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Determination Of Risk Parameters In The Detection Of Asymptomatic Bone Metastases Of Kidney And Prostate Cancer

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ABSTRACT

Using multivariate analysis to identify predictive risk parameters in the diagnosis of asymptomatic osteogenic metastasis of renal and prostate cancer. The work was based on the results of observations of 105 patients with a morphologically confirmed diagnosis of malignant neoplasm registered at the Republican Specialized Scientific and Practical Center of Oncology and Radiology (RSNPMTSO and R) and the Samarkand branch. In 62 patients with kidney cancer (RP) included in the study, the mean age of patients with RP was 58.3 years. 43 patients with prostate cancer (PC) were included in the study, the average age of patients with PC was 68 years. We analyzed such parameters as age, stage of the disease, timing of detection of bone metastasis (BM), prevalence, type and size of BM, as well as additional criteria: in case of prostate cancer - the size of the primary tumor and the degree of malignancy, in case of prostate cancer - the sum of points on the Gleason scale and the prostate -specific antigen (PSA). It was revealed that the highest risk in detecting BM in RP was noted for the stage of the disease, p = 0.006. Also, a high risk was associated with the size and grade of tumor malignancy, with CR at p = 0.006 and p = 0.008, respectively. Among the listed, the highest risk in detecting BM is observed in prostate cancer for the stage of the disease (p = 0.001). In addition, an increased risk was observed for the Gleason score and PSA level (p = 0.013 and p = 0.008, respectively). Thus, during the 2-year follow-up, BM most often develops in patients with kidney cancer at stage Tv-T3a stage and with grade G III and in patients with prostate cancer - in the presence of stage III with a Gleason score of ≥ 7 and a level PSA in the range of 21-50 ng / ml.

KEYWORDS

Patients, vessels, treatment, pathology, cancer, distant bone metastases.

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INTRODUCTION

The defeat of the bones of the skeleton of a metastatic nature in malignant neoplasms today remains a serious problem of modern oncology. [Lipton, A. The Science and Practice of Bone Health in Oncology: Managing Bone Loss and Metastasis in Patients With Solid Tumors / A. Lipton // J. Nat. Compr. Canc. Netw. – 2009. – Vol. 7. – P. 1-29].

According to the Cancer Registry, 44.8% of prostate cancer with a local form, 53.4% of cases with disseminated and metastatic form were diagnosed in Uzbekistan, ranking 7th from the total number of cancer patients. Out of 236 patients examined and treated with prostate cancer, distant bone metastases were observed mainly in 75–80% of cases with spread to skeletal bones (pelvic bones, spinal bones, humerus, femur and other organs, tissues). [Tillyashaikhov M.N, Yusupov Sh. Kh., Boyko E.V, Valieva R.M. Criteria for choosing hormonal therapy for patients with advanced prostate cancer // Bulletin of the Tashkent Medical Academy. - 2016. - No. 2 (05). - S. 95–97). The incidence of kidney cancer in Uzbekistan has significant geographic variability, "... the incidence of this tumor in 2013 had an indicator of 8.4 per 100 thousand of the population, then at the end of 2017 this figure was at the level of 8.9. In 2013, the 1-year mortality rate was within 0.5%, in 2017 the data did not change and the 1-year mortality rate was also within 0.5%, which indicates an improvement in diagnosis and treatment ... " that the detection and treatment of this pathology has improved, but bone metastases in renal cell carcinoma also remain an urgent problem [Tillyashayakhov M.N., Rahimov N.M., TillyashayakhovaR.M. Long-term results of modified surgical access to regional lymph nodes and main vessels in the treatment of renal cell carcinoma// European science review. – Vienna, 2018.-№5-6. -P. 204-207) 90% of cases of neoplastic lesions of the spine are metastases, and more often they are multiple. The problem of treatment of compression syndrome in patients with metastatic lesions of the spine is one of the most important and complex Rahimov Nodir, Shakhanova Shaxnoza Development of new approaches in treatment of metastatic renal cell carcinoma// Journal of research in health science Volume 5-6 issue. 4 2020, pp. 82-95 ISSN 2523-1251 (Online)), p 82-95

At the same time, the main problem is a sharp decline in the patient's quality of life. Providing timely and adequate care improves the condition and quality of life of these patients, although with single metastatic lesions of the bones there is the possibility of surgical treatment, but with multiple lesions with metastases this type of treatment is not rational.

