EUROPEAN UROLOGY XXX (2015) XXX–XXX

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

Fifteen-year Outcomes Following Conservative Management Among Men Aged 65 Years or Older with Localized Prostate Cancer

Grace L. Lu-Yao [a,b,*], *Peter C. Albertsen* [c], *Dirk F. Moore* [a,d], *Yong Lin* [a,d], *Robert S. DiPaola* [a,b], *Siu-Long Yao* [a,b]

[a] *Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA;* [b] *Department of Medicine, Rutgers Robert Wood Johnson Medical School, Piscataway, NJ, USA;* [c] *Department of Surgery (Urology), University of Connecticut, Farmington, CT, USA;* [d] *Department of Biostatistics, Rutgers School of Public Health, Piscataway, NJ, USA*

Article info

Article history:
Accepted March 5, 2015

Keywords:
Prostatic neoplasm
Survival
Population-based study

Abstract

Background: To understand the threat posed by localized prostate cancer and the potential impact of surgery or radiation, patients and healthcare providers require information on long-term outcomes following conservative management.
Objective: To describe 15-yr survival outcomes and cancer therapy utilization among men 65 years and older managed conservatively for newly diagnosed localized prostate cancer.
Design, settings, and participants: This is a population-based cohort study with participants living in predefined geographic areas covered by the Surveillance, Epidemiology, and End Results program. The study includes 31 137 Medicare patients aged ≥65 yr diagnosed with localized prostate cancer in 1992–2009 who initially received conservative management (no surgery, radiotherapy, cryotherapy, or androgen deprivation therapy [ADT]). All patients were followed until death or December 31, 2009 (for prostate cancer–specific mortality [PCSM]) and December 31, 2011 (for overall mortality).
Outcome measurements and statistical analysis: Competing-risk analyses were used to examine PCSM, overall mortality, and utilization of cancer therapies.
Results and limitations: The 15-yr risk of PCSM for men aged 65–74 yr diagnosed with screening-detected prostate cancer was 5.7% (95% confidence interval [CI] 3.7–8.0%) for T1c Gleason 5–7 and 22% (95% CI 16–35%) for Gleason 8–10 disease. After 15 yr of follow-up, 24% (95% CI 21–27%) of men aged 65–74 yr with screening-detected Gleason 5–7 cancer received ADT. The corresponding result for men with Gleason 8–10 cancer was 38% (95% CI 32–44%). The major study limitations are the lack of data for men aged <65 yr and detailed clinical information associated with secondary cancer therapy.
Conclusions: The 15-yr outcomes following conservative management of newly diagnosed Gleason 5–7 prostate cancer among men aged ≥65 yr are excellent. Men with Gleason 8–10 disease managed conservatively face a significant risk of PCSM.
Patient summary: **W**e examined the long-term survival outcomes for a large group of patients diagnosed with localized prostate cancer who did not have surgery, radiotherapy, cryotherapy, or androgen deprivation therapy in the first 6 mo after cancer diagnosis. We found that the 15-yr disease-specific survival is excellent for men diagnosed with Gleason 5–7 disease. The data support conservative management as a reasonable choice for elderly patients with low-grade localized prostate cancer.

* Corresponding author. Rutgers Cancer Institute of New Jersey, Room 5534, 195 Little Albany Street, New Brunswick, NJ 08903-2681, USA. Tel. +1 732 2358830; Fax: +1 732 2358808.
E-mail address: luyaogr@cinj.rutgers.edu (G.L. Lu-Yao).

http://dx.doi.org/10.1016/j.eururo.2015.03.021
0302-2838/

1. Introduction

Prostate cancer is the most common non–skin cancer and the second most common cause of cancer death in the USA [1]. Because of widespread prostate-specific antigen (PSA) screening, most contemporary men are diagnosed with localized disease [2]. Treatment options for localized disease commonly include active surveillance or conservative management, surgery (radical prostatectomy), and radiation therapy.

A recent update of the Scandinavian Prostate Cancer Group 4 (SPCG-4) trial comparing surgery with watchful waiting reported a 12.7% absolute risk reduction in overall mortality for men aged <65 yr undergoing surgery but no significant benefit for men aged ≥65 yr [3–5]. Similarly, the Prostate Intervention Versus Observation Trial (PIVOT) showed no improvement in disease-specific or overall survival for men with low-grade disease through 12 yr of follow-up [6]. More than half of the men in both trials were older than 65 yr at diagnosis. Unlike the situation for surgery, researchers have yet to publish large-scale randomized comparisons of radiation therapy and active surveillance or conservative management.

Only a small percentage of men in the USA have their prostate cancer managed conservatively [7–9]. Furthermore, among men who initially choose conservative management, up to half switch to active treatment within 5 yr of diagnosis, and many do so without clinical evidence of disease progression [10]. Presumably, these men fear disease progression and are reluctant to forgo treatment.

