

# Comparison of Surgery and Radiation as Local Treatments in the Risk of Locoregional Complications in Men Subsequently Dying From Prostate Cancer

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## Abstract

**This retrospective cohort analysis evaluated late locoregional complications in patients dying of castration-resistant prostate cancer by the type of primary local treatment previously received. Our results suggest that development of locoregional complications was associated with worse survival and more hospitalization days; however, patients previously treated with external-beam radiotherapy were not at greater risk of locoregional complications compared to those treated with radical prostatectomy.**

**Introduction:** Late locoregional complications in prostate cancer (PCa) affect quality of life and require medical interventions. Our objective was to compare late locoregional complications in men dying of castration-resistant PCa (CRPC) who previously received external-beam radiotherapy (EBRT) to radical prostatectomy (RP). No group without previous primary local treatment was included. **Patients and Methods:** The cohort consists of CRPC patients who died between 2001 and 2013 and who underwent previous EBRT or RP. The Régie de l'assurance maladie du Québec administrative databases were used to identify late locoregional complications (urologic procedures, minor rectal procedures, and other major surgical procedures) and PCa-related hospitalizations occurring in the last 2 years of life. Multivariable logistic regression and negative binomial regression analyses were performed. **Results:** The cohort comprised 1189 patients; 535 (45%) and 654 (55%) received EBRT and RP, respectively. Overall, 46.4% of patients experienced at least 1 late locoregional complication. Primary local treatment type was not associated with the odds of late locoregional complications (odds ratio [OR], 0.91; 95% confidence interval [CI], 0.72, 1.16). RP was associated with greater odds of PCa-related hospitalization (OR, 1.63; 95% CI, 1.23, 2.17) relative to EBRT, as were the usage of a CRPC treatment (OR, 3.96; 95% CI, 2.83, 5.53) and the occurrence of a late locoregional complication (OR, 2.76; 95% CI, 2.05, 3.69). For the number of PCa-related hospitalization days, RP was not found to be significant (rate ratio, 1.09; 95% CI, 0.90, 1.32). **Conclusion:** In this population-based cohort, the risk of late locoregional complications in CRPC was not associated with the type of primary local treatment (RP or EBRT).

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## Introduction

Prostate cancer (PCa) is the most common cancer in Canadian men, and it is the third deadliest cancer (9.6% of cancer-related deaths).<sup>1</sup> A sizable portion of PCa patients will develop castration-resistant PCa (CRPC), an advanced, lethal form of the disease

characterized by progression despite castrate levels of serum testosterone associated with a median survival of approximately 2 to 3 years.<sup>2,3</sup> Distant metastases can lead to many complications, such as skeletal-related events, anemia, and cancer cachexia.<sup>4</sup> Nearly all patients (over 90%) who die of PCa have bone metastases.<sup>5</sup> In

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## Surgery vs. Radiation in Risk of Locoregional Complications

addition, local progression of tumor can invade surrounding areas such as bladder, ureters, urethra, and rectum. This can consequently lead to locoregional complications such as lower urinary tract symptoms, obstructive uropathy, hematuria, pelvic pain, and rectal obstruction.<sup>4,6</sup> Additional hospitalizations, medical interventions, and surgical procedures may be required to manage these complications.<sup>6,7</sup>

Studies reporting these locoregional complications have found that about 25% to 50% of advanced PCa patients experience these symptoms,<sup>7-9</sup> and they are associated with worse prognosis.<sup>10</sup> Very few studies have investigated the relationship between primary local treatment and the development of locoregional complications resulting from local progression of disease in men in the castration-resistant phase. Most studies are retrospective single-institution reports. For example, the addition of radical prostatectomy (RP) to androgen deprivation therapy (ADT) in the setting of node-positive disease resulted in lower occurrence of local complications compared to ADT alone.<sup>8</sup> One prospective randomized controlled trial evaluated external-beam radiotherapy (EBRT) in combination with ADT compared to ADT alone in patients with locally advanced PCa. This study demonstrated that the use of EBRT reduced the rate of local recurrence.<sup>11</sup> These studies suggest that primary local treatment may confer potential benefits in terms of locoregional complications compared to patients who undergo ADT only. Furthermore, the risk of locoregional complications may be higher in patients previously treated with EBRT compared to those treated with RP, given that the prostate is left in situ in the former. However, radiotherapy to the prostate and its surrounding areas may offer an extended field of protection from potential locoregional progression, which may come with more long-term radiation-induced complications. It is unclear from the existing evidence whether the type of primary local treatment could influence locoregional complications (RP vs. EBRT). In some of the previous studies, comparison groups were not similar in terms of survival time or disease extent at the time local treatment, raising concerns about confounding by indication.<sup>12,13</sup>

The objective of the current study was to evaluate late locoregional complications in men dying from CRPC who previously underwent primary local treatment (RP vs. EBRT).

