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The course of metastatic disease originating from carcinoma of the prostate

S. PLESNIČAR

The Institute of Oncology and Faculty of Medicine,
Zaloška 2, 61105 Ljubljana, Yugoslavia

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The purpose of this work was to study the time sequence and the patterns of the multistep spread of metastases. Fifty-one patients with stage D carcinoma of the prostate, previously treated for their primary tumor by surgery or radiotherapy combined with hormonal manipulation and for metastases by hormones and chemotherapy, were included in the study. The metastatic dissemination, characterized primarily by the appearance of bone metastases, could follow two distinct patterns: The first, characterized by sequential appearance of osteoblastic metastases, followed by the development of osteolytic bone lesions, and the second pattern, characterized by the simultaneous appearance of osteoblastic and osteolytic bone lesions.

In cases with solely osteoblastic bone metastases, the lesions are hormone sensitive and long-lasting remissions could be obtained. The development of osteolytic bone lesions is usually accompanied by the recurrence of the primary tumor and appearance of metastases in other sites, such as the lymph nodes and lungs. Bone metastases became resistant to hormonal manipulation and with chemotherapy short remissions were obtained. The course of the terminal period is faster, with shorter survival times. The determination of serum acid and alkaline phosphatase levels seems to reflect the course of the disease during the initial period of the disease only, i.e. when bone metastases are sensitive to hormonal treatment.

Introduction

With the majority of tumors, patients usually succumb to pathological conditions caused by metastases. Accordingly, more profound understanding of the development, course and progression of metastases is necessary. This knowledge would allow us to improve the effectiveness of the therapeutic interventions, the quality of life and, eventually, prolong survival [3, 6]. Approximately 70–90 per cent of patients with carcinoma of the prostate develop distant metastases, preferentially in the skeleton, lymph nodes and lungs [10]. In the majority of cases the metastatic bone lesions are of osteoblastic variety, however, lytic lesions can be seen as well [7, 16]. During the growth of metastases the condition of the patient deteriorates, ending in cachexia. This condition, characterized by specific symptoms, induced by the appearance and growth of metastases, could be described as the metastatic disease [11].

Clinical observations indicate that the appearance, growth and cascade dissemination of metastases are not random processes. It appears, instead, that metastatic dissemination could be considered as a sequence of predetermined multistep events [14] in which one metastatic organ is required for seeding another predetermined site or organ.

Therefore, the purpose of the present investigation was to study the time sequence and the pattern of the multistep spread of metastases arising from carcinoma of the prostate.

For the present purpose patients with distant metastases arising from carcinoma of the prostate were studied. The study included patients, treated for their primary tumor, in whom metastases developed subsequently, and those in whom metastases had already been diagnosed at the time of their first examination.

Materials and methods

Patients

The group consisted of a consecutive series of 51 cases with stage D2 or IV (T2-4, NX, M1a–b) and stage C or III (T3b-4, NX, MO) adenocarcinoma of the prostate [1, 13], treated at the Institute of Oncology in Ljubljana, Yugoslavia, from 1971 to 1980. Their ages ranged from 47 to 83 years, with a median age of 69 years. Twenty-two patients were older than 70 years, five of them were over 80 years of age.

The histological or cytological diagnosis at first admission was a well-differentiated adenocarcinoma in 17 cases, a moderately differentiated one in 19 cases, and a poorly differentiated carcinoma in eight cases. In seven cases an undifferentiated carcinoma of the prostate was diagnosed.

The treatment of the primary tumor consisted of transurethral resection or radical irradiation, followed by orchiectomy or diethyl-stilbestrol treatment. Metastases were treated by endocrine therapy (phosphoestrol, estramustin) and by irradiation of painful bone lesions. The chemotherapy protocol included the use of 5-fluorouracil and cyclophosphamide.

Follow-up analysis

Each patient's file was reviewed and the course of the disease assessed for: (1) Past history and the extent of the disease at first admission, particularly with regard to a possible presence of bone lesions. (2) The time of the appearance of osteoblastic and osteolytic bone metastases and the pattern of dissemination. (3) Appearance of metastatic involvement in other organs and sites. (4) Duration of remissions after the treatment of primary tumor and metastases, and the total survival time. (5) Changes in the serum acid and alkaline phosphatase concentrations during the course of metastatic disease.

All cases were followed during the whole course of the disease until their death.

Statistical evaluation

Durations of different remission and survival periods were expreseed by arithmetic mean and standard error. Differences in survival length or duration of remission were analysed by the use of the chi-squared test.

Results

The duration of the metastatic disease with bone metastases

For carcinoma of the prostate the bones are most frequently and usually the first to be involved by metastases (table 1).