The nature of the damage to the skeletal system in malignant neoplasms is diverse and includes complications of the skeletal system associated with antitumor treatment (osteopenia and osteoporosis), in itself its damage by a tumor or metastases, as well as complications associated with bone metastases Bunyod Saidkulov, Jurabek Abduraxmonov, Rahimov Nodir. Recurrent ovarian cancer: mechanisms of development of peritoneal malignant ascites//.

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Bone metastases develop in 30% of cancer patients, and most often secondary bone damage occurs in patients with breast cancer, cancer, kidney cancer (RP), prostate cancer (PC), and lung cancer and myeloma [S Ziyadullaev, O Elmamatov, N Raximov, F Raufov Cytogenetic and immunological alterations of recurrent bladder cancer// European Journal of Molecular & Clinical Medicine 2020, Volume 7, Issue 2, p 1877-1883.

The survival rate of patients with metastatic lesions of the skeleton directly depends on the timing of the detection of metastases. Unfortunately, the vast majority of patients at the stage of diagnosis of bone metastases (BM) already have pain syndrome, which is often the only manifestation of skeletal damage. It should be noted that as a result of the progression of the tumor process, bone complications inevitably develop (pathological fractures, malignant hypercalcemia, etc.), which significantly reduce the quality of life of patients and directly affect its duration. [Bunyod Saidkulov, Jurabek Abduraxmonov, Rahimov Nodir. Recurrent ovarian cancer: mechanisms of development of peritoneal malignant ascites//. European Journal of Molecular & Clinical Medicine ISSN 2515-8260 Volume 7, Issue 2, 2020, p 2423-2428]. The median overall survival of patients after the development of bone metastases is 2–3 years. By themselves, bone metastases in breast cancer are rarely an immediate cause of death. At the same

In this regard, special attention is paid to the study of the skeleton, which is carried out to assess the prevalence of the tumor process, study the objective response to treatment and monitor the course of the disease. [Rahimov Nodir, Shakhanova Shaxnoza Development of new approaches in treatment of metastatic renal cell carcinoma// Journal of research in health science Volume 5-6 issue. 4 2020, pp. 82-95 ISSN 2523-1251 (Online)), p 82-95]. In the treatment of patients with bone metastases, systemic anticancer and radiation therapy, surgery and drugs aimed at suppressing bone resorption can be involved. The specific role of each method is determined by the prevalence of bone lesions, tumor type, and life expectancy. Surgical treatment of osteogenic metastases has narrow indications, and external beam radiation therapy is also limited in the treatment of multiple bone metastases of solid tumors. aggressive surgical tactics are considered justified in case of solitary skeletal lesions. Due to the fact that ESWL and brachytherapy are local types of antitumor effects, these methods of treatment have limitations in case of multiple metastatic lesions of the skeleton. Treatment of patients with CM is a promising area that requires active development and widespread implementation in clinical practice. It has been shown that with a modern and timely therapeutic approach in patients with metastatic skeletal lesions, in most cases, as a result of palliative treatment, a positive effect can be achieved, consisting in an increase in the objective response, a decrease in the frequency of bone complications and an increase in the survival rate of patients while maintaining a high level of quality of life.

Purpose: Using multivariate analysis to identify predictive risk parameters in the diagnosis of asymptomatic osteogenic metastasis of renal and prostate cancer

MATERIALS AND METHODS

The work was carried out at the Department of Oncology of the Samarkand Medical Institute.

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A retro and prospective study was carried out to study the results of palliative treatment of patients with kidney and prostate cancer with clinically asymptomatic bone metastases, who were treated on an outpatient and inpatient basis at the Republican Specialized Scientific and Practical Center of Oncology and the Samarkand regional branch.

The work was based on the results of observations of 105 patients with a morphologically confirmed diagnosis of malignant neoplasm.

The distribution of patients with RP by age was carried out according to the WHO classification and is presented in Table 1. Of the 62 patients with RP included in the study, the vast majority were aged 45 to 59 years (46.3%) and from 60 to 74 years (41%) ... At the same time, the average age of patients with RP was 58.3 years.

