Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 4, pp. 997–1004, 2011

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.07.014

CLINICAL INVESTIGATION **Prostate**

USE OF THE CHARLSON COMBINED COMORBIDITY INDEX TO PREDICT POSTRADIOTHERAPY QUALITY OF LIFE FOR PROSTATE CANCER PATIENTS

Thomas Wahlgren, M.D., Ph.D.,* Seymour Levitt, M.D.,*† Jan Kowalski, B.Sc,‡ Sten Nilsson, M.D., Ph.D.,* and Yvonne Brandberg, Ph.D.*

*Department of Oncology-Pathology, Karolinska University Hospital and Institutet, Stockholm, Sweden; †Department of Therapeutic Radiology, University of Minnesota, Minneapolis, Minnesota; and ‡Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden

Purpose: To determine the impact of pretreatment comorbidity on late health-related quality of life (HRQoL) scores after patients have undergone combined radiotherapy for prostate cancer, including high-dose rate brachytherapy boost and hormonal deprivation therapy.

Methods and Materials: Results from the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire survey of 158 patients 5 years or more after completion of therapy were used from consecutively accrued subjects treated with curative radiotherapy at our institution, with no signs of disease at the time of questionnaire completion. HRQoL scores were compared with the Charlson combined comorbidity index (CCI), using analysis of covariance and multivariate regression models together with pretreatment factors including tumor stage, tumor grade, pretreatment prostate-specific antigen level, neoadjuvant hormonal treatment, diabetes status, cardiovascular status, and age and Charlson score as separate variables or the composite CCI.

Results: An inverse correlation between the two HRQoL domains, long-term global health (QL) and physical function (PF) scores, and the CCI score was observed, indicating an impact of comorbidity in these function areas. Selected pretreatment factors poorly explained the variation in functional HRQoL in the multivariate models; however, a statistically significant impact was found for the CCI (with QL and PF scores) and the presence of diabetes (with QL and emotional function). Cognitive function and social function were not statistically significantly predicted by any of the pretreatment factors.

Conclusions: The CCI proved to be valid in this context, but it seems useful mainly in predicting long-term QL and PF scores. Of the other variables investigated, diabetes had more impact than cardiovascular morbidity on HRQoL outcomes in prostate cancer. © **2011 Elsevier Inc.**

Localized prostate cancer, HDR brachytherapy, Health-related quality of life, Comorbidity, Charlson score.

INTRODUCTION

Health-related quality of life (HRQoL) has emerged as a significant medical outcome measure, and its enhancement is an important goal in oncology and other clinical disciplines. This is certainly true for prostate cancer (PC), in which curative rates are similar among different treatment modalities, such as surgery and radiotherapy; thus, qualitative outcomes are being used for patient guidance (1, 2). In light of emerging screening activity in which more and more patients are being diagnosed, there is a need to better understand the relative contributions of several factors affecting patients' perceptions and reports of HRQoL and satisfaction with life. One of the most crucial factors is comorbidity, the pretreatment burden of illness and its potential quantitative impact on treatment results (in terms of effects on cure and survival), as well as qualitatively (in terms of effects on treatment or disease-related symptoms and HRQoL).

The Charlson combined comorbidity index (CCI) was originally designed to classify prognostic comorbidity in longitudinal studies (3). It has been used in a number of studies to stratify patients in order to control for the confounding influence of comorbid conditions on overall survival. In larger studies involving more than 1 or 2 years of follow-up, both age and comorbidity were found to independently predict the probability of risk of death from comorbid disease (4). An index combining comorbidity and age, the CCI, was

Note—An online CME test for this article can be taken at http://astro.org/MOC.

Reprint requests to: Thomas Wahlgren, M.D., Ph.D., Department of Oncology-Pathology, Karolinska University Hospital and Institutet, S-17176 Stockholm, Sweden. Tel: (+46)-768-892947; Fax: (+46)-8-55052010; E-mail: thomas.wahlgren@telia.com

This work was supported by grants from the Swedish Cancer Society and Cancer Society in Stockholm.

Supplementary material for this article can be found at www.redjournal.org.

Conflict of interest: none.

Received April 21, 2010, and in revised form July 2, 2010. Accepted for publication July 5, 2010.

thus proposed later and validated (5). This index has been used in several longitudinal cancer studies (6, 7), including prognostic studies of prostate cancer (PC) (8).

The impact of comorbidity on survival outcomes in patients with PC, using the Charlson score, has been reported, both with conservative management (9) and active treatment (10). Likewise, there are reports of treatment complications in relation to pretreatment comorbid conditions, linking the Charlson score to higher complication rates, for instance, after PC brachytherapy (11).

Though many studies demonstrate the negative impact of comorbidity on posttreatment HRQoL in PC patients (12-14), few of them use the CCI.

