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Challenges in the Analysis of Outcomes for Surgical Compared to Radiotherapy Treatment of Prostate Cancer

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Abstract. *Background/Aim: Prostate cancer can be treated with radical prostatectomy (RP), external-beam radiotherapy (EBRT), or brachytherapy (BT). These modalities have similar cancer-related outcomes. We used an innovative method to analyze the cost of such treatment. Materials and Methods: We queried our Institution's Insurance Division [University of Pittsburgh Medical Center (UPMC) Health Plan] beneficiaries from 2003-2008, who were diagnosed with prostate cancer and also queried the UPMC tumor registry for all patients with prostate cancer treated at our Institution. In a de-identified manner, data from the Health Plan and Tumor Registry were merged. Results: A total of 354 patients with non-metastatic disease with treatment initiated within 9 months of diagnosis were included (RP=236, EBRT=55, and BT=63). Radiotherapy-treated patients tended to be older, higher-risk, and have more comorbidities. Unadjusted median total health care expenditures during the first year after diagnosis were: RP: $16,743, EBRT: $47,256, and BT: $23,237 (p<0.0005). A propensity score-matched model comparing RP and EBRT demonstrated median total health care expenditures during year one: RP: $8,189, EBRT: $10,081; p=0.48. In a propensity-matched model comparing RP and BT, the median total health care expenditures during year one were: RP: $18,143, BT: $26,531; p=0.015 and per year during years 2 through 5 from diagnosis were: RP: $5,913, BT: $6,110; p=0.68. Conclusion: This pilot study demonstrates the feasibility of combining healthcare costs from the payer's perspective with clinical data from a Tumor Registry within an IDFS and represents a novel approach to investigating the economic impact of cancer treatment.*

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While the choice of a treatment option for cancer care continues to depend in large measure upon individual patient preference, dramatic changes in healthcare delivery for patients with cancer require not only understanding of the effectiveness of new treatment modalities, including new surgical techniques, new chemotherapy drugs, and new radiotherapy technologies, but also the financial impact.

We investigated challenges associated with determining the overall healthcare costs of patient choices with respect to treatment of prostate cancer. We analyzed two sets of de-identified data from each of two arms of an integrated delivery and finance system (IDFS). One set of data came from the medical records of men diagnosed with prostate cancer, and another set from the insurance arm of a financially-linked insurance system. This first pilot study was carried out to determine the challenges faced when trying to obtain and analyze data from these two sources.

Prostate cancer is the most common non-cutaneous malignancy in men, with an estimated 161,000 new cases to be diagnosed in 2017 in the United States (1). Several different curative treatment modalities exist for men diagnosed with prostate cancer. The most common of these include radical prostatectomy (RP), external beam radiotherapy (EBRT), and brachytherapy (BT) (2). In addition to these curative modalities, active surveillance (AS) has emerged as a viable and often preferred approach

for men with localized prostate cancer (2-4). Limited prospective data exist comparing these approaches, but available data suggest similar outcomes among these strategies in appropriately selected patients, with variable side-effects (5-7). This leaves the majority of men with localized prostate cancer a choice among several treatment options. In the era of healthcare reform and rising costs, there has been increasing attention to the relative value of treatment, especially in a situation such as the management of prostate cancer where survival outcomes appear similar among various approaches (8-10).

The healthcare landscape in the United States has rapidly changed in the past few decades. In order to maintain financial viability for all interested parties in a time of decreasing margins and increasing regulation, the formation of vertical, integrated healthcare systems has been adopted (11). A natural progression of this model has been the corporate merging of healthcare delivery (patient care) and healthcare financing (insurance). The effects of such models on overall healthcare quality and costs is a matter of debate (12), including in the care of patients with prostate cancer (13). The creation of large IDFSs has paved the way for innovative research involving the generation and analysis of vast datasets. In particular, the ability to study overall costs from the payer's perspective and clinical data from the providers creates a unique opportunity to investigate comparative outcome and cost effectiveness. We report a novel approach for examining the relative costs of prostate cancer treatment within our IDFS.

