Title

Relative Incidence of Emergency Department Visits After Treatment for Prostate Cancer With Radiation Therapy or Radical Prostatectomy

Journal

Practical Radiation Oncology, 12(5)

ISSN

1879-8500

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Publication Date

2022-09-01

DOI

10.1016/j.prro.2022.05.001

Abstract

Purpose

Side effect profiles play an important role in treatment decisions for localized prostate cancer. Emergency department (ED) visits, which may be due to side effects from treatment, can be measured in real-world, structured, electronic health record (EHR) data. The goal of this study was to determine whether treatments for localized prostate cancer are associated with ED visits, as a measure of side effects, using EHR data.

Methods and Materials

We used a self-controlled case series study (SCCS) design, including patients treated at an urban academic medical center with radiation therapy (RT) or radical prostatectomy (RP) for prostate cancer between 2011 and 2020 who had visits documented for ≥ 6 months before and after treatment and ≥1 ED visit. We estimated relative incidences (RI) of ED visits, comparing incidence in the exposed and unexposed periods, with the exposed period being between start of treatment and 1 month after completion, and the unexposed period consisting of all other documented time.

Results

Among men who had at least one ED visit and after adjusting for age, there were higher rates of ED visits after RP (RI 20.4, 95% confidence interval [CI] 15.4-27.0, $p<0.001$), RT overall (RI 2.4, CI 1.7-3.4, $p<0.001$), intensity

modulated radiation therapy with high dose-rate brachytherapy (HDR) (RI 3.4, CI 1.7-6.8, p<0.001) or stereotactic body radiation therapy boost (RI 7.1, CI 3.4-14.8, p < 0.001), and HDR alone (RI 16.3, CI 7.2-36.9, p<0.001), compared to unexposed time. The number needed to harm to result in an ED visit was less for RP (17, CI 13-23) than RT overall (43, CI 25-126), but varied by RT modality.

Conclusions

In summary, relative rates of ED visits vary by treatment type, suggesting differing severities of side effects. These data may aid in selecting treatments and demonstrate the feasibility of using the SCCS study design on ED visits in real-world, structured EHR data to better understand side effects of treatment.

Introduction

Treatment options for localized prostate cancer, including radical prostatectomy (RP) and several forms of radiation therapy (RT), are, for the most part, considered to be equally effective in terms of disease control[1–7]. So, treatment decisions are heavily influenced by patient preference, which is often based on side effect profiles. Side effects for RP and RT affect similar systems, mostly the genitourinary (GU) and gastrointestinal (GI) systems[8–10]. Therefore, a better understanding of the severity and likelihood of side

effects associated with RP and RT will benefit patients in choosing a treatment for their prostate cancer.

Structured electronic health record (EHR) data are becoming increasingly available in clinical data warehouses (CDWs) as hospitals and clinics have moved to EHRs, creating new opportunities to use real-world data to understand side effects[11–13]. Although side effects are not directly captured in structured EHR data, emergency department (ED) visits can be measured in these data. In this context, ED visits during or shortly after treatment may be related to side effects associated with treatment, symptoms of the underlying prostate cancer, or may be due to unrelated comorbidities. ED visits for treatment-related side effects can be distinguished from other causes using a self-controlled case series (SCCS) study design[14,15]. Currently, the relationship between the various forms of treatment for localized prostate cancer and ED visits is unknown.

The goal of this study was to determine if the various forms of treatment for prostate cancer are associated with ED visits, as a measure of side effects. We used a SCCS study design, in which only patients that have experienced both the exposure (RT or RP) and the event (ED visit) are included and each patient serves as his own control, implicitly controlling for time-invariant confounders such as co-morbidities, underlying disease severity, and

socioeconomic status. We hypothesized that the relative rates of early ED visits differ by treatment type.

Methods

Study Design

Using a SCCS study design, we estimated the relative incidence (RI) of ED visit events in the exposed period, which was defined as during or within 1 month of treatment with RT or RP for prostate cancer, compared to the unexposed period, which was all other observed time (**Fig. 1a**)[14,15]. As required by the SCCS method, patients were included in the study if and only if they experienced both the event (ED visit) and the exposure (treatment for prostate cancer). This method also adjusts for variability in the duration of the exposed period.

