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Comorbidity and adrogen ablation

The impact of comorbidities on the benefits of prolonged androgen ablation in patients with T3-4 prostate cancer treated with external beam radiation therapy ☆

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ABSTRACT

Purpose: To determine whether the survival benefit associated with prolonged androgen deprivation therapy (ADT) and radiotherapy (EBRT) varies with baseline estimates of overall survival in cT3-4 prostate cancer patients (PCa).

Methods and materials: In 1997, the BC Cancer Agency adopted as standard a policy of prolonged ADT (>18 months) with EBRT for locally advanced PCa. Two cohorts of cT3-T4 PCa treated with EBRT were selected: 1993–1995 (early: $N = 725$) and 1999–2001 (late: $N = 584$). Duration of ADT and baseline prognostic factors (age, clinical stage, grade, presenting PSA, and Charlson index (CCI)) were abstracted from charts. Estimates of 10-year (E10) survival using an age-adjusted CCI were calculated and patients were grouped into low (<60%), medium (60–90%) and high (>90%) E10. In each E10 group, actual overall survivals were compared by era using log rank test.

Results: There were 318 low, 544 medium, and 447 high E10 patients with median follow-up of 11.1 years. Gleason grade and T stage were not statistically different between E10 groups. As expected, median age and baseline CCI were higher in lower E10 groups ($p < 0.0001$). Overall survival was higher in the late era, but varied with E10 group: low (43% vs. 49%, $p = 0.54$), medium (55% vs. 64%, $p = 0.02$) and high (66% vs. 77%, $p = 0.01$).

Conclusion: The policy of prolonged ADT with EBRT provides a survival benefit that varies with baseline risk of death from other causes. Absolute benefit from ADT is largest in those with medium or high E10.

Following the publication of the EORTC and RTOG trials, the standard non-surgical treatment for high-risk prostate cancer became external beam radiotherapy (EBRT) with the addition of long-term androgen ablation (ADT) [1–4]. The age at diagnosis of most men is above 65, and the prevalence of this disease is likely to increase with an aging population. Due to the long natural history of most prostate cancers, many patients ultimately die of unrelated comorbid conditions. It remains controversial if the survival benefits of ADT with EBRT are seen in high-risk patients with a high competing risk of death from other causes due to advanced age and/or comorbidity.

We have previously shown that a change of policy from one that did not recommend ADT to one that did, has resulted in improved overall and cause-specific survival at a population-based level for patients with cT3-4 prostate cancer [5]. In this publication we demonstrated that the use of prolonged (>6 months) ADT increased from 14% to 97% after adoption of this policy as we have described previously [5]. The objective of the current study is to determine whether these survival benefits vary with baseline estimates of overall survival based on age and comorbidities. This may help identify a subgroup of patients in contemporary clinical practices who may less likely benefit from the addition of ADT, and may be candidate for less aggressive therapy.

Materials and methods

Study population and treatment

In British Columbia (BC), the BC Cancer Agency (BCCA) provides all radiotherapy services in the province, and all ADT is either

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dispensed or reimbursed by the provincial pharmacy by a single-payer system. All patients with T3-T4 prostate cancer, as staged clinically at time of diagnosis by digital rectal exam, CT scan and endorectal ultrasound if available, treated with EBRT in BC in two different treatment eras (early cohort: 1993–1995 and late cohort: 1999–2001) were selected. These time cohorts were chosen to correspond to 2 years before and after the publication of the EORTC trial, which was practice changing and defined the current standard of care for these patients. Patients were identified from a provincial cancer database where clinical stage and treatment information were prospectively collected.

Eligible patients must have received a dose of EBRT which was considered curative-intent, defined as a total dose of at least 50 Gy using >2 Gy/day (hypofractionated regimen) or 60 Gy using 2 Gy/-day (conventional fractionation). Patients who received curative-intent pion therapy (37.5 Gy in 15 fractions over 3 weeks) in the context of a randomized clinical trial were also included, as no difference in disease-specific survival (DSS) or OS was shown after a median follow-up time of 42 months, when compared to standard EBRT [6]. EBRT was delivered to the prostate-only or to the whole pelvis with a boost to the prostate at the discretion of the treating oncologist. Standard isocentric technique with CT-based simulation and 3D-planning was employed in most patients.

ADT consisted primarily of LHRH-agonist, and was usually initiated prior to or concurrently with radiotherapy. The length of ADT was at the discretion of the treating oncologist, but typically ADT was discouraged in the early era, but was standard practice with a recommended duration of 2–3 years in the later era [5,7].

