Original Article

Is the Prognosis of Primary Metastatic Carcinoma of the Prostate in Younger Men Really Worse than that in Older Men?

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Background: To investigate the prognosis and predictive factors of primary metastatic prostate carcinoma (M1CaP) in men younger than 60 years. **Methods:** From April 1986 to December 1999, 18 patients with M1CaP were enrolled. Cause-specific and progression-free survival rates were estimated using the Kaplan-Meier method and compared with those of patients aged over 60 years with M1CaP in the same time period. **Results:** The 5- and 10-year cause-specific survival rates were 33.7% and 0%, respectively, in the younger men compared with 57.1% and 41.9%, respectively, in the older age group ($p < 0.001$). In multivariate analysis using Cox's proportional hazards model for cause-specific survival, pretreatment serum PSA was the only significant predictor ($p < 0.02$). **Conclusions:** The prognosis of M1CaP in men younger than 60 is worse than for those aged over 60. Therefore, it is necessary to use a combination therapy (e. g. hormonal plus chemotherapy) for these patients.

Key Words: prostate specific antigen, young men, cause-specific survival, prognosis.

Introduction

Prostate cancer is one of the most common cancers in Western countries¹⁾ and its incidence in Japan has gradually increased²⁾ as localized prostate cancers are found in younger men at initial diagnosis through screening for prostate specific antigen (PSA) and through advances in ultrasonography. However, as primary metastatic cancer (M1CaP) is now being found more often in younger Japanese men (<60 years old), we retrospectively investigated its characteristics, prognosis and predictive factors and compared them with those of men aged over 60 years with M1CaP in the same time period.

Patients and Methods

Patients

Between April 1986 and December 1999, 205 patients were newly diagnosed with M1CaP at Tokyo Medical University Hospital, and of these 18 (10.6%) were under 60 years at the time of diagnosis (median age, 56 years; range, 43-59 years). Follow-up periods ranged from 5.3 to 86.8 months (median, 17.3). All patients were Japanese.

Diagnosis and Clinical Staging

All 205 patients were diagnosed histologically by transrectal needle biopsy and the tumor was classified into three groups: well (Gleason score

2-4), moderately (Gleason score 5-7) or poorly (Gleason score 8-10) differentiated. (None of the patients were diagnosed by transurethral resection or from simple prostatectomy for benign prostatic hyperplasia.) Clinical staging according to the TNM classification³⁾ was done by digital rectal examination, chest X-ray, computed tomography of the abdomen and pelvis, and bone scan. PSA was measured using the Tandem-R test (Beckman Coulter, San Diego, CA, USA).

Treatment

All 205 patients had undergone initial hormonal therapy (i. e. surgical or chemical castration; complete androgen blockade; estrogen). Luteinizing hormone releasing hormone (LHRH) goserelin (3.6 mg s. c. depot each month) or luteorelin acetate (3.75 mg s. c. depot each month) were used for chemical castration, and LHRH goserelin or luteorelin acetate plus flutamide (375 mg tid) for complete androgen blockade. When PSA and/or clinical failure occurred, the second-line therapy was determined by each patient's attending doctor. PSA failure was defined as an increase of PSA on two successive measurements, and clinical failure as detection of new lesions or worsening of the primary lesion on radiology.

Follow-up

All patients were followed up with serum PSA measurements monthly until serum PSA nadir. Thereafter, serum PSA was measured every 3-6 months. When new symptoms appeared and suggested a recurrence or metastasis, DRE, CT and bone scan were performed.

Analysis

We analyzed three characteristics of M1CaP (serum PSA, histological differentiation and extent of disease (EOD)) and the cause-specific

and progression-free survival rates were compared with those of patients aged over 60 years with M1CaP in the same time period. Three patients under 60 years old and 45 older patients (n=48) who did not have serum PSA measured at diagnosis were excluded from the progression-free survival analysis.