Table 1- Age characteristics of patients with RP

Age	Number of patients with RP
18–44 лет	6 (9,6%)
45–59 лет	28 (45,1%)
60–74 лет	25 (40,3%)
75–90 лет	3 (4,9%)
≥ 90 лет	---
Всего	62 (100%)

The distribution of patients with RP by the size of the primary tumor is shown in Table 2. In most cases, the size of the primary tumor in patients with RP was T2v-T3a (75.7%). Much less often renal neoplasms were T4 (17.7%) and T2a (7.5%).

Table 2 - Characteristics of patients with RP by the size of the primary tumor

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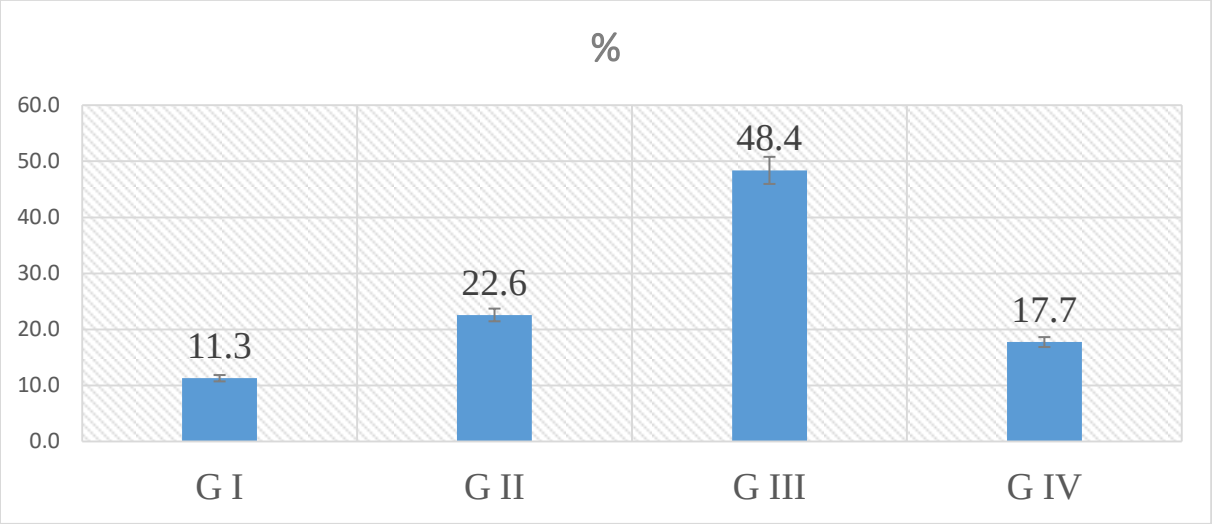
Tumor size	Number of patients with RP
T2a	4 (7,5%)
T2в	22 (35,4%)
T3a	25 (40,3%)
T4	11 (17,7%)
Total	62 (100%)

In all patients, the diagnosis of RP of varying degrees of malignancy was confirmed by morphological examination. Data on the degree of malignancy of the primary tumor in patients with RP are presented in Table 3. In almost half of the patients with RP (50.7%), the primary tumors had grade III. Less often, primary RP tumors were grade II (29.1%) and I (20.2%).

Figure 1 Characteristics of patients with RP by the degree of malignancy of the primary tumor



At the start of the study, 9 (14.5%) of 62 patients with RP with BM had distant metastases of extraosseous localization. Subsequently, during the study, in 19 (30.6%) patients with RP with metastatic lesions of the skeleton, secondary foci outside the skeletal system were identified. Thus, in 23 (37.1%) patients with RP, in addition to BM, metastases of extraosseous localization were recorded (Table 5). The discrepancy between the number of extraosseous metastases and the total number of patients is explained by the fact that in some cases, one patient simultaneously developed metastases in different organs.

Table 5 - Characteristics of extraosseous metastases in breast cancer patients

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Localization of extraosseous metastases	Number of extraosseous metastases
Liver	7 (11,3%)
Lungs	5 (8,1%)
Pleural carcinomatosis	5 (8,1%)
Distant lymph nodes	6 (9,7%)
Brain	1 (1,6)
Soft tissue	1 (1,6%)
Total	25

The age characteristics of 43 patients with prostate cancer are presented in Table 7. According to the data presented, patients with prostate cancer prevailed at the age of 60 to 74 years (23 patients) and from 75 to 90 years (11 patients). The average age of patients with prostate cancer was 68 years.

