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SURVIVAL OF THE PATIENTS WITH METASTATIC PROSTATE CANCER DIAGNOSED AT INITIAL PRESENTATION: A 14-YEAR FOLLOW-UP IN KARLOVAC GENERAL HOSPITAL

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Summary

Despite a very favorable stage migration, there are still patients with bone and/or nodal metastasis at the time of initial diagnosis of prostate cancer (CaP). The incidence of these patients varies significantly from country to country depending on whether or not programs for CaP screening are implemented in their health policy. In contrast to vast interest for prognosis of patients who develop metastasis after radical treatment of presumed localised CaP, there are only a few studies in recent literature analyzing survival of patients diagnosed with metastasis at initial presentation. In our study, we analyzed 128 patients with CaP in whom metastasis were assessed at the time of diagnosis. Ninety-five (74.2%) of all metastatic patients had bone metastasis ($T_{1-4}N_0M_1$), 17 (13.3%) had metastasis in lymph nodes ($T_{1-4}N_1M_0$) and in 16 (12.5%) patients metastasis were assessed both in bones and lymph nodes ($T_{1-4}N_1M_1$). Patients with both bone and nodal metastasis ($T_{1-4}N_1M_1$) had a significantly higher average PSA value and significantly higher average Gleason score. The median time to progression for all pateints was 12 (1-86) months while the median survival time was 18 (1-135) months. The tumor-specific survival of the patients with both bone and nodal metastasis ($T_{1-4}N_1M_1$) was significantly worse than the survival of the patients with only bone or only nodal involvement.

In conclusion, despite the introduction of new hormonal and cytotoxic agents and strategies, prognosis for patients with metastatic prostate cancer remains poor, especially if they initially present with both bone and nodal metastasis.

KEYWORDS: *prostate cancer, metastasis, survival, prognosis*

PREŽIVLJENJE BOLESNIKA S KARCINOMOM PROSTATE S METASTAZAMA UTVRĐENIM KOD POSTAVLJANJA DIJAGNOZE: 14-GODIŠNJE PRAĆENJE U OPĆOJ BOLNICI KARLOVAC

Sažetak

Unatoč tendenciji otkrivanja karcinoma prostate u sve ranijem stadiju, i dalje se javljaju bolesnici s koštanim i/ili limfnim metastazama utvrđenim u trenutku postavljanja dijagnoze primarnog tumora. Pojavnost ovih bolesnika bitno se razlikuje od zemlje do zemlje ovisno o primjeni probira na karcinom prostate u zdravstvenom sustavu. Za razliku od širokog zanimanja za prognozu bolesnika koji su razvili metastaze karcinoma prostate nakon radikalnog liječenja, suvremena literatura nudi svega nekoliko istraživanja koja se bave preživljenjem bolesnika kod kojih su metastaze utvrđene u trenutku postavljanja dijagnoze. U našem istraživanju analizirali smo 128 bolesnika koji su imali metastaze u trenutku postavljanja dijagnoze karcinoma prostate. Kod 95 (74,2%) bolesnika metastaze su utvrđene u kostima ($T_{1-4}N_0M_1$), kod 17 (13,3%) u limfnim čvorovima dok su kod16 (12,5%) bolesnika metastaze u trenutku postavljanja dijagnoze primarnog tumora bile prisutne i u kostima i u limfnim čvorovima ($T_{1-4}N_1M_1$). Bolesnici koji su imali i koštane i limfne metastaze($T_{1-4}N_1M_1$) imali su značajno višu prosječnu vrijednost PSA te znatno viši prosječni Gleason score. Srednje vrijeme do progresije bolesti iznosilo je za sve bolesnike 12 (1-86) mjeseci, dok je prosječno trajanje života iznosilo 18 (1-135) mjeseci. Prosječno preživljenje bolesnika koji su imali i koštane i limfne metastaze ($T_{1-4}N_1M_1$) bilo je značajno kraće u odnosu na bolesnike koji su imali samo koštane ili samo limfne metastaze.

