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SURVIVAL ANALYSIS OF PATIENTS DIAGNOSED WITH METASTATIC PROSTATE CANCER IN 2008-2016

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Keywords: cancer, prostate cancer, metastatic prostate cancer.

Summary

Background and objectives. Prostate cancer is the second most common cancer diagnosis made in men. Given that 2,293,818 new cases are expected worldwide by 2040, it is important to conceptualize the disease and primary stage of cancer, distant metastases, testosterone concentration, and previous treatments help to understand and predict this disease.

The aim of the study is to determine the impact of prognostic factors, comorbidities and systematic treatment on the survival of patients with metastatic prostate cancer.

Material and Methods. It is a retrospective analysis of data from 76 patients treated for metastatic prostate cancer (C61) at the Afiliate of Lithuanian University of Health Sciences Kaunas Oncology Hospital between 2008 and 2016. The following data were collected: age of patients, date of diagnosis, clinical stage of diagnosis (cTNM), baseline PSA level (at diagnosis), Gleason score, treatment method used, localization of metastases, the period during which resistance to hormonal therapy developed, date of death. The date of diagnosis was considered to be the date on which the prostate carcinoma was confirmed by histological examination. The data obtained in the study were analyzed using the programs IBM SPSS v28.0.

Results. A statistically significant correlation was found between the dependence of patient survival time and tumor differentiation grade (p=0.041) , the Charlson Comorbidity Index (p<0,001), treatment method used in prostate cancer unresponsive to hormone therapy (p=0.049), location of metastases (p=0.021), the time during which resistance to hormone therapy developed (p<0.001).

Conclusions. The risk of dying from prostate cancer depends on the period during which resistance to hormone therapy has developed and the Charlson comorbidity index. The higher the Charlson comorbidity index, the lower the survival rate. In patients with hormone-sensitive prostate cancer, the choice of treatment does not affect survival, and in patients with hormone-resistant prostate cancer, survival is prolonged by treatment with abiraterone acetate.

Introduction

Prostate cancer is the second most common cancer diagnosis made in men. In 2018, 1,276,106 new cases of prostate cancer were reported worldwide, resulting in 358,989 deaths (3.8% of all cancer-related deaths in men) [1]. According to the National Cancer Institute in Lithuania, 2967 cases of prostate cancer were detected in 201, of which 96 (3.2%) were at stage IV. The overall incidence of prostate cancer was 221.8 cases per 100,000 [2]. Given that 2,293,818 new cases are expected worldwide by 2040 [3], it is important to conceptualize the disease.

The aim of the study is to determine the impact of prognostic factors, comorbidities and systematic treatment on the survival of patients with metastatic prostate cancer.

Methods

It is a retrospective analysis of data from 76 patients treated for metastatic prostate cancer (C61) at the Afiliate of Lithuanian University of Health Sciences Kaunas Oncology Hospital between 2008 and 2016. The following data were collected: age of patients, date of diagnosis, clinical stage of diagnosis (cTNM), baseline PSA level (at diagnosis), Gleason score, treatment method used, localization of metastases, the period during which resistance to hormonal therapy developed, date of death. The date of diagnosis was considered to be the date on which the prostate carcinoma was confirmed by histological examination.

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Statistical analysis

The data obtained in the study were analyzed using the programs IBM SPSS v28.0 and MS Excel 2016. The distribution according to the aspect considered was described by absolute numbers (n) and percentages. The Kaplan - Meier method was used for survival analysis, and the log-rank test was used for group dependence of characteristics. Comparisons between groups were performed with the chi-square test and were considered statistically significant if the significance level was $p \leq 0.05$. The influence of prognostic factors on survival was evaluated using univariate and Cox regression analysis with calculation of relative risk (RR) and 95% confidence interval CI. The data obtained are summarized and presented in tables and figures.

Results

Influence of age on survival. We find that the shortest survival time (10 months) is in patients older than 75 years. The longest survival time had patients younger than 60 years (median 15 months, min. 3 months, max. 50 months) and in the age group 66-74 years (median 17 months, min. 4 months, max. 77 months) (p=0.709).

Dependence of survival time on initial PSA blood concentration. Patients were divided into 5 groups according to the PSA concentration found at the time of diagnosis. The lowest concentration found was 6 ng/ml, the highest was 4326 ng/ml, and the mean initial PSA concentration of all subjects was 283.95 ng/ml. In almost half (44.7%) of the patients, the primary PSA concentration was in the group with PSA concentration from 51 to 100 ng/ml.