Table 7 - Age characteristics of patients with prostate cancer

Age	Number of patients with prostate cancer
18–44 years	---
45–59 years	9 (20,9%)
60–74 years	23 (53,5%)
75–90 years	11 (25,6%)
Over 90 years old	---
Total	43 (100%)

The prevalence of the tumor process in patients with prostate cancer was presented as follows: T3 stage - 9 (20.9%) patients and T4 stage - 34 (79.1%) patients.

Characteristics of prostate cancer patients by PSA level are presented in Table 8. At the time of the diagnosis of prostate cancer, the majority of patients (64.5%) had PSA levels in the range from 21 to 50 ng / ml. In a significantly smaller number of cases (30.2%), the PSA level was increased to 20 ng / ml, and very rarely (5.3%) the indicator was at the level from 51 to 100 ng / ml.

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Table 8 - Characteristics of prostate cancer patients by PSA level

PSA level	Number of patients with prostate cancer
up to 20 ng/ml	13 (30,2%)
21–50 ng/ml	28 (65,1%)
51–100 ng/ml	2(4,7%)
more than100 ng/ml	---
Total patients	43 (100%)

According to the morphological study of biopsy material, a moderate degree of tumor aggressiveness according to the Gleason scale (7 points) prevailed, which was detected in 19 (44.2%) patients with prostate cancer. An almost equal number of patients with prostate cancer had high (2–6 points) and low (8–10 points) tumor differentiation - 10 (23.3%) and 14 (32.6%) patients, respectively (Table 9).

Table - 9 Characteristics of prostate cancer patients according to the Gleason scale

Points total	Number of patients with prostate cancer
2-6 points	10 (23,3%)
7 points	19 (44,2%)
8–10 points	14 (32,6%)
Total	43(100%)

At the beginning of the study, 7 (16%) of 43 patients with prostate cancer with BM had distant metastases of extraosseous localization: lung damage - 4 (56%) and liver - 3 (44%). At the same time, in addition to BM, 1 patient with prostate cancer was found to have multiple combined metastatic lesions of the lungs and liver.

The somatic status in patients with prostate cancer on the ECOG scale ranged from 0 to 2 points (Table 10). Most often, the ECOG status was 0 points (60.5%), less often the functional state of patients was assessed at 1 (23.3%) and 2 (16.3%) points.

Table 10 - Characteristics of patients with prostate cancer by ECOG status.

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Points	Number of patients with prostate cancer
0	26 (60,5%)
1	10 (23,3%)
2	7 (16,3%)
Total	43 (100%)

The groups of patients with prostate cancer and prostate cancer with symptomatic and asymptomatic BM were comparable in terms of age, clinical and morphological characteristics of the tumor, stage, localization of BM, which made it possible to correctly conduct a comparative analysis of treatment results.

Quality of life analysis was carried out 3 months after the start of palliative treatment using questionnaires from the European Organization for Research and Treatment Cancer. The survival rate of patients after palliative treatment was determined according to the following criteria: median time to progression, median overall survival, and 3-year survival of patients with BM. Observed survival curves were plotted according to the survival method.

RESULTS

According to the analysis, at the end of 36 months of observation, 19 (30.6%) of 62 patients with RP were diagnosed with CM. When BM was detected at the indicated time, all 19 patients with RP were aged from 45 to 59 years, had IIb – III stage of the disease, the size of the primary tumor T2b-T3a and the grade of malignancy G III. In other cases, in 43 (69.8%) patients with RP, the covariates were different and BM was diagnosed at a later follow-up period.

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Table 11 - The results of constructing a proportional risk model for BM detection in patients with RP

Variables in an equation		Covariates			
		Age	Tumor size	Stage	Grade of malignancy
B (coefficient regression)		– 0,020	0,258	1,120	0,773
S.E. (standard mistake)		0,014	0,095	0,359	0,293
Wald (Wald test)		2,131	7,407	9,730	6,967
df (degree of freedom)		1	1	1	1
p (significance)		0,144	0,006	0,002	0,008
Exp (B) or risk coefficient (KP))		0,980	1,294	3,065	2,167
95,0% CI для Exp (B)	Lower	0,953	1,075	1,516	1,220
	Upper	1,007	1,558	6,195	3,848

The data presented indicate a statistically significant effect on the development of the event (CM) of such covariates as the size of the primary tumor, the stage of the disease, and the tumor grade. The highest risk in detecting BM in RP was noted for the stage of the disease, the CR was 95% CI 3.065 (from 1.516 to 1.558), p = 0.006. In addition, a high risk was associated with the size and grade of tumor malignancy; the CR was 95% CI 1.294 (from 1.075 to 1.558), p = 0.006 and 95% CI 2.167 (from 1.220 to 3.848), p = 0.008, respectively.

