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 expressed 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