Influence of the degree of differentiation on survival time. When examining the tumor differentiations diagnosed by the subjects, it was found that the subjects‘ results were distributed among three grades: G2 - moderately differentiated (sum of Gleason scores 5-6), G3 - poorly differentiated (sum of Gleason scores 7-8), and G4 - undifferentiated (sum of Gleason scores 9- 10). Almost half (48.7%) of the subjects were diagnosed with moderately differentiated prostate adenocarcinoma, and one-third (36.8%) were diagnosed with poorly differentiated prostate adenocarcinoma. The longest survival was 21 months in patients with a tumor differentiation grade of G2. The shortest survival (11 months) was observed in patients with Gleason scores of 9-10.

Dependence of survival on the Charlson Comorbidity Index (CCI). Patients with Charlson Comorbidity Index scores of 6-8 had the longest median survival (22 months), the longest patient in this group survived 77 months, and the shortest - 7 months. Patients with CCI scores of 15-16 had the lowest median survival (4 months). The dependence of patients‘ survival time is statistically significantly ($p<0,001$) correlated with CCI ($\chi2=25,69$).

Survival dependence on the treatment method used in prostate cancer responsive to hormone therapy . When the tumor responded to hormonal therapy, it was prescribed alone or together with palliative treatment of metastases by radiotherapy. The median survival time of patients receiving hormone therapy alone was 18 months, and the median survival time of patients receiving hormone therapy and palliative radiotherapy for metastases was 17 months. We can say that the choice of treatment for patients with prostate cancer responding to hormone therapy was not affected (p=0.361).

Survival dependence on the treatment method used in prostate cancer unresponsive to hormone therapy. Patients diagnosed with hormone - refractory prostate cancer received systemic treatment with docetaxel or abiraterone acetate. The number of patients in both groups was equal. The median survival time of the patients varied by almost double. The median survival time was 13 months in patients receiving abiraterone acetate and 7 months in those receiving docetaxel. The correlation found ($\chi2=3.864$) between patients receiving different systemic treatments was statistically significant (p=0.049).

Dependence of survival on the localization of metastases. Analysis of subject data revealed five localizations of metastases: ribs, pelvis, spine, lungs, and multiple bone metastases. More than two-thirds (71.1%) of subjects were diagnosed with multiple bone metastases. One-tenth (10.5%) of the metastases were in the pelvic bones, and the fewest metastases were found in the bones of the spine, ribs, and lungs (7.9%, 5.3%, and 5.3%, respectively). Patients with metastases in the spine (20 months) and pelvic bones (21 months) had the longest median survival. Patients with lung metastases (10 months) and multiple bone metastases (15 months) had the shortest median survival. When analyzing the dependence of patient survival on the localization of tumor metastases, a statistically significant association was found ($\chi2=11.56$) (p=0.021).

Dependence of survival on the time during which resistance to hormone therapy developed. Patients were divided into four groups according to the period during which resistance to hormone therapy developed: Resistance persisted since diagnosis, resistance developed within 1-7 months, 8-17 months, and 17-52 months. Patients who developed resistance to hormone therapy within 17-52 months survived the longest (median 27 months). Patients who developed resistance within 1-7 months had the lowest median survival (9 months).

Univariate and multivariate analysis of statistically significant prognostic factors . In the multivariate Cox regression analysis model adjusting for the degree of tumor

differentiation, the localization of metastases, the period during which resistance to hormonal therapy developed, the Charlson comorbidity index, and the patients who received chemotherapy, it was found that the patient's risk of death increased with the increase in the period during which resistance to hormonal therapy developed by 0.934 times (RR = 0.934, 95% CI: 0.907 - 0.963, p<0.001). A univariate Cox regression analysis model showed that each Charlson comorbidity index score increased the risk of death by 1.174 times (RR = 1,174, 95% PI:1,073 – 1,283, p<0,001).

Discussion

In the United States, the median age of men diagnosed with prostate cancer is 72 years, and in the United Kingdom, 36% of men diagnosed were younger than 75 years [4]. In this study, the median age at diagnosis was 69 years. (min. 50 years, max. 89 years) and age was found to correlate with survival time, but this dependence was not statistically significant(p=0.709).

The initial blood PSA concentration is rarely used to assess the prognosis of metastatic prostate cancer, the change in PSA concentration is more important for assessing the treatment effect of metastatic disease [5]. In this study, it was also found that baseline PSA level was not statistically significant in predicting patient survival (p=0.639).

The degree of prostate cancer differentiation based on the sum of Gleason scores remains one of the most reliable prognostic factors. In a review by B. Helpap et al, 10-year survival was found to decrease to 20-30% with a Gleason score > 7 and an intermediate- to high-risk prostate cancer, compared with a Gleason score <6 and a low- to intermediate-risk prostate cancer. The 10-year survival rate is 88% [6].

In this study, patients with a Gleason score between 5 and 6 points, had the longest survival. - the median survival time is 21 months, and the shortest when the sum of Gleason scores is 9-10 b, the median survival time is 11 months. The localization of metastases also has a significant effect on survival time (p=0.021). Patients with metastases to the bones of the spine and pelvis had the longest survival time, while patients with multiple metastases and metastases to the lungs had the shortest survival time.