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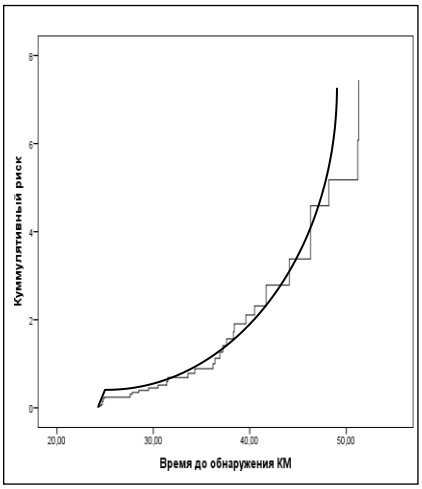

Cumulative predicted risk of BM detection in RP for the mean values of each of the covariates. In this case, the horizontal axis is the time before the event, and the vertical axis is the cumulative risk. A small segment of the initial section of the curve, corresponding to 24 months, represents a steep rise, since at this stage 13 cases were noted with the influence of all significant covariates at the same time. After this period of time, the risk curve looks more flattened.

When analyzing the proportional hazards model in patients with prostate cancer, it was found that after 24 months of follow-up, 7 (26.9%) of 26 patients with prostate cancer were diagnosed with BM. When BM was detected at the indicated time, all 7 patients with prostate cancer were between the ages of 60 and 74 years, had stage III of the disease, the Gleason score ≥ 7, and the PSA level in the range of 21-50 ng / ml. In other cases, in 19 (73.1%) patients with PCa, the covariates were different and BM was detected at a later date. The calculation results are presented in Table 12.

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Table 12 - Construction results proportional risk models of BM detection in patients with prostate cancer

Variables in an equation		Covariates			
		Age	Stage	Gleason score	PSA
RC (regression coefficient)		– 0,009	2,013	0,518	0,067
S.E. (standard error)		0,031	0,616	0,208	0,293
Wald (Wald test)		0,095	10,686	6,216	6,967
df (degree of freedom)		1	1	1	1
p (significance)		0,758	0,001	0,013	0,008
Exp (B) or risk coefficient (KP)		0,991	7,488	1,679	2,167
95.0% CI for Exp (B)	Lower	0,932	2,239	1,117	1,220
	Upper	1,052	25,039	2,524	3,848

The results of the statistical data shown in Table 24 indicate that the stage of the disease, the sum of the Gleason scores, and the PSA level have a significant effect on the onset of an event in prostate cancer. Among the listed covariates, the highest risk in detecting CM is observed for the stage of the disease, the CR at which was 95% CI 7.488 (from 2.239 to 25.039), p = 0.001. In addition, an increased risk was observed for the Gleason score and PSA level. With these covariates, the CR was 95% CI 1.679 (1.117 to 2.524), p = 0.013 and 95% CI 2.167 (1.220 to 3.848), p = 0.008, respectively.

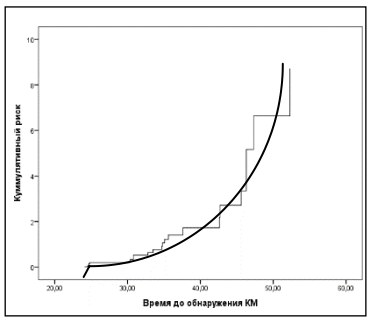

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Figure: 4. Risk function for mean values of covariates at RP

There was no statistically significant effect of the age of prostate cancer patients on the onset of the event, since the CR was 95% CI 0.991 (from 0.932 to 1.052), p = 0.758. Thus, the risk of CM in patients with RP increases

with stage III by 7.5 times, with a Gleason score of 1.7 times and a PSA level in the range from 21 to 50 ng / ml by 2.2 times.