Materials and Methods

Data source and patient selection. The UPMC Health Plan and UPMC Network in the IDFS consists of an insurance division that covers in excess of 2.5 million lives and a network of hospitals and outpatient cancer centers with over 25 locations. After attaining Institutional Review Board approval, we queried our insurance division database for patients diagnosed with prostate cancer between 2003 and 2008 based on ICD-9 code, who were seen by a provider at our Institution and were continuously enrolled in the insurance plan for at least 5 years following first diagnosis of prostate cancer, thereby attaining detailed accounting of costs (Figure 1). To attain clinical data, we queried our hospital-based tumor registry for all patients with prostate cancer. Due to concerns for patient privacy, identifiable patient descriptors (name and date of birth) were encrypted uniformly by both the insurance division and the tumor registry. Then patients from the two datasets were matched by an outside honest healthcare data broker and de-identified. After matching patients from the insurance division and the tumor registry, we were left with 418 evaluable patients.

Definition of variable. Initial treatment strategy was defined as the first course of treatment received within 9 months of diagnosis, as this was felt to be a reasonable window to capture the vast majority of patients who wished to pursue active treatment at the time of diagnosis and in order to capture the expenses of such treatment within the first year from diagnosis. If no active treatment was pursued within 9 months of diagnosis, the patient was classified as receiving active surveillance. Risk groups were defined as low, intermediate, or high based upon National Comprehensive Cancer Network (NCCN) stratification (4). The Charlson-Deyo Comorbidity Index (CCI) was used to measure the overall health of individuals (14). For each patient, every remittance made by the insurance plan was provided. Global healthcare cost was defined as the summative value of all remittances for an individual patient from the date of first positive biopsy. Global healthcare cost was then also subdivided into medical costs and outpatient prescription costs. Costs were also subdivided into costs during the first year after diagnosis (to capture the costs associated with active treatment) and costs during years 2 through 5 after diagnosis (to capture the cost of ongoing care). All costs were inflation-adjusted to the equivalent of 2015 United States Dollars.

Statistical evaluation. All statistical analysis was performed using SPSS version 24 (IBM Corporation, Armonk, NY, USA). The global healthcare costs of patients with the three most common initial treatment strategies (RP, BT, and EBRT, respectively) were compared. Differences among treatment groups were evaluated both in an unadjusted model and in a propensity score-matched model in order to adjust for potential selection bias (15). Propensity scores indicative of the conditional probability for treatment selection (RP *vs*. EBRT and RP *vs*. BT) were created using logistic regression analysis with patient age, CCI, and NCCN risk group entered into the model, as these variables were the strongest available predictors of treatment selection. Propensity_matched cohorts using 1:1 nearest-neighbor technique were created. Kruskal–Wallis non-parametric testing with Bonferroni correction for multiple tests was used to compare groups. By using such statistics, which compare the distribution among groups by rank-order, the effect of statistical outliers (as is possible when evaluating global healthcare costs) is greatly reduced. Reported *p*-values have been adjusted using the Bonferroni correction, and an alpha value of 0.05 was used to define statistical significance.

Results

Patient characteristics. Of the 418 patients, who met the inclusion criteria, 236 underwent RP, 55 received EBRT, and 63 received BT for a total of 354 patients with non-metastatic disease who received one of the three most common treatments. The remaining 64 patients either had metastatic disease or received a less common treatment approach, including 17, who received active surveillance. Baseline patient characteristics for patients who opted for RP, EBRT, or BT are given in Table I. Men treated with RP tended to be younger than men treated with EBRT or BT ($p<0.0005$ for both) with median ages of 59, 71, and 70 years, respectively. Men treated with EBRT had a higher median comorbidity index than both those treated with RP (4 *vs*. 2, $p=0.002$) and those treated with brachytherapy (4 *vs*. 3, $p=0.042$). Those treated with BT had the highest incidence of low-risk disease, while those treated with EBRT had the highest incidence of high-risk disease.