Patients were excluded if they had previous radical prostatectomy, had histology other than adenocarcinoma, had bilateral orchiectomy or lacked comorbidity information. No patients were treated with brachytherapy, as both treatment eras predate the use of brachytherapy in high-risk patients in BC. Patients with NCCN high-risk disease by Gleason score criterion but without T3-4 disease were excluded, as it has been recognized that there has been a "Gleason shift" which led to higher histological grading in patients diagnosed in the later cohort, which may artificially improve outcomes of these patients [8]. ADT usage was abstracted from chart review and from the provincial pharmacy database, as previously described [5]. Initial PSA (iPSA) and comorbidities for each patient at the time of consultation were abstracted retrospectively by chart review, and the magnitude of comorbidity was scored using the Charlson comorbidity index (CCI) [9]. The score was adjusted for age to derive a combined score by adding 1 for every decade of life over the age of 50 using the method described by Charlson [10].

Patient subgroups

Patients were divided into three subgroups based on the estimated 10-year overall survival (E10) derived from comorbidity and age: high (>90%), medium (60–90%) and low (<60%). E10 was calculated using a theoretical low-risk population whose 10-year survival was 98.3%, using the following equation from Charlson et al. [10]:

$$E10 = 0.983^{(\exp[0.9\times \text{combined score}])}$$

Statistical analysis

Tumor and patient characteristics were compared at baseline by E10 subgroups, using Pearson's Chi-Square and Fisher's exact test for categorical variables, and student t-test for continuous variables. For each subgroup, overall survival was estimated by the Kaplan–Meier method and compared using the log-rank tests. Univariate and multivariate Cox proportional hazards models were used for analysis of overall survival.

The cumulative incidence of all-cause death was estimated using nonparametric methods for the three survival groups within each treatment era. Similarly, the cumulative incidence of all other cause mortality, adjusted for the competing risk of prostate cancer death was estimated. Within each survival group, differences between the cumulative incidence functions for Era 1 and Era 2 were tested using Gray's method [11].

We employed a multivariate competing risk model for prostate cancer survival, accounting for the competing risk of death from causes other than prostate cancer [11]. Treatment era serves as a surrogate for the addition of ADT in the management of locally advanced prostate cancer. The analysis for this paper was generated using SAS 9.3 software for windows. Copyright © 2011 SAS Institute Inc.

Results

Cohort characteristics

A total of 1339 patients were identified from provincial registry data. After excluding 30 patients because of evidence of previous prostatectomy ($N = 5$), previous hormonal treatment ($N = 3$), non-adenocarcinoma histology, presence of metastatic disease ($N = 12$), lack of comorbidity information ($N = 5$), or treatment which was deemed of palliative intent by treating physician ($N = 5$), 1309 cases were eligible for the study (725 patients from the early era, and 584 patients from the later era). In the early cohort 14% of patients had more than 6 months of ADT compared to 97% of cases in the later era (58.7% had 18 months or more of ADT). The median ADT duration was 0 months in the early era and 22 months in the late era. Median follow-up for the patients was 11.2 vs 11.1 years respectively. Baseline characteristics of these patients were previously reported and are summarized in Table 1 [5]. As expected, patients with a high E10 had younger age (Median 64 years vs 72 vs 73, $p < 0.0001$) and less comorbidity (CCI = 0 in 96% vs 75% vs 8%, $p < 0.0001$). The T-stage and Gleason score between E10 subgroups was similar. The proportion of patients with initial PSA > 20 was highest in patients with high E10 ($p = 0.0067$).

Overall survival and cumulative incidence of death

The actual 10-year overall survival by E10 cohort was 72%, 60% and 46% for the high, medium and low E10 subgroups, respectively (Fig. 1, $p < 0.001$). Other factors associated with improved overall survival on univariate analysis include: Gleason score, initial PSA and T-stage (data not shown).

In terms of all-cause mortality, when comparing the cumulative incidence (CI) of all-cause death for each E10 subgroup by treatment era (Table 2), patients treated in the later era had a lower CI of all-cause cause death, with a smaller absolute difference at 10 years in those with a low E10 (7% absolute difference), and larger in those with a high E10 (11% absolute difference). The cumulative incidence for all-cause death for the two eras were significantly different in the medium and high E10 groups ($p = 0.02$ and $p = 0.01$, respectively) but not in the low E10 group ($p = 0.54$).

Table 2 also indicates that patients in the low E10 group had similar 10-year event rate for other cause death in the two eras (0.14% absolute difference). Patients in the high E10 group had a lower 10-year CI of other cause death in the later era (7% absolute difference). The cumulative incidence for other cause death in the two eras were not significantly different for the low, medium or high E10 group ($p = 0.47$, $p = 0.45$, and 0.08, respectively).