U zaključku ističemo da prognoza bolesnika s metastatskom bolešću utvrđenom prilikom postavljanja dijagnoze karcinoma prostate, usprkos uvođenju novih hormonskih i citotoksičnih lijekova i novih strategija, ostaje loša, posebno za bolesnike s metastazama i u kostima i u limfnim čvorovima.

KLJUČNE RIJEČI: *karcinom prostate, metastaze, preživljenje, prognoza*

INTRODUCTION

The rate of patients diagnosed with metastatic CaP at initial presentation varies significantly from country to country depending on whether or not programs for CaP screening are implemented in their health policy. In developed Western countries, with well-established preventive programs, metastatic prostate cancer at diagnosis is a very rare entity, with more than 90% patients diagnosed with localized disease (1-3). On the other hand, patients with distant metastasis are still an everyday reality in less developed countries without screening programs for CaP. These patients are not candidates for curative treatment, but a standard treatment option for them is palliative androgen deprivation therapy. In a majority of these patients endocrine therapy will result in temporary regression of the disease, but with the imminent development of hormone-independent cancer cells, a majority of the tumors will progress again. Despite the introduction of some new systemic agents, like docetaxel, abiraterone, etc., for metastatic castration-resistent CaP, median progression-free survival of these patients remains about 6 months, and overall survival remains about 2-3 years (4-6). In contrast to vast interest for prognosis of patients who develop metastasis after radical treatment of presumed localized CaP, there are only a few studies in recent literature analyzing survival of patients diagnosed with metastasis at their initial presentation.

In our country there is no organized screening program for CaP. We are faced with a significant rate of patients diagnosed with metastatic CaP at initial presentation. The aim of our study was to analyze clinical and prognostic parameters of patients diagnosed with metastatic CaP. We compared survival of our patients with survival of relevant patients in some other published studies. We analyzed the significance of metastasis localization (bone or nodal) and outcome in our patients with metastatic CaP.

PATIENTS AND METHODS

Hundred and twenty-eight patients with metastatic CaP at initial presentation diagnosed in Karlovac General Hospital from January 1994 to January 2010 were followed prospectively. In 91 patients the cancer was proved pathologically after transrectal ultrasound-guided biopsy and in 37 patients the cancer was assessed cytologically after fine-needle biopsy. A standard pretreatment work-up consisted of routine laboratory tests, chest X-ray, bone scintigraphy, pelvic CT scan and cystoscopy. Bone radiography and PET scan were performed when indicated. The group of patients with nodal involvement consisted of patients with non-regional lymph node metastasis. Patients with nodal involvement proven intraoperatively, during routine lymphadenectomy before planned radical prostatectomy and with no evidence of non-regional nodal metastatic deposits were not included in the study. Patients were classified into 3 tumor grades where grade 1 related to tumors with Gleason score 2-6 (with no single 4), grade 2 to Gleasone score 7 tumors and grade 3 to tumors of the Gleasone score 8 and more. All the patients with metastasis received some kind of endocrine therapy which was accomplished either by surgical or chemical castration. Antiandrogens were added when indicated.

The follow-up was provided through 3- or 6-month visits. The standard post-treatment check-ups consisted of physical examination and PSA testing in all patients, and in pelvic CT scan, bone scintigraphy in selected cases. PSA progression was defined as a first increase of at least 30% to a value greater than 4 ng/mL.

Statistics

Yates-corrected chi-square test and T-test were used for testing of qualitative and quantitative parameters, respectively. Survival rates were estimated using the Kaplan-Meier product-limit me-

thod. Differences between the groups were calculated using the Log-Rank test.