Reports of multivariate models evaluating pretreatment factors that might be related to HRQoL outcomes after cancer treatment are scarce. In a study in South America, Dapueto *et al*. (15) reported the impact of various disease-related, psychosocial and socioeconomic factors on HRQoL, using multivariate regression models. However, no comorbidity data were presented, and comorbidity was not among the independent variables assessed.

In a survey of 2,415 PC participants, Karakiewitz *et al*. (12) demonstrated that comorbidity and socioeconomic status are clearly related to sexual, urinary, and general HRQoL with univariate and multivariate analyses after radical prostatectomy. Although the results of that study are interesting, the CCI was not used in that study.

We previously reported our study of long-term HRQoL in 158 disease-free patients who underwent combined radiotherapy for localized PC, including high-dose rate (HDR) brachytherapy boost and hormone deprivation therapy (16).

The aim of the present study was to noninterventionally investigate, using multivariate modeling, the association between several pretreatment factors (baseline and patient characteristics from records including CCI), and the five functional scales and global quality of life from the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire, collected in our previous study (16). Our hypothesis was that the CCI would explain some variation in the outcome of the long-term HRQoL function after PC radiotherapy.

METHODS AND MATERIALS

Patients

Between June 1998 and August 2000, a total of 234 patients diagnosed with localized PC (T1-T3aN0M0) were consecutively treated with a combination of external beam irradiation and HDR brachytherapy at the Radiumhemmet, Karolinska University Hospital, Stockholm, Sweden.

Some patients received external beam treatment at Söder Hospital, Stockholm. In August 2005, 196 living patients were offered participation in our long-term HRQoL study (16). The HRQoL had previously been assessed prospectively in 80 patients from this cohort, using the same questionnaires at 0 to 18 months and/or 18 to 36 months after treatment. A baseline retrospective assessment before treatment was not considered valid due to potential recall bias (17). A total of 182 responses were retrieved, yielding a response rate of 93%. In total, 158 patients with no signs of recurrent disease or other malignancy were eligible for this study.

Pretreatment investigation and primary treatment techniques

The investigation procedure and primary treatment technique were previously described in detail (17). In summary, patients were staged using prostate-specific antigen (PSA) levels, a digital rectal examination. and either cytology (1998–1999) or core biopsies (2000). In tumors entailing a high risk of nodal involvement (18) (poorly differentiated, Gleason-4-predominant or PSA of >10 ng/l) a bone scan and lymph node dissection were performed. The PSA cutoff of 10 ng/l was selected to safely predict negative pelvic lymph node involvement in agreement with findings reported by Narayan *et al*. (19). All patients received neoadjuvant androgen deprivation treatment for at least 3 months before radiotherapy (mean total treatment period, 7 months; range, 3-12 months) with a total androgen blockade including a luteinizing hormone-releasing hormone agonist and an antiandrogen. The hormone deprivation therapy was stopped at the end of radiotherapy.

Three-dimensional conformal external beam radiotherapy using a four-field (Radiumhemmet, Karolinska University Hospital, Stockholm) or three-field (Söder Hospital, Stockholm) technique, delivered a total of 50 Gy in 2-Gy fractions to the prostate and seminal vesicles. A margin of 2 cm was used to create the external beam planning tumor volume (PTV), with the exception of the posterior (rectal) margin, which was limited to 1.5 cm. After 13 fractions, the external beam treatment was stopped, and a boost of HDR brachytherapy, 20 Gy in 2 fractions with a 10-day interval between treatments, was given. We inserted 10 to 20 needles transperineally, guided by transrectal ultrasound, and the iridium-192 HDR source was temporarily implanted using a remote afterloading device.

Following this, external beam treatment was resumed. Brachytherapy pretreatment dosimetry was performed using an ultrasound-based treatment planning system. The brachytherapy clinical target volume (CTV) included the entire prostate gland but excluded the seminal vesicles. A margin of 3 mm was used to create the brachytherapy PTV. The prescribed dose to the PTV was 10 Gy per fraction, and the dose constraints were included for the CTV and the PTV, the volume receiving more than 100 Gy (V_{100}) of >90% and the V_{200} of <10%, and the maximum dose (D_{max}) for the urethra of <110% and V_{100} of <70%. The dose restriction for the rectum was D_{max} of <60%.

Pretreatment factor collection

Information regarding tumor status, including tumor stage and grade, as well as pretreatment PSA, were collected from patient records. Furthermore, information about comorbid conditions had been collected in a similar fashion and converted to a CCI score, according to the outline given below. For every patient, the presence or absence of diabetes or cardiovascular disease was noted and defined as current or previous hypertension and cerebrovascular or cardiac conditions.

HRQoL data collection

In September 2005 (70-88 months after treatment), all patients were mailed a questionnaire and an invitation to participate in the study. Completed forms were returned by mail in a prepaid envelope. Patients not responding within 4 weeks received a reminder. Informed consent was not formally requested as this was a questionnaire study; questionnaire completion was considered consent to participate. A response rate of 93% was achieved.