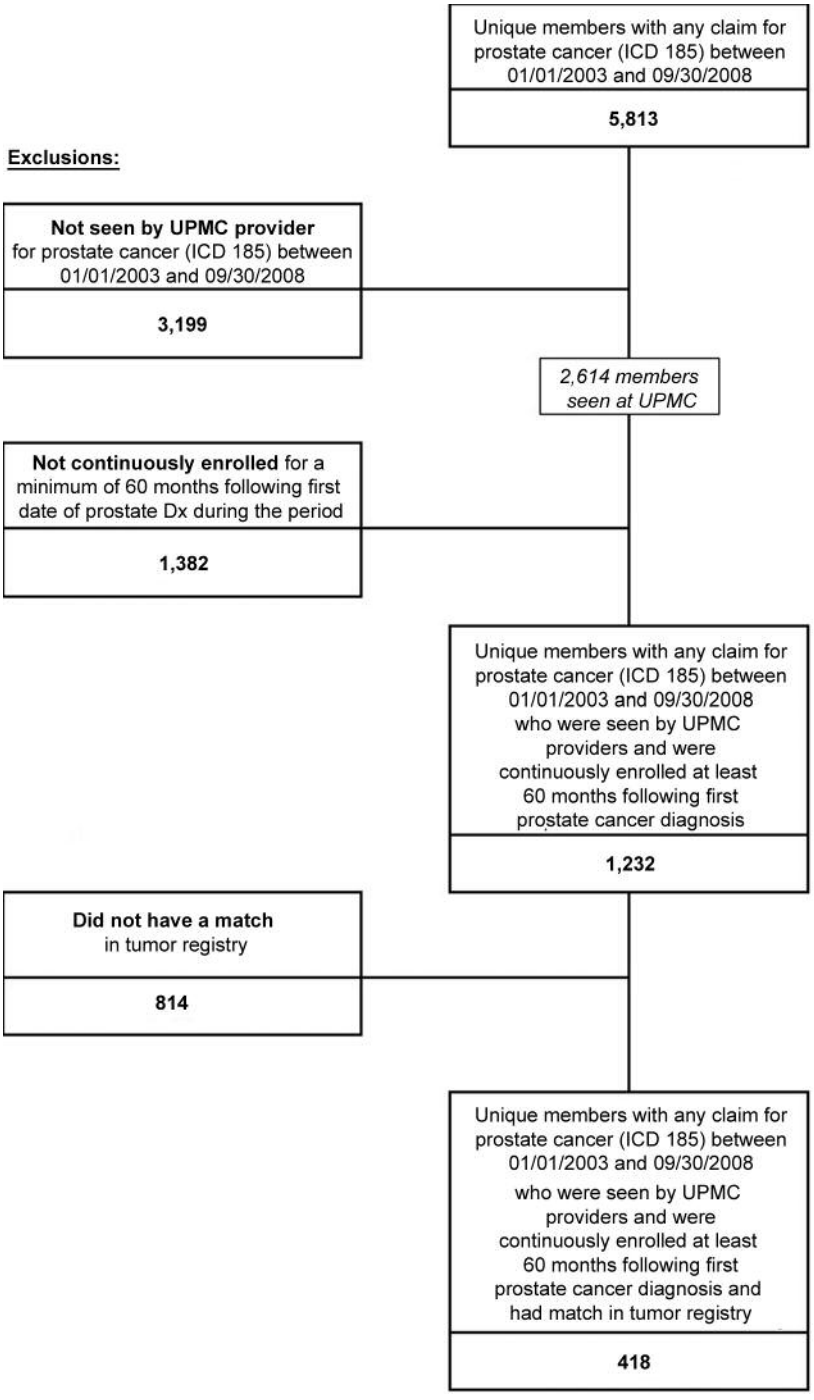

Figure 1. *CONSORT diagram for patient selection.*

Healthcare expenditures during the first year after diagnosis. Men treated with prostatectomy had a median [interquartile range (IQR)] global healthcare expenditure of $16,743 (IQR= $13,934-22,199) during the first year after diagnosis. This was statistically significantly less than men treated with EBRT ($47,256 IQR=37,239-59,499; $p<0.0005$ and men treated with brachytherapy ($23,237 IQR=19,099-33,218; $p<0.0005$). Furthermore, treatment with EBRT was significantly more costly than brachytherapy ($p<0.0005$) (Figure 2A). When medical expenses were isolated from