Statistics

Statistical analyses were performed with Statview-J 5.0 for Macintosh (Abacus concepts Inc., Berkeley, CA, USA). The difference in characteristics between the two age groups was tested by t-test and chi-squared test. P values <0.05 were considered statistically significant. The cause-specific and progression-free survival rates were calculated by the Kaplan-Meier method⁴⁾ for estimation and the differences were tested using Wilcoxon test. Cox's proportional hazards analysis⁵⁾ was used to assess multiple variables to determine the independent prognostic factors of survival in patients under 60 years old.

Results

Comparison of the clinical characteristics of M1CaP in the two age groups (Table 1)

All 205 patients had adenocarcinoma. Although in the younger patients the median serum PSA was higher and there were more cases of poorly differentiated M1CaP (68% vs 48%) and more cases with an EOD score of 3-4 (50% vs 28.2%), there was no statistical significance between the two groups. The site of distant metastasis was mostly bone (s) only, but 5 patients under 60 years old had other metastatic sites (3 in bone (s)+non-regional lymph node (s), 1 in bone (s)+lung, 1 in bone (s)+lung+non-regional lymph node (s)). Additionally, in the patients over 60 years old, 35 had other metastatic sites (19 in bone (s)+non-regional lymph node (s), 11 in bone (s)+lung, 3

Table 1 Characteristics of patients with primary metastatic prostate cancer

	Under 60 y.o.	Over 60 y.o.	p
Median PSA (ng/mL)	178.2 (1.2 ~12,162)	155.3 (1.8 ~14,189)	n.s.
Differentiation of biopsy			n.s.
Well (GS 2-4)	0	17	※ 1
Moderately (GS 5-7)	6	77	
poorly (GS 8-10)	12	85	
EOD score			n.s.
0~2	8	127	
3~4	8	50	

※ 1 Differentiation of biopsy for 8 cases over 60 y.o. was unclear. ※ 2 EOD scores for 10 cases over 60 y.o were unclear.
EOD: the extent of the disease n. s.: no significance

Fig. 1 The cause specific survival curves for men aged over 60 years and under 60 with M1CaP (over 60 years : 187 patients, under 60 years : 18 patients). A significant difference of survival was found among 2 groups ($p<0.001$).

in bone (s)+liver, 2 in bone (s)+lung non-regional lymph node (s)). Although all younger patients with M1CaP had bone metastases, ten patients aged over 60 years old did not have bone metastasis (10 in non-regional lymph node (s)). There was no statistical significance between the two groups.

Cause-specific survival and progression-free survival (Figs. 1 and 2)

The 5-and 10-year cause-specific survival rates were 34% and 0%, respectively, in men

Fig. 2 The progression free survival curves for men aged over 60 years and under 60 with M1CaP (over 60 years : 142 patients, under 60 years : 15 patients). A significant difference of survival was found among 2 groups ($p<0.001$).

aged under 60 years compared with 57% and 42%, respectively, in those aged over 60 years ($p<0.001$). The 5-and 10-year progression-free survival rates were both 0% in the younger men compared with 31% and 0%, respectively, in the older group ($p<0.001$).

Multivariate analysis of the prognostic factors for cause-specific survival (Table 2)

The prognostic factors analyzed by Cox's proportional hazards model were serum PSA,

Table 2 Multivariate analysis using the Cox's proportional hazards model for cause specific survival of patients under 60 years old with M1CaP

Parameter	patients	P value	Parameter	patients	P value
PSA (ng/mL) *		0.02	periods to first visit from appearance of some symptom (M)		0.10
<178.2	8		≥ 3	10	
≥ 178.2	7		< 3	8	
Differentiation		0.06	age		0.68
Poorly (GS 8-10)	12		≥ 56	10	
Moderately (GS 5-7)	6		< 56	8	
EOD score		0.06			
1, 2	8				
3, 4	8				
Metastatic sites other than bone		0.36			
+	5				
-	13				

* PSA value of 3 cases was not able to measure because 3 cases were diagnosed before 1990.

histological differentiation, EOD score, metastatic sites other than bone and time to first visit from appearance of some symptom (s) and of these, only serum PSA was an independent factor ($p < 0.02$).