On the curve of the risk function of detecting BM in prostate cancer, shown in Figure 4, in the initial section corresponding to 24 months of observation, a segment with a steep rise is presented, due to the same reasons as in breast cancer. After this period of time, the risk curve looks more flattened.

DISCUSSION

Santoni et al. studied patients with bone metastases from RCC and found that patient age, ECOG status, histology, MSKCC prognostic score, presence of concomitant metastases, and time from nephrectomy to bone metastases [TTBM] are significant factors associated with prognosis [Santoni M., Conti A., Procopio G., Porta C., Ibrahim T., Barni S. Bone metastases in patients with metastatic renal cell carcinoma: are they always associated with poor prognosis? J. Exp. Clin. Canc. Res. 2015; 34 (1): 1]. In our case, the influence of age as a prognostic factor was not identified.

Kume et al. analyzed 94 patients with mRCC with bone metastases and using multivariate analysis found that sarcomatoid differentiation of RCC, involvement of the spinal bones in the process, extraosseous metastases were significant risk factors that adversely affect overall survival [Kume H., Kakutani S., Yamada Y., Shinohara M., Tominaga T., Suzuki M. Prognostic factors for renal cell carcinoma with bone metastasis: who are the long-term survivors? J. Urol. 2011; 185 (5): 1611-1614]. The results of our research work showed that the size of the primary tumor, the stage of the disease and the grade of malignancy are a significant prognostic marker (p = 0.006).
Age was found to be unrelated to survival in 80% of the included studies. Sex was not associated with survival - 79% Masood Umer, Yasir Mohib, * Muhammed Atif, and Muhammad Nazim Skeletal metastasis in renal cell carcinoma: A review \\ Ann Med Surg (Lond). 2018 Mar; 27: 9–16.Published online 2018 Jan 31. doi: 10.1016 / j.amsu.2018.01.002. The results of our study also confirmed that gender in metastatic kidney cancer is not a significant prognosis criterion.

As indicated by Bollen L. on the assessment of prognostic factors in patients with metastases in the spinal bone, seventeen adverse prognostic factors were identified, including the classification of the primary tumor and the assessment of efficacy. Bollen, L., Jacobs, W.C.H., Van der Linden, Y.M. et al. A

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systematic review of prognostic factors predicting survival in patients with spinal bone metastases. Eur Spine J 27, 799-805 (2018). https://doi.org/10.1007/s00586-017-5320-3

As a result of scientific work, we also come to the conclusion that visceral metastasis with osteogenic metastasis are unfavorable indicators. However, the large degree of heterogeneity found in most pooled risk factors indicates that meta-analysis may not be the most ideal approach to addressing this topic.

Bone alkaline phosphatase (ALP), when used in combination with PSA, may be an effective independent marker for predicting the risk of metastatic disease in bone, as reported in Study 203. Men with previously untreated asymptomatic prostate cancer Crawford, ED, et al. , Challenges and recommendations for early identification of metastatic disease in prostate cancer. Urology, 2014.83 (3): p. 664-9. In our case, a significant factor was the stage of the disease and the sum of points on the Glisson scale and the PSA level (p = 0.001).

According to F Ruatta, in 64 patients (21%) bone was the only site of metastasis, 236 patients (79%) had concomitant metastases elsewhere. In multivariate analysis, concomitant metastases remained predictors of poor prognosis European Journal of Cancer.

Prognosis of Renal Cell Carcinoma With Bone Metastases: Experience From a Large Cancer Center Eur. J. Cancer 2018 Dec 11; 107 (xx) 79-85, F Ruatta, L Derosa, B Escudier, E Colomba, A Guida, G Baciarello, Y Loriot, K Fizazi, L Albiges, which is confirmed by our research.

FINDINGS

Thus, BM most often during the 2-year follow-up period develops in patients with kidney cancer at stage Tv-T3a and stage C and grade G III, in patients with PCa - in the presence of stage III with a Gleason score of ≥ 7 and PSA level in range of 21-50 ng / ml. Patients with PC and PC with a high risk of BM development 24 months after the completion of radical treatment are shown to use the entire diagnostic algorithm in order to identify asymptomatic bone metastases, assess the effectiveness of treatment, and also for dynamic monitoring of this category of patients.

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