RESULTS

There were 746 patients diagnosed with CaP in Karlovac General Hospital, Dept. of Urology from January 1994 to January 2010. In 128 (17.1%) of them, a metastatic disease (M+ or/and N+) was assessed at initial staging. From 1994 to 2002, 19.2% of overall 312 patients had metastatic disease versus 15.7% of overall 434 patients diagnosed between 2003 and 2010 (p=0.28). Ninety-five (74.2%) of all metastatic patients had bone metastasis ($T_{1-4}N_0M_1$), 17 (13.3%) had metastasis in lymph nodes ($T_{1-4}N_1M_0$) and in 16 (12.5%) patients metastasis were assessed both in bones and lymph nodes ($T_{1-4}N_1M_1$). The mean age of patients in the metastatic group was 70.9 years (51-92). There were no age differences between the groups of patients with different metastasis localization (p=0.23). Median PSA for all patients with metastasis was 328 ng/mL (4.7-5000.0). These values in the groups of patients with bone metastasis, nodal involvement and both bone and nodal involvement were 483 ng/mL (4.7-5000.0), 185 ng/mL (6.8-711.0) and 683 ng/mL (49.0-2838.0), respectively. The grade of the tumor was assessed in 120 patients. Fourteen (11.6%) tumors were classified as grade 1, 53 (44.2%) as grade 2 and 53 (44.2%) as grade 3. Grade 3 tumors were assessed in 39 (44.8%) patients with bone metastases only, in 5 (29.4%) patients with nodal metastases only and in 9 (56.2%) patients with both bone and nodal involvement (Table 1).

The median follow-up was 18 months (range 1-135). During the follow-up clinical or biochemical progression of the disease was noticed in 110 (85.9%) patients. The median time to progression for all the patients was 12 months (1-86). The median time to progression in the group of patients with bone metastasis and the group of patients with nodal involvement were 12 months (1-86) and 12 months (3-72), respectively. The median time to progression in the group of patients with both bone and nodal metastasis was 7 months (1-19) and it was significantly shorter than in the previously mentioned groups (Table 1).

The median time to progression in patients with grade 1 tumors was 22 month (3-72). In patients with grade 2 tumors and in patients with grade 3 tumors the median time was 12 months (1-48) and 10 months (1-86), respectively.

During the follow-up, 8 (6.2%) patients developed pathological bone fracture, while spinal compression was assessed in 9 (7.0%) of 128 patients in the study.

During the observed period 105 (82.0%) patients died. Ninety-seven (92.4%) of them died with clinical or biochemical signs of tumor pro-

Table 1.

PATIENT CHARACTERISTICS, DESCRIPTIVE STATISTICS AND OUTCOME

	N_0M_1	N_1M_0	N_1M_1	All patients
No. of patients (%)	95 (74.2)	17 (13.3)	16 (12.4)	128 (100.0)
Age, yr				
Mean	71.5	69.3	68.6	70.9
Range	51-75	59-77	51-88	51-88
PSA, ng/ml				
Median	483	185	683	328
Range	4.7-5000.0	6.8-711.0	49.0-2838.0	6.7-5000.0
Pathologic grade (%)				
Grade1	8 (8.4)	5 (29.4)	1 (6.2)	14 (10.9)
Grade 2	40 (42.1)	7 (41.2)	6 (37.5)	53 (41.4)
Grade 3	39 (41.1)	5 (29.4)	9 (56.3)	53 (41.4)
Grade X	8 (8.4)	0	0	8 (6.3)
Time to progression, ms				
Median	12	12	7	12
Range	1-86	3-72	1-19	1-86
Survival time, ms				
Median	21	20	12	18
Range	1-104	5-135	1-31	1-135

