35% of our patients had markedly elevated TPSA values greater than 100 ng/mL at time of diagnosis. Countries, such as Sudan and Saudi Arabia, with health systems and health awareness like our country, have reported similar TPSA levels at time of diagnosis.[23, 24] In contrast, studies from Asian countries have reported a significantly lower TPSA level at time of diagnosis of less than 20 ng/ml in most of the patients reaching up to 82% in Philippines and around 50% of the cases in Hong Kong and Taiwan. [25] While studies from USA have even shown a dramatically lower PSA level with reported mean PSA level of 5.7 ng/ml.[26] Such a TPSA level of less than 20 ng/ml was only seen in 19% of the cases in our study. These results clearly demonstrate the differences between our patients and those from the Asian and more developed countries which, in addition to the health system, awareness, and routine PSA testing, could also reflect the delay in diagnosis and perhaps a more aggressive phenotype. However, a much larger national study is needed to support or to refute our speculation.

For confirming the diagnosis of prostate cancer histopathology examination of the tumor is mandatory in most of the cases. The most frequently reported histopathological subtype is adenocarcinoma seen in more than 90% of prostate cancer cases.[27] This is consistent with our study where adenocarcinoma was

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the predominant histopathological subtypes detected in about 98% of the cases.

Further-more, lympho-vascular invasion (LVI), perineural invasion (PNI) and extracapsular extension are important prognostic features which also affect treatment decision when they are present especially when combined with higher grade and stage of prostate cancer that raise the risk of biochemical failure and metastases, and shorten the overall survival after radical prostatectomy.[28] The high frequency of PNI (48.5%) and LVI (34.5%) reported in our study further magnify the tumor aggressiveness of our prostate cancer patients.

In addition, tumor grade is also regarded as a strong predictor for disease outcome in prostate cancer patients.[29, 30] In our study, based on the Gleason Scoring system and NCCN grading system for grading of adenocarcinoma patients, poorly differentiated was the most frequently diagnosed carcinoma accounting for 61.3% of the cases. In contrast, the well differentiated cancers were the least common and only seen in 9.8% of the cases. This finding is comparable to a study done in Saudi Arabia, were they have reported poorly differentiated carcinomas as the most frequently reported grad.[29] Similar results were reported in Vietnam and Indonesia.[25] However, in studies from Thailand, Philippines and Jordan poorly differentiated cancers were less frequently reported (34%, 33% and 27% respectively).[25] On the other hand, in a recent study conducted by K. Boehm and his colleagues poorly differentiated tumors were the least common among their series reaching up to 8%.[30] The high proportion of high grades disease in our patients perhaps partly reflect the nature of disease in our region is aggressive and partly could be due to the sequel of late referral and late diagnosis.

Staging of prostate cancer, as any other cancer types, is fundamental for prediction of the prognosis and selection of the appropriate treatment option.[13] Based on the published international data about 84% of prostate cancer patients have a local or a locoregional disease at the time of diagnosis.[12] While De novo metastatic prostate cancer account for about 4% in western countries.[31] In this study, most of our patients 62.4% have advanced stage at time of diagnosis. Similar results have been recorded in Jordan in where about 77% of the cases have been diagnosed in advanced stage.[25] However, in the study done by Marilyne Daher et al, in 2021 in Lebanon, including men from countries of Middle East, the percentage of advanced disease was (22.7%) and Iraqi men had higher metastatic disease 48%.[16]

In contrast, published studies from Japan and USA reported very different results from ours as advanced stage at diagnoses was seen between 5 to 10% while localized disease reported in 56% and 77% of the cases, respectively.[32, 33] These differences could be explained by the lack of awareness and screening programs in our locality as well as by the delay referral from primary care centers to oncology centers.

Pre -treatment stratification of prostate cancer patient into risk category groups enable clinician to predict the outcome of treatment, disease recurrence and prognosis.[34]

D'Amico classification is most frequently adopted internationally for risk categorizing of prostate cancer patients by the American Urologic Association (AUA)[35] and European Association of Urology (EAU).[33] In our study, high risk group reported the most frequent group about (90%), while intermediate risk group account (8%). In a study done in Germany, 674 patients from 1336 about (50%) had fallen in high risk group, and intermediate risk group about (37%).[30] In USA, high risk group account (25%), while intermediate risk (47%) despite the more frequent screening.[36] In study done in India, from 181 patients who included in study, 53 patients (42.2%) had fallen in intermediate risk group, while high risk and low risk

group had (29.4%, 28.4%) respectively.[26] Measurement of TPSA level is an integral part of assessing any prostate cancer patient which can in addition to aiding the diagnosis and monitoring treatment can also correlate with the disease stage. This positive correlation is already established by many published studies such as those from India, China and UK showing that raising of TPSA level are highly indicative of more advanced stages.[37] In our study, a statistically highly significant correlation was noticed between TPSA level with tumor stage and tumor grade. This agrees with all other published data in this regard including countries from the middle east. [24, 38]

Conclusion

Based on our study, patients diagnosed with prostate cancer in our region are more likely to fall into a high-risk group with aggressive disease and have advanced stage at time of diagnosis. However, they have similar demographics and epidemiology as reported in the recent international literature for the world population as well as for the region of Middle East. The limitations of our study mostly stem from its retrospective methodology and the limited sample size. We Advise A comprehensive prospective study enrolling prostate cancer patients from prominent oncology facilities in Iraq is essential and will yield the most reliable and consistent data for drawing robust conclusions and recommendations.

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Competing interests

The authors declare that they have no competing interests.

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