Prognostic Impact of Synchronous Second Primary Malignancies on the Overall Survival of Patients with Metastatic Prostate Cancer

Kyo Chul Koo, Hanna Yoo, Ki Hong Kim, Sang Un Park, Kyung Seok Han, Koon Ho Rha, Sung Joon Hong, Seung Choul Yang and Byung Ha Chung*

From the Department of Urology, Urological Science Institute (KCK, KHK, SUP, KSH, KHR, SJH, SCY, BHC) and Biostatistics Collaboration Laboratory (HY), Yonsei University College of Medicine, Seoul, Republic of Korea

Purpose: We determined the prognostic impact of a synchronous second primary malignancy on overall survival in patients with metastatic prostate cancer. Identifying features that stratify the risk of overall survival is critical for judiciously applying definitive therapy.

Materials and Methods: We retrospectively analyzed the records of 582 consecutive patients with prostate cancer diagnosed with metastasis between May 7, 1998 and August 27, 2011. Patient age, body mass index, ECOG performance status, Charlson comorbidity index, prostate specific antigen, T and N stages, Gleason and ASA® scores, progression to castration resistant prostate cancer, prior local treatments and synchronous second primary malignancies at metastasis were assessed. A synchronous second primary malignancy was defined as a cytologically or histologically proven solid malignancy. Cox proportional hazards regression analysis was done to estimate overall survival by second primary type and evaluate predictive variables.

Results: A total of 164 patients (28.1%) had a synchronous second primary malignancy, of which colorectal (9.1%), stomach (7.3%) and lung (7.1%) cancers were the most prevalent types. During a median followup of 34.1 months patients without a synchronous second primary malignancy had a significantly higher overall survival rate than those with lung or stomach cancer. However, men without a second malignancy had outcomes comparable to those in men with colorectal cancer. Clinical stage T4 or greater, ASA score 1 or greater and lung or stomach cancer were independent predictors of overall mortality.

Conclusions: A substantial proportion of patients with metastatic prostate cancer present with a synchronous second primary malignancy. Definitive therapy targeting prostate cancer may confer a limited survival benefit in patients with synchronous lung or stomach cancer.

Key Words: prostatic neoplasms; neoplasm metastasis; neoplasms, multiple primary; mortality; prognosis

Abbreviations and Acronyms

ECOG = Eastern Cooperative Oncology Group
mPCa = metastatic PCa
OS = overall survival
PCa = prostate cancer
PSA = prostate specific antigen
RT = radiation therapy
SPM = second primary malignancy

Accepted for publication October 20, 2014.
Study received institutional ethics committee approval.

* Correspondence: Department of Urology and Urological Science Institute, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 135-720, Republic of Korea (telephone: +82-2-2019-3470; FAX: +82-2-3462-8887; e-mail: chung646@yuhs.ac).

During the course of the PSA era downward migration in the clinical and pathological stage at which PCa is detected has been noted.[1] However, a synchronous metastasis is found in up to 9% of initially diagnosed Korean patients with PCa and an overall increase in cancer specific mortality has been observed.[2] Given the heterogeneous natural course of mPCa, determining clinicopathological features that stratify the risk of OS

0022-5347/15/1934-1239/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2014.10.088
Vol. 193, 1239-1244, April 2015
Printed in U.S.A.

remains critical for patient counseling and judicious application of definitive therapies targeted at PCa.

Efforts have been made to establish predictors of progression and survival in patients with mPCa. Prognostic variables such as age, post-hormone therapy PSA response, Gleason grade, prior local therapy and metastasis-free survival are known to determine OS in patients with mPCa.[3–5] However, considering that a significant proportion of patients with mPCa present at an advanced age and commonly harbor a synchronous SPM, incorporating merely classic PCa specific prognostic variables to define OS predictors without considering the impact of SPMs may limit prognostic accuracy.

