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

European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by Markus Graefen and Hartwig Huland on pp. 681–682 of this issue

Do Margins Matter? The Influence of Positive Surgical Margins on Prostate Cancer–Specific Mortality

Andrew J. Stephenson[a,*], *Scott E. Eggener*[b], *Adrian V. Hernandez*[a,c], *Eric A. Klein*[a], *Michael W. Kattan*[c], *David P. Wood Jr.*[d], *Danny M. Rabah*[e], *James A. Eastham*[f], *Peter T. Scardino*[f]

[a] *Glickman Urological & Kidney Institute, Cleveland Clinic, Cleveland, OH, USA;* [b] *Section of Urology, University of Chicago Medical Center, Chicago, IL, USA;* [c] *Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH, USA;* [d] *Department of Urology, University of Michigan, Ann Arbor, MI, USA;* [e] *Division of Urology, Department of Surgery, Princess Johara Alibrahim Center for Cancer Research, King Saud University, Riyadh, Saudi Arabia;* [f] *Urology Service, Department of Surgery, Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center, New York, NY, USA*

Article info

Article history:
Accepted August 14, 2013
Published online ahead of print on August 27, 2013

Keywords:
Prostatic neoplasms
Prostatectomy
Surgical margins
Treatment outcome
Models
Statistical

EU ★ ACME
www.eu-acme.org/europeanurology

Please visit www.eu-acme.org/europeanurology to read and answer questions on-line. The EU-ACME credits will then be attributed automatically.

Abstract

Background: Positive surgical margins (PSMs) in radical prostatectomy (RP) specimens are a frequent indication for adjuvant radiotherapy and are used as a measure of surgical quality. However, the association between PSMs and prostate cancer–specific mortality (CSM) is poorly defined.
Objective: Analyze the association of PSMs with CSM, adjusting for fixed and time-dependent parameters.
Design, setting, and participants: Fine and Gray competing risk regression analysis was used to model the clinical data and follow-up information of 11 521 patients treated by RP between 1987 and 2005. Two extended models were used that adjusted for the use of postoperative radiotherapy, which was handled as a time-dependent covariate. Postoperative radiotherapy was modeled as a single parameter and also as early and late therapy, based on the prostate-specific antigen level at the start of treatment ($\leq$0.5 vs $>$0.5 ng/ml).
Intervention: RP for clinically localized prostate cancer and selective use of secondary local and/or systemic therapy.
Outcome measurements and statistical analysis: The outcome measure was prostate cancer-specific mortality.
Results and limitations: The 15-yr CSM rates for patients with PSMs and negative surgical margins were 10% and 6%, respectively ($p < 0.001$). No significant association between PSM and CSM was observed in the conventional model with fixed covariates (hazard ratio [HR]: 1.04; 95% confidence interval [CI], 0.7–1.5; $p = 0.8$) or in the two extended models that adjusted for postoperative radiotherapy (HR: 0.96; 95% CI, 0.7–1.4; $p = 0.9$), or early and late postoperative radiotherapy (HR: 1.01; 95% CI, 0.7–1.4; $p = 0.9$).
Conclusions: PSMs alone are not associated with a significantly increased risk of CSM within 15 yr of RP. However, urologists should continue to strive to avoid PSMs, as they increase a man's risk of biochemical recurrence and need for secondary therapy and may be a source of considerable patient anxiety.

* Corresponding author. Glickman Urological & Kidney Institute, Cleveland Clinic, 9500 Euclid Avenue, Desk Q10, Cleveland, OH 44195-0001, USA. Tel. +1 216 445 1062; Fax: +1 216 636 4492.
E-mail address: stephea2@ccf.org (A.J. Stephenson).

0302-2838/$ – see back matter
http://dx.doi.org/10.1016/j.eururo.2013.08.036

CrossMark

1. Introduction

Positive surgical margins (PSMs) in radical prostatectomy (RP) specimens for the treatment of localized prostate cancer (PCa) are reported in 11–48% of men and are a recognized risk factor for prostate-specific antigen (PSA)-defined biochemical recurrence (BCR) [1–6]. We recently reported a 2.3-fold increased risk of BCR among men with PSMs treated in the later PSA era after adjusting for all standard parameters [1]. To improve the outcome of men with non–organ-confined cancer and/or PSMs after RP, three randomized trials have investigated the role of adjuvant radiotherapy [7–9]. Compared to observation, adjuvant radiotherapy significantly reduced the risk of BCR in all three trials, and one has reported a significantly improved metastasis-free and overall survival [7]. Given these results, some have advocated adjuvant radiotherapy as the standard of care for men with non–organ-confined cancer or PSMs [10,11].