Discussion

Although hormonal therapy is the gold standard for M1CaP⁶⁾, it is well known that most patients become hormone refractory some time after the therapy is initiated⁶⁾⁷⁾. Younger men with M1CaP, who have a life expectancy of more than 10 years, have attracted particular interest.

In the present study, there was no significant difference in the characteristics (PSA value, differentiation of biopsy, EOD score) of M1CaP in men younger than 60 compared with men aged over 60, but the cause-specific and progression-survival rates were worse for the younger men. Also, in patients with poorly differentiated adenocarcinoma, the cause-specific survival rate was worse for the younger men ($p < 0.05$) (Fig. 3). These results suggest that although the clinical parameters of M1CaP

Fig. 3 The cause specific survival curves for men aged over 60 years and under 60 with poorly differentiated M1CaP (over 60 years: 85 patients, under 60 years: 12 patients). A significant difference of survival was found among 2 groups ($p < 0.05$).

are similar, the prognosis of the younger men is worse than that of older men and sensitivity to hormonal therapy differs between the two groups. Further, we speculated that the cause of those was that younger men had more hormone insensitive cancer cells than older men from the first. Wilson JM et al.⁸⁾ reported that patients with CaP diagnosed before the age of 55 years had a worse outcome than patients

aged from 55 to 74 years, and Wilson DW et al.⁹⁾ suggested that this may result from late diagnosis, following failure to suspect prostatic malignancies in younger men. However, in the present multivariate analysis of prognostic factors, the time from the appearance of some symptom (s) to the first visit was not significantly different; that is, the poor prognosis for M1CaP in men younger than 60 is not because of a late diagnosis.

Younger men with M1CaP are not clearly defined in the world literatures. Therefore, in the present study, we have analyzed the age cut off of younger men under 60, since Ulrich Maier et al¹⁰⁾ used the same age cut off.

The proportion of M1 was much higher than that of M0 in the present study periods (Of 22 cases in patients younger than 60, 18 cases were M1). This cause was suggested to come from the fact that the screening for PSA and advances in ultrasonography were not widely spread until the first half of the 1990s in Japan, therefore many cases of CaP of early stages were not diagnosed. In the last 2 years, of 19 cases in patients younger than 60 at our hospital, only 1 case was M1.

According to Ribeiro et al.¹¹⁾, the two best pretreatment prognostic indicators of a favorable outcome in metastatic CaP are patients over 60 and an initial serum testosterone level higher than 10 nmol/l. Although we did not add serum testosterone to the prognostic parameters in the present study, we agree with their data, because low serum testosterone indicates androgen independence and therefore CaP with a low serum testosterone would be more aggressive.

Of all the prognostic factors of cause-specific survival investigated in the present study, only serum PSA was an independent factor ($p < 0.02$), which is not surprising considering that PSA level is proportional to the extent of disease.

Study limitations

First, the number of cases of M1CaP in men under 60 was small. Second, we had to exclude 48 patients from the progression-free survival rate analysis because 3 from the younger age group and 45 of the older men did not have serum PSA measured at diagnosis. Third, pathological factors, such as positive core numbers and cancer area of positive cores, were not included in this study because the biopsy method and core numbers differed before and after 1995.

Conclusions

M1CaP in Japanese men under 60 has less sensitivity to androgen ablation therapy and a poorer prognosis. Therefore, these patients should undergo combined hormonal therapy (e. g. plus systemic chemotherapy). However, to confirm this finding, an analysis of a large number of cases will be needed. Additionally, the only prognostic factor of M1CaP in men under 60 is serum PSA, therefore, research using molecular biology is necessary to find a definitive prognostic factor.

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