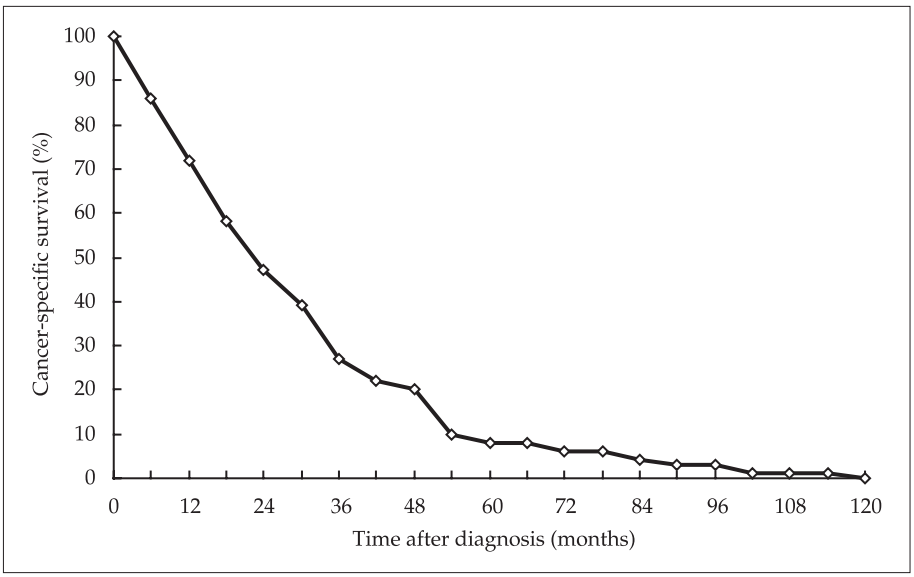

Figure 1. Tumor-specific survival of patients with distant metastasis diagnosed at the time of initial presentation (N=128)

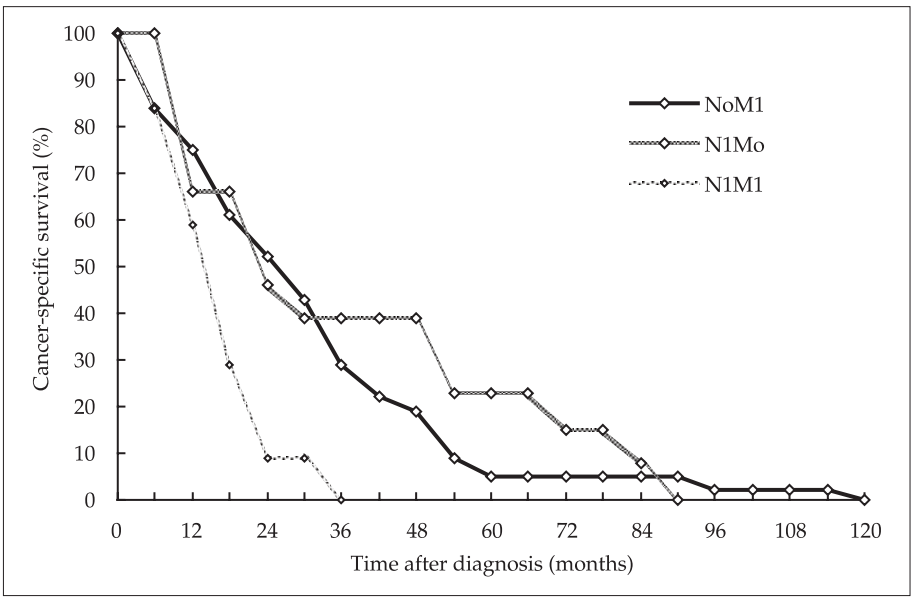

Figure 2. Tumor-specific survival of patiens with N_0M_1 CAP (—), N_1M_0 CAP (—) and N_1M_1 CAP (---) (N_1M_1 vs. N_0M_1 p=0.033, N_1M_1 vs. N_1M_0 p=0,038, N_0M_1 vs. N_1M_0 p=0.015)

gression, while 8 (7.6%) died without progression. The median survival time for all patients was 18 months (1-135). Median survival times for the groups of patients with bone metastasis, nodal metastasis and both bone and nodal metastasis were 21 month (1-104), 20 months (5-135) and 12 months (1-31), respectively (Table 1).