Patient Selection

This study, using only de-identified data, was not considered human subjects research by the institutional review board and did not require review. The cohort consisted of patients treated at the XXXX (XXXX), an urban academic medical center, with RP or a single course of RT for prostate cancer between approximately 2011 and 2020. Cases were selected from XXXX's De-Identified CDW, which represents a subset of the structured data in XXXX's EHR. Due to de-identification, dates in this study are only approximate, but

relative time periods (e.g., within 1 month of treatment) within an individual patient are accurate.

Billing transactions were used to identify patients treated with RT or RP for prostate cancer based on associated CPT and ICD-9 and ICD-10 codes (**Supplemental Methods**). Patients were excluded if they did not have at least 6 months each of lead-up and follow-up surrounding RP or RT as documented by outpatient or ED visits or hospital admissions. These criteria were included to enrich for patients that would, if needed, present at the XXXX ED for care, which would be captured in the XXXX CDW, rather than an outside ED, which would not. Additionally, patients were excluded if they did not have at least one ED visit in the exposed or unexposed periods as required for the SCCS method.

Measurements

The exposure was treatment with RT (intensity modulated radiation therapy (IMRT), stereotactic body radiation therapy (SBRT), high dose-rate brachytherapy (HDR) or low dose-rate brachytherapy (LDR) alone or IMRT with an SBRT or HDR boost) or RP (nerve sparing laparoscopic or retropubic) for prostate cancer. The exposed (i.e., risk) period for ED visit events consisted of the time between the start of treatment and 1 month after completion. The unexposed (i.e., baseline) period consisted of all other time including beyond the 1-year window surrounding treatment that was

required for inclusion, with the exception that lead-up time was limited to start on or after the first recorded ED visit in the database in approximately December 2010. The event was an ED visit for any reason or diagnosis. We classified ED visit diagnoses using ICD-10 codes (**Supplemental Methods**). Age, race/ethnicity, hormone therapy, 5-α-reductase inhibitor prescription, and prostate-specific antigen (PSA) levels were also obtained from the CDW. Patients were considered to have received 5-α-reductase inhibitors and hormone therapy if these medications were ordered or administered at any point in the exposed or unexposed periods, which includes all observed time.

Statistical Analysis

Sample size was determined by including all patients meeting inclusion and exclusion criteria. We described patient characteristics using descriptive statistics including median, interquartile range (IQR), and proportions. To compare differences in patient characteristics across treatment modalities, the Kruskal-Wallis test was used for age and maximum pre-treatment PSA, and the χ^2 test was used for counts data.

RI of ED visits were determined using the SCCS R package (version 1.4), which employs a conditional logistic regression model implemented as a Cox proportional hazards model. The model was adjusted for age, which is not time-invariant, using 10 quantiles, and stratified by treatment type including RP and the various forms of RT. An interaction between RT and hormone

therapy was also examined. Additionally, numbers needed to harm (NNH) were calculated (**Supplemental Methods**). We conducted a sensitivity analysis comparing RIs in a cohort without lead-up or follow-up criteria, but with all other criteria kept the same to determine if limited sample sizes, due to restrictive inclusion and exclusion criteria, obscured any potentially meaningful results. A second sensitivity analysis examined the effect of extending the exposed period to 3 months after treatment as compared to just 1 month after treatment to determine if a longer exposed period might be more informative.

We estimated odds ratios (ORs) of ED visits in the exposed (vs. unexposed) period having GU or GI (vs. other) primary diagnoses. Statistical significance was assessed by the Mantel-Haenszel test for RT and Fisher's exact test for RP.

SQL and R (version 4.1.0) were used for all database queries, data manipulation, and statistical analyses. Statistical significance was considered to be $p<0.05$.

Results

We identified 353 patients based on the inclusion and exclusion criteria, and characteristics are summarized in Table 1 (**Methods, Fig. 1b**). The median age was 66 (range 42-79) at RP and 69 (range 47-87) at RT. Age was

associated with treatment type (p<0.001). Of the 211 patients treated with RP, 210 underwent a laparoscopic procedure, while 111/179 (52%) patients treated with RT underwent IMRT alone. The median length of hospitalization for RP procedures was 1 day (interquartile range: 1-2). Thirty-seven patients underwent RP and later were treated with RT. There were 878 ED visit events observed in the cohort. The median observation period (lead-up plus follow-up time) was 8.9 years (range 1.3-10.1).