To document the progression of low-grade prostate cancer, we previously reported 10-yr outcomes for a cohort of 14 516 men with localized T1/T2 prostate cancer diagnosed during 1992–2002 and managed conservatively [11]. Unfortunately, as documented in the watchful waiting arm of the SPCG-4 study, disease progression continues well beyond 10 yr [5]. We performed this study to provide long-term 15-yr follow-up data for men managed conservatively for newly diagnosed, localized prostate cancer.

2. Patients and methods

2.1. Data sources

Data were obtained from Medicare claims files linked to the population-based Surveillance, Epidemiology, and End Results (SEER) cancer registries, which are 98% complete for case ascertainment [12]. The SEER regions encompassed approximately 14% of the US population before 2000 and 25% thereafter [12]. The Medicare database covers approximately 97% of US individuals aged ≥65 yr. Linkage to the SEER database is complete for approximately 93% of the patients [12].

SEER data files provided information on cancer stage and grade for each case. Before 2003, Gleason 2–4, 5–7, and 8–10 cancers were grouped as well-, moderately, and poorly differentiated cancers, respectively. In 2003, Gleason 7 was grouped with Gleason 8–10 in SEER. In 2004, primary and secondary Gleason score information became available. In this study, we combined patients with Gleason 8–10 as poorly differentiated cancer except for 2003, for which Gleason 7 was included in the poorly differentiated group.

2.2. Study participants

The study cohort consisted of men aged ≥65 yr who were SEER residents and diagnosed with stage T1–T2 prostate cancer during 1992–2009 (n = 382 673). Those who died or were censored within 180 d of cancer diagnosis or who had another cancer diagnosis were excluded (n = 93 020) to ensure that all cancer therapies were for prostate cancer. Men who had surgery, radiation, or cryotherapy within 6 mo of diagnosis (n = 171 361) or did not have both Medicare Part A and Part B as their primary health insurance coverage (n = 47 016) during the study period were excluded. In addition, those with an unknown cancer grade or T1a/T1b cancer and those receiving androgen deprivation therapy (ADT) or palliative radiation therapy within 6 mo of diagnosis (n = 40 139) were excluded. We excluded men with T1a/T1b cancers because they differ from contemporary patients with screening-detected cancer. We characterized the remaining 31 137 men as receiving conservative therapy.

2.3. Outcome assessment

Overall and prostate cancer–specific survival was available through December 31, 2011 and December 31, 2009, respectively. SEER data files provided information on the underlying cause of death. Previous studies have shown high agreement (87–92%) between the cause of death in the SEER database and that determined through medical record review [13,14]. Detailed definitions of various cancer therapies have been described previously [11].

2.4. Statistical analyses

The primary study endpoints were time to death from prostate cancer and time to death from all causes, stratified by patient age, cancer grade, and stage at diagnosis. We estimated cumulative incidence accounting for the competing risks of death from other causes (Fig. 1, Tables 2 and 4) [15]. When analyzing the 15-yr risk of secondary cancer therapy, we computed the risk of each outcome independently because one individual could have had more than one secondary treatment. To provide smooth estimates of the survival curves, we used a nearest-neighbor hazard smoother with an Epanechnikov kernel [16] as implemented in the R statistical system (R Foundation for Statistical Computing, Vienna, Austria). We obtained 95% pointwise confidence bands for the smoothed hazard estimates using a bootstrap resampling procedure with 1000 bootstrap replications. The confidence bands at each time point reflect the upper and lower 2.5 percentile of the bootstrap replications at that point.

3. Results

Our study identified 31 137 men aged ≥65 yr diagnosed with localized prostate cancer during 1992–2009. The median age at diagnosis was 75 yr and the median follow-up time was 6.4 yr among survivors (3rd quartile, 9.5 yr). Table 1 summarizes the baseline characteristics of the study population. Most men (87%) had Gleason 5–7 tumors and 40% of men had PSA-detected disease (T1c).

There were 5257 patients alive in year 10 and 1138 patients in year 15. For men with Gleason 5–7 disease, the 15-yr prostate cancer–specific mortality (PCSM) was 5.7% for men aged 65–74 yr and 10% for men aged ≥75 yr (Table 2). For men with PSA-detected Gleason 8–10 disease, PCSM rates were much higher, at 22% and 27%, respectively.

Figure 1 shows a competing-risks analysis of death according to age at diagnosis, cancer stage, and grade. The

Please cite this article in press as: Lu-Yao GL, et al. Fifteen-year Outcomes Following Conservative Management Among Men Aged 65 Years or Older with Localized Prostate Cancer. Eur Urol (2015), http://dx.doi.org/10.1016/j.eururo.2015.03.021