Tumor-specific survival time calculated by Kaplan-Meier product-limit method for all patients is presented in Figure 1. Tumor-specific survival of patients with both bone and nodal metastasis (N_1M_1) was significantly worse than the survival of patients with only bone (N_0M_1) or only nodal (N_1M_0) metastasis (N_1M_1 vs. N_0M_1 p=0.033, N_1M_1 vs. N_1M_0 p=0.038). There was no difference in tumor-specific survival between the group of patients with bone (N_0M_1) and the group of patients with nodal metastasis (N_1M_0) (p=0.15) (Figure 2).

DISCUSSION

In Croatia, the incidence of CaP increased from 7% of all malignancies in 1993 to 13% of all

malignancies in 2005, with the recent incidence rate of 70.6/100,000 males (7). Although there is no organized screening program for prostate cancer in our country, an increased number of CaP diagnosis results from an increased rate of patients diagnosed with localized tumor as a result of wide use of PSA testing and some other activities for early CaP detection. There is no data for stage distribution of patients with CaP in Croatia, but it seems that the number of patients with metastatic disease, despite a shift to lower stages, remains relatively high. In our study, 17.1% of patients presented with metastasis at diagnosis, with only a 3.5% decrease over the observed 16-year period. Ryan et al. in their two studies derived from USA CaPSURE registry found a significantly lower 2.6% and 2.4%, respectively, incidence of metastatic disease between over than 10,000 patients diagnosed with CaP from 1990 to 2004 (1, 6). They noticed a further decrease in the rate of metastatic CaP, too (1). There was no age difference between nonmetastatic and metastatic patients in our study (71.6 versus 70.9 years). There was no age difference between the groups of our patients with different metastatic localization. The presence of distant metastasis in patients with a relatively low PSA value in our (4.7 ng/mL) has to be considered when acquiring guidelines for rational diagnostic work-up for patients with newly diagnosed CaP.

The grade of our metastatic tumors was significantly worse than in nonmetastatic CaP. Tumors in patients with only nodal metastasis showed a relatively favorable distribution of grades, while tumors in patients with both bone and nodal involvement had the most unfavorable average grade, with 56.2% tumors classified pathologically as grade 3.

Bone fracture was a rare complication in patients with bone metastasis of CaP in our study. This observation could be explained by dominantly osteoblastic nature of bone metastasis in CaP patients. Spinal compression was also a rare, but serious complication requiring urgent treatment. It was usually not related to bone fracture, but to soft tissue metastatic mass in the spinal channel. In some patients in our study, paraplegia of the lower limbs caused by spinal compression was the first sign of CaP in patients with no earlier sign or history of CaP.

In our study the follow-up was relatively short, but long enough to reach the median time to progression and median survival time. The median time to progression (12 months) in our study is comparable with the data from the Robinson´s EORTC genito-urinary group trial (8). A shorter median time to progression in the Bellmunt´s study (6 months) could be a consequence of a different definition of PSA progression used in the study (5).

Time to progression in our study was significantly shorter in the group of patients with both bone and nodal metastasis than in the other two groups with only bone or only nodal metastasis. Prognosis for patients with metastatic CaP remains poor. In our study the median survival time was 18 months and it was comparable with the survival of patients in some other published studies (5). The two-year cancer specific survival for our patients was 47%. Ryan et al., in their study from CaPSURE registry report a surprisingly high 5-year cancer-specific survival of 71% in their 277 patients with metastatic CaP (1). Their study includes patients with only bone metastasis. Another explanation for such a high survival rate could result from different criteria for assessing the cause of death (cancer related or not) in their study.

In conclusion, despite a very favorable stage migration, there are still patients with bone and/or nodal metastasis at the time of initial diagnosis of prostate cancer. As curative treatment is not possible, palliative hormonal therapy is a mainstay for such patients. Despite the introduction of new hormonal and cytotoxic agents and strategies, there is no sign of significant prolongation of tumor specific survival of these patients. So the prognosis for patients with metastatic prostate cancer remains poor, especially if they initially present with both bone and nodal metastasis. Although some negative aspects of screening for CaP, like problems with overdiagnosis and overtreatment, are well recognized today, it has been proven that screening has a power to reduce the number of patients with distant metastasis at diagnosis of CaP.

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