A higher Charlson comorbidity index suggests a shorter survival time in patients with prostate cancer [7]. In a study by Rajan and colleagues, CCI was found to be associated with improved overall patient survival, which is not necessarily specific to prostate cancer. Regardless of radical treatment, increasing CCI levels do not significantly increase the risk of mortality in prostate cancer [8]. In this study, an increase in the Charlson Comorbidity Index was found to statistically significantly shorten survival (p<0.001).

In patients diagnosed with prostate cancer responsive to hormonal therapy, no statistically significant difference was found between treatment with radiotherapy alone or in combination with palliative treatment of metastases (p=0.361).

Patients with prostate cancer who did not respond to hormonal therapy received systemic treatment with docetaxel or abiraterone acetate. Survival time was statistically significantly different (p=0.049) between patients receiving these drugs, with almost twice as long after treatment with abiraterone acetate.

This study also examined the dependence of survival time on the duration of development of resistance to hormone therapy, and the results were statistically significant (p=0.021). Survival time increased proportionally with time to resistance to hormone therapy. Patients who were immediately resistant to hormone therapy had a median survival time of 10 months.

Conclusions

1. Prognostic factors for the survival of patients with metastatic prostate cancer include the degree of tumor differentiation, the localization of tumor metastases, and the period during which resistance to hormonal therapy has developed.

2. The risk of dying from prostate cancer depends on the period during which resistance to hormone therapy has developed and the Charlson comorbidity index. The higher the Charlson comorbidity index, the lower the survival rate. In patients with hormone-sensitive prostate cancer, the choice of treatment does not affect survival, and in patients with hormone-resistant prostate cancer, survival is prolonged by treatment with abiraterone acetate.

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PACIENTŲ, SIRGUSIŲ METASTAZAVUSIU PROSTATOS VĖŽIU 2008–2016 METAIS, IŠGYVENAMUMO ANALIZĖ

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Raktažodžiai: vėžys, prostatos vėžys, metastazavęs prostatos vėžys.

Santrauka

Prostatos vėžys yra antra pagal dažnumą vyrų vėžio diagnozė. Atsižvelgiant į tai, kad iki 2040 m. pasaulyje tikimasi 2 293 818 naujų atvejų, svarbu konceptualizuoti šią ligą, o pirminė vėžio stadija, tolimosios metastazės, testosterono koncentracija ir ankstesni taikyti gydymo būdai padeda suprasti ir numatyti šią ligą.

Tyrimo tikslas. Nustatyti prognozinių veiksnių, gretutinių ligų ir sisteminio gydymo įtaką pacientų, sirgusių prostatos vėžiu 2008-2016 metais, išgyvenamumui.

Metodika. Tyrimui atrinkti 76 pacientai, kurie 2008–2016 metais LSMUL KK filiale Onkologijos ligoninėje buvo gydyti dėl metastazavusio prostatos vėžio. Surinkti šie tyrimui reikalingi duomenys: paciento amžius, diagnozės nustatymo data, klinikinė stadija diagnozės nustatymo metu (cTNM), pirminė PSA koncentracija kraujyje (diagnozės nustatymo metu), Gleason balų suma, taikytas gydymo metodas, metastazių lokalizacija, laikotarpis, per kurį išsivystė atsparumas hormonoterapijai, mirties data. Diagnozės nustatymo data buvo laikoma histologinio tyrimo metu patvirtinto prostatos vėžio data. Tyrimo metu gauti duomenys buvo analizuoti naudojant IBM SPSS v28.0 programą.

Rezultatai. Nustatyta statistiškai reikšminga koreliacija tarp pacientų išgyvenimo laiko priklausomybės ir naviko diferenciacijos laipsnio ($p=0,041$), Charlson gretutinių ligų indekso ($p<0,001$), taikomo gydymo metodo, sergant hormonų terapijai nejautriu prostatos vėžiu ($p=0,049$), metastazių lokalizacijos ($p=0,021$) ir laiko, per kurį išsivystė atsparumas hormonų terapijai ($p<0,001$).

Išvados. Prostatos vėžio mirties rizika priklauso nuo laikotarpio, per kurį išsivysto atsparumas hormonų terapijai ir Charlson gretutinių ligų indekso. Didėjant Charlson gretutinių ligų indekso balų skaičiui, mažėja išgyvenamumo trukmė. Pacientams, sergantiems hormonoterapijai jautriu prostatos vėžiu, gydymo pasirinkimas išgyvenamumo trukmei įtakos nedaro, o pacientams, sergantiems hormonoterapijai atspariu prostatos vėžiu – ilgesnė išgyvenamumo trukmė yra skiriant gydymą abiraterono acetatu.

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