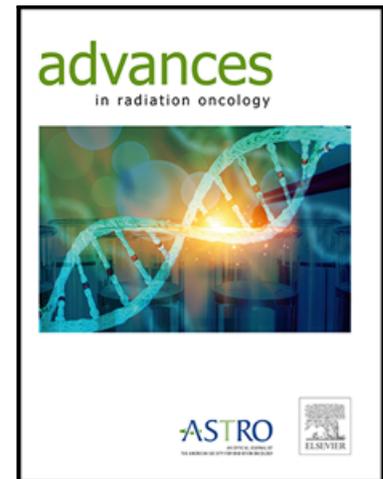


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## Trends in Radiation Oncology Treatment Fractionation at a Single Academic Center, 2010-2020

**Running Title:** Trends in RT Fractionation

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**Conflict of interest statement:**

RJ has stock options as compensation for her advisory board role in Equity Quotient, a company that evaluates culture in health care companies; she has received personal fees from the Greenwall Foundation, Doris Duke Foundation, and the National Institutes of Health and grants or contracts for unrelated work from the National Institutes of Health, the Doris Duke Foundation, the Greenwall Foundation, the Komen Foundation, Genentech, and Blue Cross Blue Shield of Michigan for the Michigan Radiation Oncology Quality Consortium. She has served as an expert witness for Sherinian and Hasso, Dressman Benzinger LaVelle, and Kleinbard, LLC. RJ is a former member of the Board of Directors of the American Society of Clinical Oncology and chair of the American Society for Radiation Oncology Ethics Committee.

BAYC, MD, CW, MS, JH and CM have no conflicts of interests to declare.

**Funding statement:** This work required no external funding.

**Data sharing statement:** Data may be available upon reasonable request to the senior authors.

**IRB Approval:** This study was determined exempt from review by our university's Institutional Review Board (HUM00194966).

**Short running title:** Trends in Hypofractionation Adoption

**Abstract:**

**Purpose:** Recent clinical trials suggest hypofractionated treatment regimens are appropriate for treatment of many cancers. It is important to understand and document hypofractionation adoption because of its implications for treatment center patient volumes. There is no recent U.S. study of trends in hypofractionation adoption that includes comparisons of multiple disease sites and data since the onset of COVID-19. In this context, this study describes trends in treatment fractionation at a single academic center from 2010-2020.

**Methods:** From an institutional database, records were extracted for treatment of four disease site categories: all cancers, breast cancer, prostate cancer, and bone metastases. For each disease site, the mean number of fractions per treatment course was reported for each year of the study period. To explore whether the COVID-19 pandemic was associated with increased hypofractionation adoption, piecewise linear regression models were used to estimate a changepoint in the time trend of mean monthly number of fractions per treatment course and evaluate whether this changepoint coincided with pandemic onset.

**Results:** The dataset included 22,865 courses of radiation treatment and 375,446 treatment fractions. The mean number of fractions per treatment course for all cancers declined from 17.5 in 2010 to 13.6 in 2020. There was increased adoption of hypofractionation at this institution for all cancers and specifically for both breast and prostate cancer. For bone metastases, hypofractionation had largely been adopted before the study period. For most disease sites,

adoption of hypofractionated treatment courses occurred before pandemic onset. Bone metastases was the only disease site where a pandemic-driven increase in hypofractionation adoption could not be ruled out.

**Conclusions:** This study reveals increasing use of hypofractionated regimens for a variety of cancers throughout the study period, which largely occurred before the onset of the COVID-19 pandemic at this institution.

## Introduction

Recent landmark clinical trials in radiation oncology suggest hypofractionated treatment regimens are appropriate for treatment of many cancers. For example, moderate hypofractionation (15-16 fractions, possibly followed by boost) is now the preferred standard regimen for many women with breast cancer,<sup>1</sup> and evidence is emerging to support even more extremely hypofractionated approaches.<sup>2,3</sup> Similarly, for prostate cancer, professional society consensus guidelines now recommend that moderately hypofractionated regimens of 20-28 fractions be offered to men who desire external beam radiation therapy for treatment of their localized prostate cancer, regardless of their clinical risk grouping,<sup>4</sup> and even more extremely hypofractionated regimens utilizing stereotactic body radiotherapy are being developed.<sup>5</sup> In the palliative setting, single-fraction treatment for bone metastases<sup>6</sup> has long been known to be appropriate to replace what once required several weeks of daily treatment for many patients.