Table I. *Baseline characteristics for patients initially managed with radical prostatectomy (RP), external beam radiotherapy (EBRT), or brachytherapy (BT) (n=354).*

Variable	RP	EBRT	BT
Number of patients (n)	236	55	63
Median age (range), years	59 (38-74)	71 (54-83)	70 (50-86)
Median CCI (range)	2 (0-15)	4 (0-16)	3 (0-9)
Median pre-treatment PSA (IQR), ng/ml	5.3 (4.1-7.1)	6.5 (4.9-11.4)	5.1 (4.4-7.8)
Clinical T stage			
T1	36.0%	43.6%	73.0%
T2a	6.8%	12.7%	14.3%
T2b	5.1%	9.1%	0%
T2c	15.7%	18.2%	1.6%
T3	1.3%	0%	0%
T4	0.8%	1.8%	0%
Unknown	34.3%	14.5%	11.1%
Gleason score			
6	24.2%	21.8%	54.0%
7	50.8%	32.7%	22.2%
8	3.4%	21.8%	0%
9	6.4%	9.1%	3.2%
Unknown	15.3%	14.5%	20.6%
NCCN risk group			
Low	8.1%	12.7%	42.9%
Intermediate	41.5%	36.4%	23.8%
High	13.1%	32.7%	3.2%
Unknown	37.3%	18.2%	30.2%

CCI: Charlson-Deyo Comorbidity Index, IQR: interquartile range, NCCN: National Comprehensive Cancer Network, PSA: prostate specific antigen.

outpatient prescription drug costs, RP remained the least costly option and EBRT the most costly (RP: $15,663, IQR=13,404-20,689; EBRT: $39,294, IQR=33,692-56,219; BT: $20,646, IQR=16,477-31,520; $p<0.0005$ for all interactions). Prescription drug costs were higher for EBRT patients than RP patients, but no different between RP and BT patients (RP: $618, IQR=140-1,538; EBRT: $2,975, IQR=856-7,366; BT: $1,960 IQR=655-4,133; $p<0.0005$ for RP *vs*. EBRT and RP *vs*. BT, $p=0.704$ for BT *vs*. EBRT.

Healthcare expenditures during years 2-5 after diagnosis. Global healthcare expenditures per year during years 2-5 following diagnosis were higher for those who received EBRT than those who underwent RP (RP: $5,721, IQR=2,483-11,489; EBRT: $8,881, IQR=4,500-17,751; BT: $7,233, IQR=4,472-14,878; RP *vs*. EBRT $p=0.015$, RP *vs*. BT $p=0.114$, EBRT *vs*. BT $p=1.0$) (Figure 2b). Medical costs per year during years 2-5 were not statistically different among groups: RP: $4,210, IQR=1,664-8,907; EBRT: $5,162, IQR=2,325-13,708; BT: $5,239, IQR=2,287-10,337; $p=0.142$ across samples). Outpatient prescription drug costs per year during years 2-5 were lowest with RP (RP: $754, IQR=133-1,898; EBRT: $2,007, IQR=392-4,565; BT: $1,775, IQR=405-3,742; RP *vs*. EBRT $p=0.001$, RP *vs*. BT $p=0.003$, EBRT *vs*. BT $p=1.0$.

Propensity score matching. Baseline characteristics for propensity-matched cohorts are shown in Table II. The propensity-matched groups were well balanced with no statistically significant differences in age, NCCN risk group, or comorbidity index. Nagelkerke R2 values for the RP *vs*. EBRT and RP *vs*. BT analyses were 0.409 and 0.568, respectively. In the propensity-matched model comparing RP and EBRT median global healthcare expenditures during the first year following diagnosis were significantly higher for men who received EBRT (RP: $20,490 *vs*. EBRT: $46,096, $p<0.0005$) (Figure 3A). However, median total healthcare expenditures per year during years 2 through 5 from diagnosis were not statistically different (RP: $10,082, $p=0.481$) (Figure 3b). In the propensity-matched model comparing RP and BT, median global healthcare expenditures during the first year following diagnosis were higher with brachytherapy (RP: $18,143 *vs*. BT $26,531, $p=0.015$) (Figure 4a). However, median healthcare expenditures per year during years 2 through 5 from diagnosis were not statistically different (RP: $5,913 *vs*. BT $6,110, $p=0.681$) (Figure 4b).