In two of the randomized trials, the benefit of adjuvant radiotherapy was most evident in men with PSMs [9–12], consistent with its association with local recurrence [13]. However, a policy of adjuvant radiotherapy for all men with PSMs represents overtreatment for the majority, as an estimated 60% will be free of cancer recurrence after RP alone [1]. As with external-beam radiotherapy as primary therapy, adjuvant radiotherapy may adversely affect urinary, bowel, and sexual function and may increase the risk of secondary pelvic malignancies [14–18]. Furthermore, in the one trial that has reported an improved metastasis-free and overall survival, a major effect of adjuvant radiotherapy was reducing deaths from competing causes (93 vs 114 events), and there was a smaller effect on preventing distant metastases (20 vs 37 events) [7]. A recent update of a larger European trial of similar design but composed of more contemporary patients reported no significant difference in the rate of distant metastasis or overall survival over a median follow-up of 10.6 yr [8]. Thus, close observation and salvage radiotherapy at the earliest sign of BCR (ie, when the PSA first reaches detectable levels) is a reasonable alternative strategy [13,19,20].

A strong argument against adjuvant radiotherapy for PSMs is the lack of evidence that the latter significantly increases a man's risk of PCa-specific mortality. In an analysis of 23 910 men treated by RP at five high-volume hospitals, we previously identified the presence of pathologic Gleason 8–10 cancer and seminal vesicle invasion as the prime determinants of cancer-specific mortality (CSM) [21]. Neither PSM nor extraprostatic extension was significantly associated with CSM in the multivariable analysis. The lack of association between PSMs and CSM may be due to the variable natural history of BCR; within 15 yr, only one-third of men with BCR will die of PCa, which is similar to the risk of death from competing causes [22]. Alternatively, we hypothesized that this lack of association may be due to the protective effect of postoperative radiotherapy. To explore this possibility, we analyzed the long-term risk of CSM based on the pathologic features of PCa, adjusting for the use and timing of postoperative radiotherapy.

2. Patients and methods

Between 1987 and 2006, 12 310 consecutive men with localized PCa were treated by RP at Cleveland Clinic (Cleveland, OH, USA), Memorial Sloan-Kettering Cancer Center (New York, NY, USA), University of Michigan (Ann, Arbor, MI, USA), and Baylor College of Medicine (Houston, TX, USA). We excluded 462 patients (3.7%) who received prior androgen deprivation therapy or radiation therapy or who had missing information for PSA values, pathologic Gleason score, or pathologic stage. Thus, a total of 11 521 patients were available for analysis. Clinical information was obtained from prospectively maintained, institutional review board-approved data bases.

Surgical specimens were totally embedded and step-sectioned at 3- to 5-mm intervals from apex to base, examined as whole or quarter mounts, and evaluated by genitourinary pathologists at each institution. Pathologic stage was assigned according to the American Joint Committee on Cancer criteria [23]. A PSM was defined as tumor at the inked margin of the resected specimen. In general, patients were followed for recurrence postoperatively with serum PSA level determinations and clinical assessment at 3- to 6-mo intervals for the first 3–5 yr, then annually thereafter. Secondary therapy was uncommonly administered in the absence of BCR. Death was attributed to PCa if, upon review of the medical record, there was evidence of progressive metastases and PCa was listed as the primary cause of death on the death certificate.

Estimates of CSM were calculated using the competing risk method [24]. Univariable and multivariable analyses of CSM were performed with Fine and Gray competing risk regression analysis [24]. The PSA levels before RP and year of surgery were modeled with restricted cubic splines because of a skewed distribution and/or suspected nonlinear effects. Primary and secondary Gleason grades were modeled as binary categorical variables ($\leq$3 and $\geq$4). The presence of extraprostatic extension, PSM, seminal vesicle invasion, and lymph node metastasis were modeled as binary categorical variables.

PSM is a frequent indication for postoperative radiotherapy, which substantially alters the risk of BCR and/or survival following RP [7–9,13,19,25]. As such, we endeavored to explore whether PSM is associated with CSM after adjusting for the use of postoperative radiotherapy. Given that the use and timing of postoperative radiotherapy was not standardized, an extended competing risk regression model was used to adjust for postoperative radiotherapy, which was handled as a time-dependent covariate [26]. As the benefit of postoperative radiotherapy appears to be greatest when administered at preradiotherapy PSA levels $\leq$0.5–0.6 ng/ml [13,19], it was also modeled as early and late therapy based on a preradiotherapy PSA level $\leq$0.5 and $>$0.5 ng/ml, respectively.

All decisions with respect to variable coding were made a priori without knowledge of CSM association. All statistical analyses were performed using S-Plus software (S-plus 2000; Insightful Corp, Redmond, WA, USA) with additional functions (called "Design") added. All p values resulted from use of two-sided statistical tests. The study was conducted according to Health Insurance Portability and Accountability Act guidelines.

3. Results

The clinical and pathologic features of patients in this study are summarized in Table 1. Overall, 2607 (23%) patients had PSMs, including 1291 of 8064 (16%) with organ-confined cancer and 1316 of 3457 (38%) with non–organ-confined cancer. A total of 788 men received postoperative radiotherapy, 756 (96%) of whom had a detectable preradiotherapy PSA level (median: 0.50 ng/ml; interquartile range [IQR]: 0.24–1.10). Overall, 1045 (9%) men received androgen deprivation therapy after RP for BCR or clinical progression.