To our knowledge no prior study has been done to investigate OS in patients with mPCa while incorporating SPMs as a confounder. SPMs have been excluded in clinical trials because they preclude survival calculations pertaining to treatment efficacy. Thus, there are no prognostic survival models, and the optimal management and treatment extent remain unclear. Indeed, avoiding active treatment in patients with mPCa who are more threatened by disease other than primary cancer is an important goal since it may prevent unnecessary treatment related toxicity and cost. Specifically patients who die of another cause and are then diagnosed with mPCa may be best treated without aggressive therapy because it may be detrimental to quality of life and performance status without a survival benefit.

With continuing enhancements in clinical awareness, diagnostic technology and survival of patients with cancer as the result of improved treatment modalities an increasing number of patients with mPCa are likely to present with a SPM. Thus, clinicians will more often face dilemmas regarding the extent of definitive treatment in these patients. In this study we 1) identified predictors associated with OS and 2) evaluated the differential impact of SPMs on OS stratified by the 3 most prevalent SPMs in our cohort, including colorectal, lung and stomach cancers.

MATERIALS AND METHODS

Study Population

We reviewed the records of a prospectively collected database of 2,724 consecutive patients treated for pathologically confirmed PCa between May 1998 and August 2011. PCa stage was determined according to the 7th AJCC (American Joint Committee on Cancer) TNM system. The definition of distant metastasis was based on demonstrable metastatic deposits on imaging (bone scan, computerized tomography, magnetic resonance imaging or positron emission tomography) or pathological confirmation of PCa from tissue outside the prostatic fossa. SPM was defined according to the criteria established by Warren and Gates in which each tumor must present a distinct picture of malignancy.[6] Study exclusion criteria were 1) incomplete clinical data, 2) loss to followup, 3) unknown cause of death or 4) metachronous SPM, defined as a SPM diagnosis more than 6 months after metastasis was first noted. We subsequently identified 582 patients diagnosed with mPCa who had a synchronous SPM or did not have a SPM. Notably 12 patients with a metachronous SPM were excluded from study. In all patients survival and cause of death were investigated based on the NCRD (National Cancer Registry Database) or on institutional electronic medical records. This study was approved by the institutional ethics committee after a review of the protocol and procedures used.

Prior Definitive Treatments

Radical prostatectomy was performed for localized and locally advanced disease before metastasis. The extent of pelvic lymph node dissection was based on the risk of lymph node metastasis. RT was generally recommended in patients with extracapsular tumors, or seminal vesicle invasion with or without positive surgical margins and in select patients with lymph node metastasis. The initiation and regimen of intermittent or continuous androgen deprivation therapy, secondary hormonal manipulation and cytotoxic chemotherapy were based on physician discretion.

Prognostic Factors and Outcome Variables

Covariates included patient age, PSA at diagnosis of metastasis, body mass index, ECOG performance status, ASA score, Charlson comorbidity index, Gleason score, clinical T and N stages, previous local therapy, progression to castration resistant PCa and SPM. OS was defined as the interval from the date of the first radiographic metastasis to the date of death from any cause. Patient data were considered missing if any of these data were absent.

Study End Points

The primary end point was to identify prognostic factors associated with OS. The secondary end point was to evaluate the survival impact of the 3 most prevalent SPMs observed in our cohort, including colon, lung and stomach cancers.

Statistical Analysis

Demographic characteristics of patients and tumors were compared using descriptive statistics. Appropriate comparative tests such as the Mann-Whitney U and the Fisher exact tests were used to compare continuous and categorical variables. OS rates were analyzed by the Kaplan-Meier method. Univariate and multivariate analyses were performed using Cox proportional hazards regression models to adjust for potential confounders of OS prediction. Variables considered potential predictors on multivariate modeling were selected by univariate analysis. Multivariable Cox proportional hazards risk models assessing the impact of different SPMs on OS were fitted after adjusting for ECOG performance status, pain, history of chemotherapy or RT, Gleason score and T stage. Statistical analysis was performed using SPSS®,