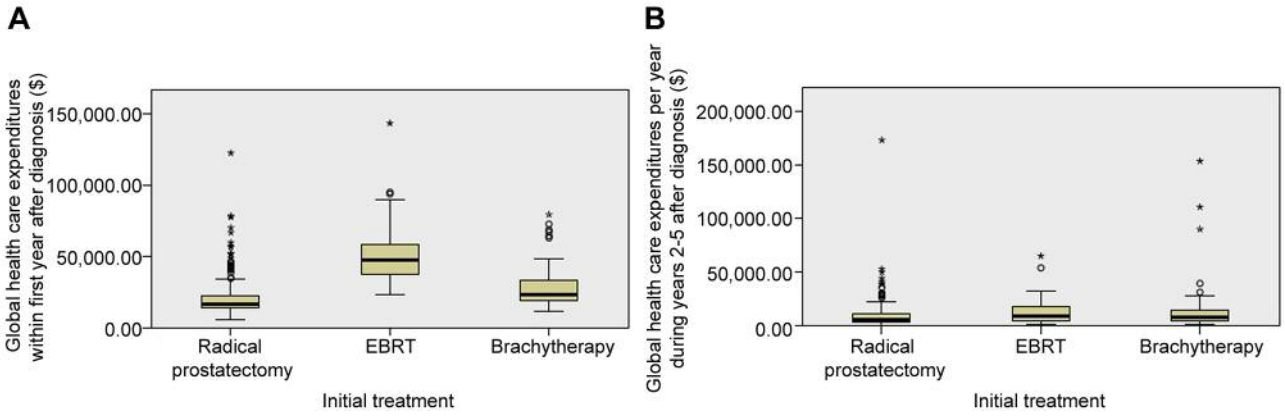

Figure 2. *Unadjusted healthcare costs per year for men diagnosed with prostate cancer and treated with radical prostatectomy, external beam radiotherapy (EBRT), or brachytherapy during the first year following diagnosis (A) and years 2-5 following diagnosis (B).*

Table II. *Baseline characteristics within propensity-matched cohort of patients initially managed with radical prostatectomy (RP), external beam radiotherapy (EBRT), or brachytherapy (BT).*

	RP *vs*. EBRT		RP *vs*. BT	
Variable	RP	EBRT	RP	BT
Number of patients (n)	22	22	18	18
Median age (range), years	66 (54-74)	65 (54-76)	65 (52-74)	65 (52-72)
Median CCI (range)	3 (2-7)	3 (0-7)	3 (0-8)	3 (0-7)
Median pre-treatment PSA (IQR), ng/ml	5.7 (4.7-8.1)	6.7 (4.2-12.4)	5.3 (4.3-6.1)	4.8 (4.0-7.0)
NCCN risk group				
Low	22.7%	13.6%	44.4%	55.6%
Intermediate	63.6%	59.1%	55.6%	44.4%
High	13.6%	27.3%	-	-

CCI: Charlson-Deyo Comorbidity Index, IQR: interquartile range, NCCN: National Comprehensive Cancer Network, PSA: prostate specific antigen.

Discussion

The available options for treatment of patients with cancer continue to pose challenges not only for the patient, but also for healthcare providers and insurance systems. Providing patients with an informed database for making decisions on their care will increasingly depend upon an analysis of not only clinical outcomes, but also cost. The daunting task of merging datasets on clinical outcomes comparing two or three different choices for management of newly diagnosed prostate cancer is in itself a significant issue.

We attempted to analyze total healthcare costs for men, successfully treated, and 'cured' of prostate cancer. Merging the two datasets was required in order to study healthcare delivery, and insurance issues. Such understanding will be necessary, particularly if the clinical outcomes are equivalent. In the present study, we sought to identify the challenges in carrying out such a study.