We calculated RIs of ED visits for the various treatments for prostate cancer (**Table 2**). After adjusting for age, there were higher rates of ED visits after RT overall (RI 2.4, 95% confidence interval [CI] 1.7-3.4, p<0.001) and RP (RI 20.4, CI 15.4-27.0, p<0.001), compared to unexposed time. We did not find a statistically significant interaction between RT and hormone therapy. IMRT with an HDR boost (RI 3.4, CI 1.7-6.8, p<0.001) or SBRT boost (RI 7.1, CI 3.4-14.8, p<0.001) and HDR alone (RI 16.3, CI 7.2-36.9, p<0.001) had higher rates of ED visits compared to unexposed time, but IMRT and SBRT alone did not. For LDR, the RI was undefined because no ED visits were captured in the exposed period for these patients.

To test the sensitivity of these results to requiring 6 months of lead-up and follow-up time, we calculated RIs on a cohort without any lead-up or follow-up criteria, but with all other criteria kept the same. This more than doubled the number of patients included to 558 (RT: 270 and RP: 288), but RIs for all

of the various forms of treatment (RT overall: RI 2.7, CI 2.0-3.7, p<0.001; RP: RI 21.0, CI 16.9-26.9, p<0.001; IMRT with an HDR boost: RI 3.4, CI 1.8-6.5, p<0.001; IMRT with an SBRT boost: RI 4.5, CI 2.2-9.4, p<0.001; HDR: RI 19.2, CI 9.7-38.0, p<0.001; IMRT: RI 1.4, CI 0.8-2.3, p=0.19; SBRT: RI 1.3, CI 0.4-4.0, p=0.69; LDR: RI undefined) remained similar to those for the cohort in which the lead-up and follow-up criteria were included (**Supplementary Table 1**).

To test the sensitivity of the results to the length of the exposed period we calculated RIs for an extended exposed period consisting of the time from start of treatment to 3 months after completion of treatment. The same modalities had elevated RIs as did with the shorter exposed period (RT overall: RI 1.7, CI 1.3-2.3, p<0.001; RP: RI 9.6, CI 7.4-12.4, p<0.001; IMRT with an HDR boost: RI 2.5, CI 1.3-4.7, p=0.1; IMRT with an SBRT boost: RI 3.9, CI 1.9-8.0, p<0.001; HDR: RI 6.4, CI 3.0-14.0, p<0.001) (**Supplementary Table 2**). Although the estimated RI values for these modalities were lower than the RI values for the exposed period ending 1 month after completion of treatment, only the RI for RP was statistically significantly different based on 95% confidence intervals (3 month: CI 7.4-12.4 vs. 1 month: CI 15.4-27.0). Since the calculated RIs represent an average relative rate over the exposed period as compared to the unexposed period, these results may be consistent with the rate of ED visits in the second and third months after the end of treatment being lower than

from the start of treatment until 1 month after treatment. In support of this interpretation, the number of ED visits events in the first month after completion of treatment for RT overall and RP were 20 and 62 as compared to 13 and 19 in the second and third months combined.

RIs cannot be directly compared between modalities and, in this context, are only applicable to patients who have had at least one ED visit out of the larger population of patients that were treated with RT or RP for prostate cancer. To allow comparisons between modalities and estimate the impact on the whole population of patients, we estimated NNH (reciprocals of absolute risk increases), which for RT overall, HDR alone, RP, IMRT with HDR boost, and IMRT with SBRT boost were 43 (CI 25-126), 25 (CI 11-107), 17 (CI 13-23), 13 (CI 5-50), and 11 (5-40), respectively (**Table 2**).