In the present series of patients with bone metastases the overall survival, from diagnosis to the death of patients, was 883 days. The duration of the survival for the period from the diagnosis to the appearance of metastases (596 days), and for the period from the appearance of metastases to the death of patients (495 days) were

Table 1. Mean survival times for different periods of the disease in patients with carcinoma of the prostate.

Periods of disease	Number of patients	Survival time (days)		
		Mean	1 s.e.	Range
From diagnosis to death	45	883	92	300–2968
From diagnosis to appearance of metastases	28	596	118	21–2196
From appearance of metastases to death	45	495	45	75–1219

compared. Although the mean survivals differ in duration the difference is not statistically significant.

The mean survival time was calculated for patients divided into groups according to the degree of differentiation of the primary prostatic tumor, verified at the moment of diagnosis. For 16 patients with highly differentiated prostatic carcinoma the mean survival time from the appearance of metastases to the death of patients was 496 days (1 s.e. = 70 days), for 21 patients with moderately differentiated carcinoma 464 days (1 s.e. = 61 days), and for 8 patients with poorly differentiated carcinoma of the prostate the mean survival was 575 days (1 s.e. = 204 days). The data indicate similar survival periods for the patients in all three groups studied.

Subsequently, the course of the metastatic disease with bone metastases was studied. It seems that the development of bone metastases could occur in two distinct ways: (1) Sequential development of bone metastases, with first, the appearance of osteoblastic bone metastases, followed during the course of the disease by the formation of osteolytic bone lesions. (2) Simultaneous appearance of both, osteoblastic and osteolytic bone metastases.

The sequential development of skeletal metastases

In 19 cases the sequential appearance of skeletal metastases was observed. Consequently the course of metastatic disease could be divided into two distinct periods. The first or initial period is characterized by the development of osteoblastic bone metastases, while during the second, terminal period of the disease, osteolytic bone metastases appeared. During the first or initial period the condition is responsive to endocrine manipulation, the number of remissions thus obtained ranged up to a maximum of three, one and two remissions being observed most frequently. The second, terminal period of the metastatic disease is characterized by the appearance of osteolytic bone metastases, resulting in a mixed, osteoblastic and osteolytic appearance of the affected bones. During the terminal period metastases were observed in other sites in 5 of the 19 cases, involving lymph nodes, the lung, pleura, adrenals and the central nervous system. The bone lesions were resistant to hormonal treatment, short-lasting remissions were obtained with chemotherapy. The condition of the patients was usually rapidly deteriorating, ending in cachexia and death. During the initial period the primary prostatic carcinoma recurred and progressed in 17 of the 19 cases studied in which, however, the treatment resulted in regression. Nevertheless, in 11 cases a primary tumor recurred again during the terminal period. In 17 cases the primary tumor was a highly differentiated, in 8 a moderately and in 4 cases a poorly differentiated adenocarcinoma of the prostate.

Table 2. Mean survival times for different periods of the metastatic disease in patients with sequentially appearing bone metastases arising from carcinoma of the prostate.

Group of patients	Number of patients	Survival time (days)		
		Mean	1 s.e.	Range
All patients	19	572	82	98–1143
Differentiation grade of prostatic cancer				
Highly	7	557	131	181–886
Moderately and poorly	12	578	108	98–1143
Periods of disease				
Initial (osteoblastic)	19	406	93	98–1101
Terminal (osteolytic)	13	216	45	54–480

The mean survival time from the appearance of metastases to the death of patients was 572 days (table 2). The mean survival for highly differentiated prostatic carcinoma (557 days) is similar to the corresponding value for patients with moderately and poorly differentiated prostatic carcinoma (578 days). However, significant differences in the length of survival were observed when the mean survival time for the initial period (406 days) was compared to the mean survival time for the terminal period (216 days) of the metastatic disease ($P=0{\cdot}05$). It could be concluded that the overall survival time is determined predominately by the duration of the initial period with osteoblastic metastases responsive to hormonal treatment.

The simultaneous appearance of osteoblastic and osteolytic bone metastases

In 25 cases the osteoblastic and osteolytic bone metastases were observed to appear simultaneously. The course of the metastatic disease was characterized by the progressive appearance of additional, prevalently osteolytic lesions, together with general deterioration of patients' condition. Metastases in other organs were diagnosed in five cases in the lymph nodes, lungs, pleural cavity and kidneys. In all cases the primary tumor recurred and progressed during the course of the disease.

In 9 cases the primary tumor was a highly differentiated, in 12 cases a moderately differentiated and in four cases a poorly differentiated carcinoma of the prostate.