## Methods

### Data Source

The cohort was identified retrospectively using the Régie de l'assurance maladie du Québec (RAMQ) and the Maintenance et exploitation des données pour l'étude de la clientèle hospitalière (MED-ECHO) administrative databases. All Quebec residents are eligible for the public health care insurance plan, which covers physician visits and medical services provided at hospitals and clinics. The RAMQ is the governmental body that administers provincial public health care insurance programs for Quebec residents. Their databases contain information regarding beneficiary demographic information, all inpatient and outpatient medical services provided, and drugs dispensed in the community setting. Diagnoses in the databases are classified according to the International Classification of Diseases, 9th revision (ICD-9). MED-ECHO databases are complementary and provide data from acute

care hospitalizations, which includes admission dates, duration of stay, diagnoses, and so on.

### Study Cohort

The study cohort from the RAMQ databases included all male patients 40 years and older who presumably died from PCa between 2001 and 2013. Patients were presumed to die from PCa if there was evidence of CRPC before death. The diagnosis of CRPC is not explicitly available via these databases, given that there is no ICD-9 code corresponding specifically to CRPC. Therefore, the inclusion criteria used in the study represent indirect evidence of CRPC. These inclusion criteria were derived from the Canadian Urologic Association guidelines for the management of CRPC<sup>14</sup> and treatment availability through RAMQ reimbursement. First, the cohort consists of patients who underwent ADT either by surgical castration (orchidectomy) or medical castration (use of luteinizing hormone-releasing hormone agonist or antagonist). Second, patients must have received at least 1 of the following CRPC treatments (CRPC criteria 1): chemotherapy (for PCa), abiraterone, palliative radiotherapy, or bone-targeted therapies (zoledronic acid and/or denosumab). Alternatively, patients were also considered to have reached CRPC if a diagnosis of PCa metastasis was identified and they received antiandrogens (bicalutamide, nilutamide, flutamide, or cyproterone acetate) in addition to surgical or medical castration (CRPC criterion 2). However, patients initiating antiandrogens within a 6-month period after ADT initiation were considered as receiving maximum androgen blockade without clear evidence of CRPC and were excluded from the cohort.

Identification of initial primary local treatment (RP or EBRT) was done retrospectively by their corresponding RAMQ procedure codes over the period before their CRPC phase and up to January 1996 (electronic RAMQ databases only contain data from this date onward). Patients with no identified primary local treatment were excluded ( $n = 5428$ ) and were deemed not comparable because they likely had extensive metastatic disease at diagnosis and possibly died before having the chance to develop locoregional complications. In order to distinguish initial curative treatment from potential salvage treatment, the date of initial treatment must have been within the 12-month period from the date of prostate biopsy. Patients were excluded if they died fewer than 2 years after primary local treatment ( $n = 196$ ). Further details about patient selection can be found in [Figure 1](#).

### Study Outcomes

The main study outcome was the development of late locoregional complications requiring intervention, which were defined as urologic procedures, minor rectal procedures, and other major surgical procedures performed in the last 2 years of life, as identified from the procedure codes in the RAMQ medical services database. The procedures include cystoscopy, ureteral stenting, nephrostomy tube insertion, transurethral resection of the prostate or fulguration, colonoscopy, rectal fulguration, and diversion ([Supplemental Table 1](#) in the online version). The identification of the relevant procedures was gathered from physician consensus and from the published literature.<sup>12,13,15</sup> Additionally, PCa-related hospitalizations in the last 2 years of life were also evaluated as an outcome; they were identified as hospitalizations from the MED-ECHO database associated with various PCa diagnosis codes. The 2-year

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