We next asked whether ED events in the exposed period were more likely than those in the unexposed period to have diagnoses consistent with treatment-related side effects (i.e., GU or GI diagnoses) and found that they were more likely for both RP (OR 4.4, CI 2.0-9.9, $p<0.001$) and RT (OR 3.6, CI 1.3-9.4, $p=0.005$) (**Table 3**). Admissions from ED visits were not significantly more likely during the exposed period for RT or RP. When only RT treatment modalities with elevated RIs were examined, ED visits in the exposed period were even more likely to have a GU or GI diagnosis (OR 6.8, CI 2.0-24.0, $p<0.001$). For RT treatment modalities without elevated RIs, GU and GI

diagnoses were not more likely in the exposed period (OR 0.9, CI 0.0-6.8, p>0.99). When GU and GI diagnoses were examined separately, ED visits in the exposed period were more likely to have a GU diagnosis, but not a GI diagnosis, for RT overall, RP, and RT treatment modalities with elevated RIs (**Supplementary Table 3**).

Discussion

Using real world, de-identified, structured EHR data, we found that the RIs of ED visits during or within one month of treatment varied by prostate cancer treatment type. IMRT with an HDR or SBRT boost, HDR alone, and RP had increased RIs, but IMRT alone and SBRT alone did not. To allow comparison between modalities, NNH were calculated, which showed that ED visits were more likely during or within the first month after treatment for RP as compared to RT overall. However, the NNH could not be distinguished between RP, HDR alone, or IMRT with a boost because of overlapping confidence intervals. In this study, we used a SCCS design, which estimates relative rates of events (i.e., ED visits) that are exposure-related (i.e., treatment-related) compared to those that are unrelated, which means that the elevated RIs are treatment-related rather than related to the underlying disease or other comorbidities. Furthermore, for treatments with elevated RIs of ED visits, ED visits in the exposed period were significantly more likely to have a GU or GI diagnosis than those outside the exposed period, which is consistent with these ED visits being for prostate cancer treatment-related

diagnoses. Taken together, these data suggest that some forms of treatment for prostate cancer have increased relative rates of ED visits that are due to treatment-related side effects. Moreover, RIs of ED visits can be interpreted as RIs of treatment-related side effects because excess ED visits in the exposed period are a manifestation of severe side effects. These differences in side effects may help guide treatment decisions, since the treatment options for localized prostate cancer have generally similar efficacy. Additionally, analyzing and understanding the impact of cancer treatment decisions on the rate of ED visits, as we have done in this study, is a necessary initial step towards preventing avoidable ED visits, reducing costs, and minimizing side effects[16–19].

Few studies have examined ED visits after treatment for prostate cancer, but our data are generally consistent with previous findings. One study, which examined costs of prostate cancer treatment in Ontario, Canada, found that the relative rate of costs of ED visits after RT was approximately half of that of RP in the first year[20]. This is consistent with the trend in our study with RT having about 40% the relative rate of ED visits as RP based on the NNH. Two studies examined hospitalization rates (not ED visits) using Surveillance, Epidemiology, and End Results (SEER)-Medicare data in men 65 to 79 years of age[21,22]. In these studies, hospitalization rates were higher for external beam radiation therapy (EBRT) with a brachytherapy boost than brachytherapy alone, for brachytherapy alone than IMRT, and for RP than

IMRT, but RP had similar rates to brachytherapy alone or EBRT with a brachytherapy boost. This is consistent with the trends in our study. Finally, a study using California statewide databases examined ED visit rates after brachytherapy and found a rate of about 4% at a median of 7 days post-procedure, which is similar to the rate in this study of 4% based on the NNH[23].

New approaches may allow better use of the relatively new data source in CDWs, and we present one such approach here employing a SCCS design with ED visits as the events using de-identified structured, real-world data to study side effects[12]. Advantages of this approach include the availability of ED visit data, that a separate control population is not needed, that side effects do not have to be pre-defined, and that the scale of ED-visit-or-not for measuring the severity of side effects is inherent and not arbitrary like the CTCAE or RTOG scales [24,25]. Importantly, as compared to a SCCS study design, which only includes patients experiencing the event and exposure, using the entire population, such as a with a logistic regression analysis is likely to produce more biased results because of the many unmeasured confounders, which are implicitly controlled for in a SCCS design. Additionally, the SCCS method is not as limited by low event rates as regression methods are. The main drawbacks are that the types of side effects underlying the ED visit events are not individually reported and that other risk factors aside from the exposure are not easily assessed.