The present report represents those results of a pilot project to test the feasibility of a novel cost analysis method which combines the financial data available from the insurance division of an IDFS with the clinical data available from the IDFS Network hospital's tumor registry. This pilot study demonstrates the feasibility of this approach and represents a unique way to investigate the economic impact of cancer treatment. There were several recognized challenges. Significant imbalances existed among treatment groups, as radiotherapy patients tended to be older, at higher risk, and had more comorbidities. By utilizing the clinical data available from the tumor registry, this approach provides crucial data not available in other cost models, which allows for adjustment of imbalances among treatment groups.

Other studies tested the way to harness data from an IDFS to report on the costs of medical care, although a common theme is the difficulty of capturing clinical data not usually found in claims-based records. An interesting study from the

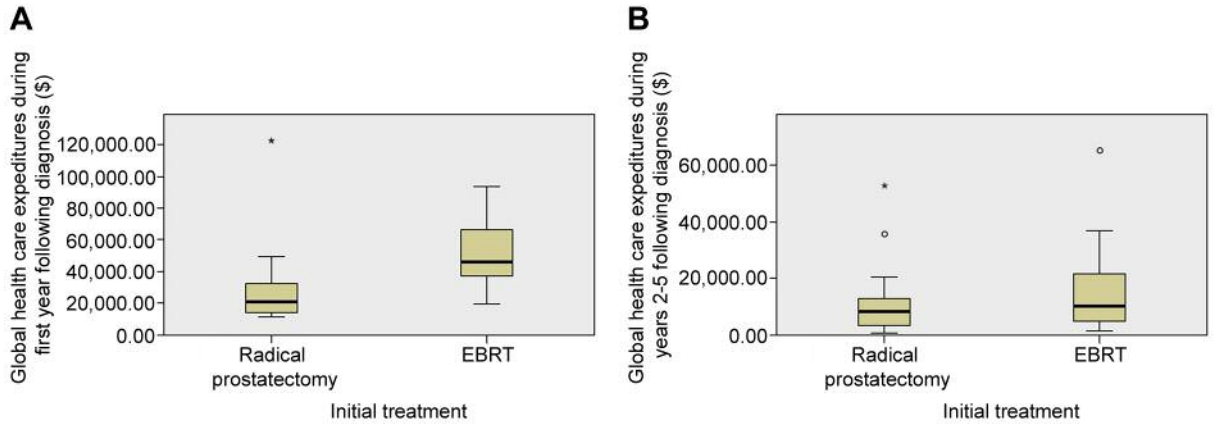

Figure 3. *Propensity score adjusted global health care expenditures for radical prostatectomy vs. external beam radiotherapy (EBRT) during the first year following diagnosis (A) and years 2-5 following diagnosis (B).*

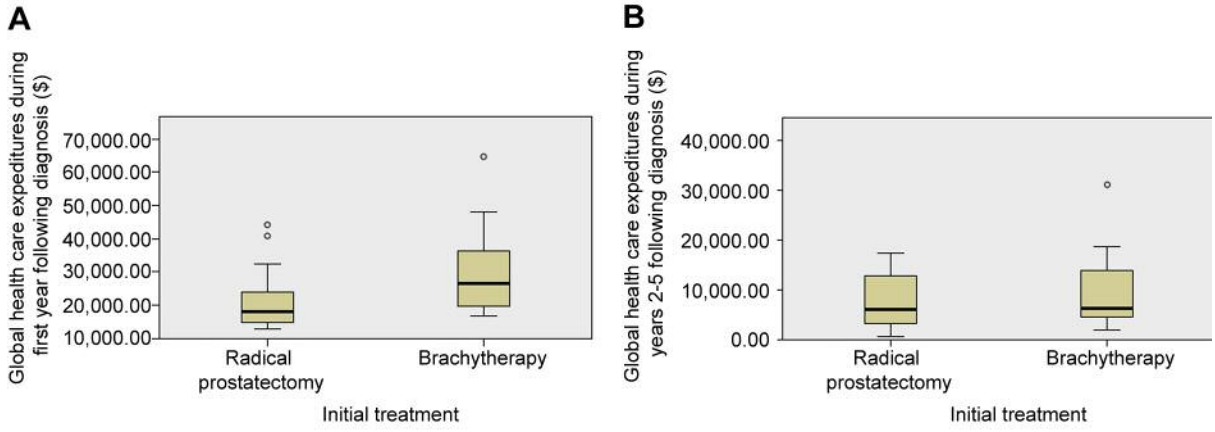

Figure 4. *Propensity score adjusted global health care expenditures for radical prostatectomy vs. brachytherapy during the first year following diagnosis (A) and years 2-5 following diagnosis (B).*

