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Basic Original Report

# Implementation of hypofractionated prostate radiation therapy in the United States: A National Cancer Database analysis

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**Abstract**

**Purpose:** Preclinical and clinical research over the past several decades suggests that hypofractionated (HFxn) radiation therapy schedules produce similar treatment outcomes compared with conventionally fractionated (CFxn) radiation therapy for definitive treatment of localized prostate cancer (PCa). We sought to evaluate national trends and identify factors associated with HFxn utilization using the US National Cancer Database.

**Methods and materials:** We queried the National Cancer Database for men diagnosed with localized (N0,M0) PCa from 2004 through 2013 treated with external beam radiation therapy. Patients were grouped by dose per fraction (DpF) in Gray: CFxn was defined as DpF ≤2.0, moderate HFxn as DpF >2.0 but <5.0, and extreme HFxn as DpF ≥5.0. Men receiving DpF <1.5 or >15.0 were excluded, as were those receiving <25 or >90 Gy total dose. Multiple logistic regression was performed to identify demographic, clinical, and treatment factor associations.

**Results:** A total of 132,403 men were identified, with 120,055 receiving CFxn, 7264 moderate HFxn, and 5084 extreme HFxn. Although CFxn was by far the most common approach over the analysis period, HFxn use increased from 6.2% in 2004 to 14.2% in 2013 ($P < .01$). Extreme HFxn use increased the most (from 0.3% to 8.5%), whereas moderate HFxn utilization was unchanged (from 5.9% to 5.7%). HFxn use was independently associated with younger age, later year of diagnosis, non-black race, non-Medicaid insurance, non-Western residence, higher income, academic treatment facility, greater distance from treatment facility, low-risk disease group (by National Comprehensive Cancer Network criteria), and nonreceipt of hormone therapy.

**Conclusions:** Although CFxn remains the most common radiation therapy schedule for localized PCa, use of HFxn appears to be increasing in the United States as a result of increased extreme HFxn use. Financial and logistical factors may accelerate adoption of shorter schedules. Considering the multiple demographic and prognostic differences identified between these groups, randomized outcome data comparing extreme HFxn to alternatives are desirable.



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Conflicts of interest: None.

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## Introduction

Definitive external-beam radiation therapy (EBRT) constitutes an accepted therapeutic approach in the management of localized prostate cancer (PCa).[1] Although men electing this option have typically received conventional fractionation (CFxn),[2] research over the past few decades has suggested that PCa and surrounding normal tissue respond differently to various fractionation schema,[3-5] thereby stimulating interest in hypofractionated (HFxn) schedules, which entail a shorter course with fewer, larger fractions.

A survey of practice patterns among PCa patients who initiated definitive EBRT in 1994 at 80 facilities across the United States identified a modal dose per fraction typical of CFxn[2]; however, to our knowledge, no subsequent analysis has been published evaluating fractionation patterns at a national level. Since the publication of these survey results in 2001, emerging data from several institutions have demonstrated the feasibility of moderate HFxn (ModHFxn),[6,7] and, more recently, early reports of randomized trials (including Radiation Therapy Oncology Group [RTOG] 0415,[8] Prostate Fractionated Irridation [PROFIT],[9] and Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer [CHHiP][10]) have demonstrated biochemical control with ModHFxn that is at least comparable to that offered by CFxn.

Technological advances have also spurred interest in extreme HFxn (ExtHFxn), typically delivered in a small number of highly conformal fractions of stereotactic body radiation therapy (SBRT). Despite encouraging early results from series of carefully selected patients undergoing ExtHFxn,[11,12] there are no published randomized data comparing such regimens with ModHFxn or CFxn.

Although some have argued that an abbreviated treatment course with logistical and possible financial advantages is an appropriate option for select patients,[13,14] it is unknown how these emerging data on HFxn have affected fractionation schedules for PCa on a national level. We therefore aimed to describe fractionation patterns among American men undergoing definitive EBRT for PCa and to describe factors associated with receipt of HFxn using the National Cancer Database (NCDB).

## Materials and methods

The NCDB, a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society, is a hospital-based registry capturing approximately 70% of incident cancer cases in the United States and drawing data from more than 1500 Commission-accredited cancer programs. The NCDB contains detailed information on demographic, clinical, and treatment-related factors. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology used or for the conclusions drawn from these data by the investigators. The present analysis was performed with the approval of our local institutional review board.

We initially queried the NCDB for cases of prostatic adenocarcinoma diagnosed from 2004 through 2013 in men aged 40 to 90 years who received radiation therapy without surgery, excluding patients with node-positive or metastatic disease and those with a prior diagnosis of malignancy (n = 176,188). We excluded those receiving any radiation modality other than EBRT and those missing complete information for their regional radiation dose, boost radiation dose, and number of fractions (n = 34,699). We then excluded patients coded as receiving palliative interventions (n = 141), those receiving <25 or >90 Gy in total dose (n = 4126), and those receiving <1 or >50 fractions (n = 1470) and divided each subject's total radiation dose in Gray by the number of fractions to calculate a dose per fraction. To account for potential inaccuracies in recorded dose and fraction number, we broadly defined 3 fractionation cohorts: a CFxn cohort receiving 1.5 to 2.0 Gy per fraction, a ModHFxn cohort receiving >2.0 but <5.0 Gy per fraction, and an ExtHFxn cohort receiving 5.0 to 15.0 Gy per fraction. Men receiving <1.5 or >15.0 Gy per fraction were excluded (n = 3349). Each patient was then classified as having either low-, intermediate-, or high-risk PCa according to his clinical T classification, prostate-specific antigen, and Gleason score, per National Comprehensive Cancer Network criteria.[1]

Besides risk group, patient-specific covariates incorporated into our analysis included age, year of diagnosis, race/ethnicity, insurance status, income (by ZIP code quartile), and comorbidity. We also analyzed facility-specific factors including geographic region (grouped into East, Midwest, South, and West), facility type, and distance from facility. Hormone therapy (HT) was incorporated as a treatment-specific covariate.

Statistical analyses were performed using SPSS V24.0 (SPSS Inc., Chicago, IL). Covariates were selected a priori. Pearson $\chi^2$ tests were used to assess associations between variables and fractionation schedule. Multivariable binary logistic regression models were used to assess the association between fractionation schedule and demographic, clinical, and treatment factors, with the results reported as odds ratios (ORs) for receipt of various fractionation schedules with corresponding 95% confidence intervals (95% CIs). All tests were 2-sided with a .05 level of significance.

## Results

In total, 132,403 men met inclusion criteria, including 120,055 (90.7%) receiving CFxn, 7264 (5.5%) ModHFxn, and 5084 (3.8%) ExtHFxn. A majority of each fractionation