The mean survival time from the appearance of metastases to the death of patients was 452 days (table 3). The comparison of mean survival values for patients with highly differentiated primary tumors (453 days) with the corresponding values for patients with moderately and poorly differentiated carcinoma (451 days) revealed that survival is almost identical for both groups. However, in 11 patients bone metastases responded to hormonal treatment. In these patients, interestingly, hormone treatment induced the transformation of osteolytic lesions into an osteoblastic variety, but it did not prevent the appearance of new lytic lesions, which were, under the influence of the hormones, continuously transforming into osteoblastic metastases. The hormone treatment seems to prolong the survival of patients with sensitive bone lesions, since the mean survival for this group (534 days) is significantly longer compared to the mean survival time of the remaining cases

Table 3. Mean survival times for different periods of the metastatic disease in patients with simultaneous appearance of bone metastases arising from carcinoma of the prostate.

Groups of patients	Number of patients	Survival time (days)		
		Mean	1 s.e.	Range
All patients	25	452	56	84–1219
Differentiation grade of prostatic cancer				
Highly	9	453	93	145–904
Moderately and poorly	16	451	72	84–1219
Hormone responsiveness				
Sensitive	11	534	82	84–904
Resistant	14	388	74	114–1219

with hormone-resistant bone metastases (388 days). The difference is statistically significant ($P=0{\cdot}05$).

It appears that the hormone sensitivity of bone metastases could be considered as a prognostic factor, and also, that cases with moderately and poorly differentiated prostatic carcinoma bone metastases could be hormone responsive.

The course of carcinoma of the prostate without metastases

In seven cases (13%) the course of the disease was characterized by the absence of metastatic dissemination. In these cases the main characteristic of the disease was the local spread of primary tumor into the neighbouring pelvic structures. The mean survival time was 807 days (1 s.e. = 211 days; range 272–1927 days). In four cases aspiration biopsy revealed an undifferentiated carcinoma of the prostate, in one case a highly differentiated carcinoma, while in two cases the degree of differentiation was not reported. It is noteworthy that in four of the seven cases without metastases, the primary tumor was an undifferentiated prostatic carcinoma. The cause of death in the seven patients was not related to the primary tumor.

Serum acid and alkaline phosphate concentrations in the course of metastatic disease

Serum acid phosphatase concentrations were elevated and similar in both the initial and terminal period of the metastatic disease (table 4). This is in agreement with the finding according to which the majority of primary prostatic carcinoma recurred and progressed during the course of the metastatic disease.

Concentrations of serum alkaline phosphatase are higher during the initial period of the metastatic disease. During the terminal period of the disease concentrations of the enzyme are elevated to a lesser extent. The newly formed metastases are predominately osteolytic in character, which presumably does not affect the serum alkaline phosphatase levels.

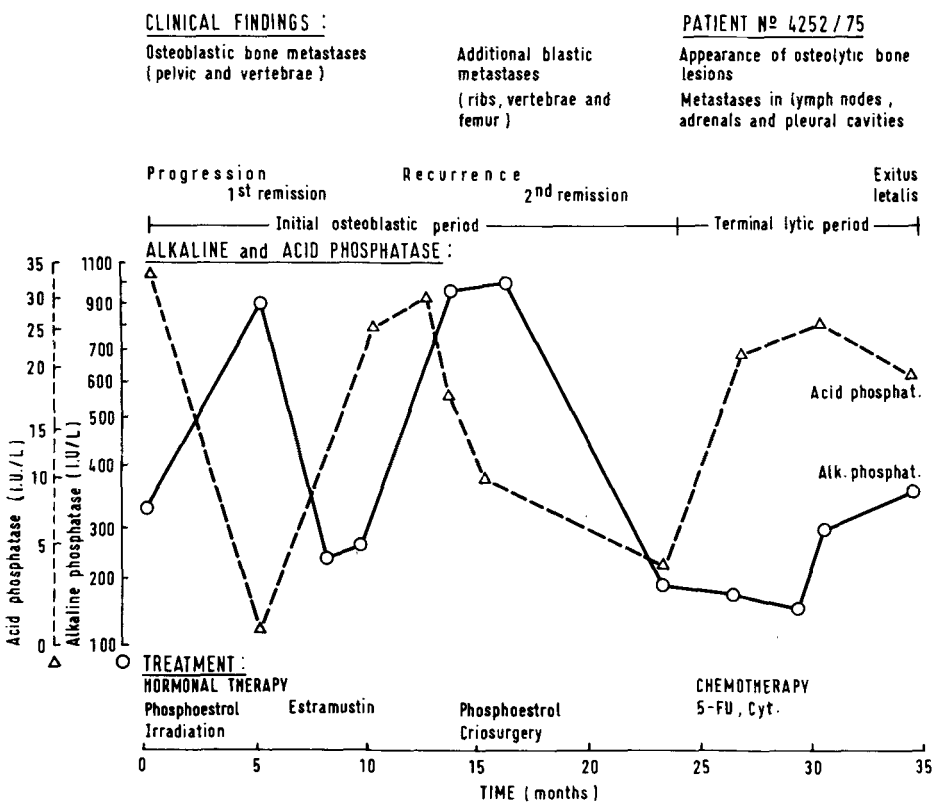
It appears that during the initial period of the metastatic disease, the marked variations in serum alkaline phosphatase concentrations do not precede but parallel the development and growth of metastases and the primary tumor. Consequently, changes in the serum concentrations of both enzymes could be considered to be a reflection of the course of the neoplastic growth. During the terminal period of the metastatic disease, although elevated, concentrations of both enzymes exhibited limited variations in their concentrations. It appears, therefore, that changes in

Table 4. Values for serum concentrations of acid and alkaline phosphatases in patients with metastatic disease arising from carcinoma of the prostate.