Limitations

ED visit events are not captured in the CDW if patients presented to an outside hospital ED instead of the XXXX ED. This may result in exclusion of patients, missing ED visit events for included patients, bias toward inclusion of patients who live closer to XXXX, and this geographic bias may be different by treatment type based on treatment length. To try to reduce the likelihood of missing data, lead-up and follow-up criteria were used to enrich for patients that have a relationship with XXXX and would, therefore, be more likely to visit the ED at XXXX, if needed. However, missing ED visit data does not appear to be a major limitation since a sensitivity analysis without these lead-up and follow-up criteria did not change the results much. This may be because patients must have had at least one ED visit at XXXX to be included based on the study design and, therefore, have already shown a propensity to present to the XXXX ED.

It is important to note that RIs in this study were calculated, as required by the SCCS method, using only patients that had at least one ED visit out of the larger population that was treated with RT or RP for prostate cancer. As a result, the RIs are only applicable to the population with at least one ED visit. NNH estimates were calculated based on documented ED visits at a single center and, therefore, may underestimate the true occurrence of ED visits.

Although we have attempted to choose comparable exposed periods for all modalities, it is possible that different choices for the length of the exposed period would result in different RIs for one or more of the treatment modalities. RI represents a relative rate of ED events during the exposed period as compared to the unexposed period. So, if ED events are uniformly distributed in a region, then the length of the exposed period in that region will have little effect on the RI. However, if ED events are not evenly distributed then an exposed period tightly focused on a higher event-rate period will result in a higher RI than one that includes time from a lower event-rate period also or only. It is possible that there are high and low event rate periods in the longer exposed periods used for IMRT with or without a boost or that only high event or only low event rate periods comprise the shorter exposed periods used for RP, HDR, or SBRT. To some extent, this is demonstrated in the sensitivity analysis examining the length of the exposed period.

Not all side effects can be captured as ED visit events. Any side effects that happen during the hospital stay, for example, for RP cannot be captured as ED visit events since these patients cannot and would not need to present to the ED. Furthermore, for all modalities, side effects that do not meet the severity threshold to motivate patients to visit the ED would not be captured with this approach but may nonetheless be clinically significant.

Additionally, as with all EHR and administrative database research, miscoding errors in the database are possible and, in this study, could have resulted in inaccuracies in patient inclusion or exclusion, treatment periods lengths, or ED visit diagnoses. Although the SCCS study design was specifically chosen to control for time-invariant characteristics like prostate cancer risk group and co-morbidities, this study does not explicitly adjust or stratify for these, and patients receiving RP versus RT may differ in these characteristics. Finally, while the results of this study are consistent with data from other sources, this study was performed using data from a single institution and may require validation with external data.

Conclusions

In this study, we applied a SCCS design to de-identified structured EHR data from an urban academic medical center to examine the rates of ED visits during and shortly after the various forms of treatment for prostate cancer. IMRT with an HDR or SBRT boost, HDR alone, and RP, had increased RIs of ED visits, but IMRT alone or SBRT alone did not. These data suggest different severities of early side effects for these various forms of treatment and may help guide treatment choices. Additionally, this study demonstrates the feasibility of using the SCCS design on ED visits in structured EHR data to study the severity of side effects of treatments in real-world data.

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Figures

Figure 1. Timelines of Exposures to Radiation Therapy or Radical Prostatectomy, ED Visit Events, and Unexposed and Exposed Periods for Each Patient

(a) A portion of the observed timeline for an individual patient is shown. The unexposed period is represented by a gray line. The exposed period is composed of the period in which the patient was treated with radiation therapy as the exposure (Treatment Period, red) plus one month (1 Month Post-treatment, blue). Specifically, the Treatment Period includes all fractions from the start of radiation to the end, including both modalities in the case of treatment with a boost (e.g. IMRT and SBRT or IMRT and HDR). In other patients, the treatment period may represent exposure to radical prostatectomy. This patient had an ED visit event during the treatment period, which is represented by a black circle. **(b)** Observed timelines for all patients included in this study are shown. Because unexposed and exposed periods are drawn to scale, short exposures for treatment with radical prostatectomy, HDR, LDR, or SBRT may not be visible. To enhance visibility, ED visit events are not drawn to scale.