Henry Ford Health System looked at the cost burden of patients with chronic pain by creating a de-identified, integrated administrative database in which both clinical information from the electronic medical record (EMR) and resource utilization data was searchable (16). This study reported on the rates of outpatient visits, imaging, opioid prescriptions, and associated costs, including global costs. What the Henry Ford Hospital experience, alongside our work, demonstrates is the relative simplicity for data analytics platforms to capture certain variables within an EMR, while simultaneously having extreme difficulty capturing others. For example, similarly to the Henry Ford experience, within our network, instruments are in place to capture rates of re-admission, mortality, prescription drug use, length of hospital stay, emergency visits, procedures performed *etc.*, and stratify by physician, diagnosis code, comorbidity index, or age. However, software platforms are deficient in the ability to query the EMR for tumor T stage or grade, as these variables are typically contained in the text of a physician note or pathology report rather than having a discrete location for entry into the medical record.

Prior studies have investigated the cost-effectiveness of various prostate cancer treatment modalities. Many of these studies have made comparisons among radiotherapy techniques, including brachytherapy and various radiotherapy techniques such as intensity-modulated radiotherapy (IMRT), stereotactic body radiotherapy (SBRT), and 3D-conformal radiotherapy (17-27). Other studies have focused on comparisons among surgical techniques (28-30). Perhaps the most pertinent studies have looked at the costs among various treatment modalities, including radiotherapy, surgery, or active surveillance (31-36). Consistent with the body of literature,

our findings suggest that the cost of EBRT significantly outpaces the costs of surgery or brachytherapy. This likely is explained by the high cost of newer radiotherapy technologies, including IMRT, which, consistent with national trends (37), was employed for the overwhelming majority of patients in our study. Interestingly, after adjusting for selection bias with propensity matching, the ongoing cost of care among patients treated with each of the three most common modalities did not statistically differ, indicating that the majority of the cost differential among treatment options is due to the initial costs of therapy rather than costs encountered in the long run due to either recurrence and subsequent treatment or toxicity requiring additional intervention.

The present study revealed several limitations. We anticipated having several thousand evaluable patients in our cohort, which would have greatly increased our power for subset analysis, including the size of the propensity-matched cohorts. Due to our stringent inclusion criteria (including a 5-year minimum of continuous enrollment) and the fact that the tumor registry did not capture patients treated at certain facilities within our network, many potential patients were 'lost' in the data acquisition process. Future work will focus on improving this methodology in order to increase the number of evaluable patients. Secondly, our study revealed a potential ascertainment bias, as we were unable to independently review the medical records of individual patients. This concern raises the possibility that some patients initially chose active surveillance and then switched to treatment within 9 months, although we feel this number was likely extremely low given the time frame of our study. Thirdly, evolution in therapeutic techniques over the past decade may have had an impact on the relative cost and value of care delivered in the present day, which was not adequately captured in this dataset. Of particular interest is emerging data on hypofractionated radiotherapy whereby a course of radiation is delivered over 2-4 weeks instead of the conventional 8-9 weeks (38, 39). While there are certainly limitations to this type of analysis, the volume and detail of data available within an IDFS create advantages not available in other cost models, and we anticipate this analysis will serve as a model for future work.

In conclusion, the era of vertically integrated healthcare delivery and finance systems has opened new opportunities for data analysis. The present study demonstrates the potential for engaging the IDFS insurance division, in partnership with providers, to investigate the costs of care for patients with prostate cancer patients. The lack of clinical data available in most large claims-based datasets can be successfully augmented by using data from an institution's tumor registry. While preliminary, our data show an increased initial financial cost associated with EBRT compared with RP or BT, despite equivalent medical expenses beyond the first year following diagnosis.

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