Periods of metastatic disease	Arithmetic mean ± 1 s.e. (i.u./l) (No. of patients)	
	Acid phosphatase	Alkaline phosphatase
Initial (osteoblastic)	11·7 ± 2·1 (10)	333·9 ± 96·3 (17)
Terminal (osteolytic)	13·1 ± 1·8 (15)	229·7 ± 41·5 (22)

Normal values: Acid phosphatase >2·0 i.u./l.
Alkaline phosphatase 60–170 i.u./l.

enzyme concentration reflect the course of the disease only during the first, initial period of the metastatic disease. These observations are illustrated in figure 1 where variations in the concentrations of both enzymes are evident during the initial period, while during the terminal period of the disease, although elevated, variations in the concentrations are minimal.



The course of the metastatic disease presented in an illustrative case with data on the clinical course, acid and alkaline phosphatase concentration variations and treatment regimens.

Discussion

In carcinoma of the prostate the course of metastatic disease is characterized by a sequence of different events appearing during the disease. The main characteristic of the metastatic spread originating from carcinoma of the prostate is the formation of metastases in the skeleton. Based on this characteristic, the results of the present study indicated that two distinct patterns of metastatic spread could be distinguished. The first, with the appearance of osteoblastic, followed in time by the formation of osteolytic, bone metastases, and the second, characterized by the simultaneous appearance of both osteoblastic and osteolytic metastases.

The course of the metastatic disease with sequential appearance of bone metastases is characterized by a slower progress when compared to that with simultaneous appearance of both types of bone metastases. Other differences between the two conditions were observed as well, and are related to differences in the appearance of other events. Among them are the time of the appearance of metastases in other organs and sites, and progression or recurrence of the primary prostatic tumor. These changes appeared in an orderly succession, which, with all probability, may be inherent in the nature of the primary prostatic tumor.

From the present observation it was not possible to identify the causative factors which induce the progression of the disease, and the spread of metastases to other organs such as the lungs and lymph nodes. In general, the course of metastatic disease was not clearly connected with the degree of differentiation, the age of patients, or the T-parameter, i.e. the anatomic extent of the primary tumor. It seems, however, that the simultaneous appearance of metastases and a faster course of the disease were more frequent among patients with moderately or poorly differentiated prostatic carcinoma, which is in agreement with observations reported elsewhere [2, 8].

Two critical notes should be added. The first concerns the collected data, which, being obtained from clinical records, are necessarily incomplete. It is known that autopsy verified metastatic involvement and spread far exceed those diagnosed during the patient's life [9, 15]. Secondly, it ought to be considered that the progress from one to another stage of the disease is not sharply delineated and occurs gradually, therefore no strict delimitation is possible. However, this has been done in order to give a schematic presentation of the course of the disease.

The prognostic value of the acid and alkaline phosphatase determination deserves comment as well. In previously published reports the determination of levels is considered helpful, while in other reports the published data indicate that changes in both enzymes could not serve as predictors of the course of the disease [4, 5, 12]. According to the observations obtained from the present material it appears that changes in the concentrations of acid and alkaline phosphatase could serve as an indicator of the activity of the metastatic disease only during the first, initial period of the disease, precisely during the period of the disease sensitive to endocrine manipulation. During the terminal period, although elevated, changes in the concentrations are limited, thus not reflecting the course of the disease.

Nevertheless, from the present observations, the sequence and timing of a particular pathological change appearing during the metastatic disease does occur according to a predetermined succession, enabling in this way identification of some prognostic factors. In fact, the sequential appearance of osteoblastic and lytic metastases indicates a slower course of metastatic disease, while the simultaneous appearance of both blastic and lytic metastases, particularly together with local recurrence, could predict a faster course of the metastatic disease.

Summarizing, from the present study of 51 cases with carcinoma of the prostate, it became apparent that the course of the metastatic disease is regulated by three different events, which are: (1) The development of bone lesions. (2) The recurrence and progression of the primary prostatic tumor. (3) The appearance of metastases in other organs and sites. This knowledge is of practical value since it permits a prognosis to be made and the course of metastatic disease predicted.

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