Several studies published before the COVID-19 pandemic described the patterns of adoption of hypofractionated treatment regimens for specific disease sites including breast,<sup>7,8</sup> prostate,<sup>9</sup> and bone metastases.<sup>10-12</sup> A smaller number of studies, including a single-center

report<sup>13</sup> and a larger-scale analysis of the National Cancer Database,<sup>14</sup> described trends in hypofractionation adoption across multiple disease sites. These studies found a slow but steady increase in the adoption of hypofractionation over time.

The COVID-19 pandemic may have increased pressure to adopt hypofractionation because of concerns about disease spread at treatment centers.<sup>15</sup> During the first several months of the pandemic, several groups published recommendations for implementing hypofractionated treatment regimens,<sup>16-18</sup> and a few studies described how hypofractionation was adopted for specific disease sites.<sup>19-21</sup> However, to our knowledge, there is no recent U.S. study of trends in hypofractionation adoption that includes comparisons of multiple disease sites and data since the onset of the COVID-19 pandemic. Therefore, we sought to describe trends in treatment fractionation at a single academic center from 2010-2020.

## Methods

From our institutional database, for the years 2010-2020, we extracted records for four groups of patients: patients who received radiation therapy for all cancers and specifically for breast cancer, prostate cancer, and bone metastases using our in-house XXXX system.<sup>22</sup> We chose these disease sites because they are the most commonly treated sites for which trials have investigated hypofractionated regimens.

For each radiation course, we extracted the total number of fractions delivered (n=22,865). A coding algorithm was created to compensate for inconsistencies arising from manual data entry in our treatment planning system (ARIA) and medical record system (Epic) regarding diagnosis in categorizing disease site cohorts. For breast and prostate, we included only radiation courses delivered to the primary site. For breast cancer, we eliminated treatment courses recorded as less than or equal to 3 fractions (n=14). For bone metastases, we eliminated

treatment courses recorded as greater than 15 fractions (n=362). We made these deletions after review suggested that these cases were miscoded by the algorithm.

For each disease site, we summarized the mean number of fractions per treatment course (mean  $\pm$  standard deviation [S.D.]) for each year of the study period. Additionally, we calculated the total number of treatment courses and percentages of treatments delivered by categories of number of fractions per treatment course.

To explore whether the COVID-19 pandemic was associated with a precipitous drop in the number of fractions per treatment course, we plotted the mean number of fractions per treatment course over time. To characterize change in the mean number of fractions we utilized piecewise linear regression models with separate models fit to each disease site.<sup>23</sup> Time was measured by month and treated continuously. The threshold (“change point”) at which the slope (average change in mean number of fractions per treatment per 1 year increase) changed was estimated via maximum likelihood with corresponding 95% confidence intervals. The average slopes both pre- and post-threshold date were also estimated via maximum likelihood. We defined the onset of the COVID-19 pandemic as March 2020, for simplicity. If the confidence interval around the changepoint estimate included this date, the change in time trend may have been associated with the onset of the COVID-19 pandemic. If the changepoint estimate and confidence interval excluded Mar 30, 2020, the change in time trend was more likely associated with factors other than the onset of the pandemic. We also estimated the mean number of fractions per treatment over time using a nonparametric generalized additive model<sup>24</sup> to explore any non-linear patterns in the data for each disease site.

Statistical analysis was conducted using R version 4.1.2. Two-sided p-values less than 0.05 were considered statistically significant. This study of de-identified data was determined to be exempt by the Institutional Review Board.

## Results

The dataset included 22,865 courses of radiation treatment and 375,446 treatment fractions, gathered with our in-house XXXX system. The mean number of fractions per treatment course declined steadily throughout the study period for all cancers as well as each specific disease site (**Table 1**). For example, the number of fractions per treatment course (mean±S.D.) for all cancers declined from 17.5±12.3 in 2010 to 13.6±11.2 in 2020.

The total number of radiation treatments for all cancers increased steadily throughout the study period except for a brief drop at the onset of the pandemic (**Figure 1A**). The estimated changepoint in the time trend of monthly number of fractions per treatment course was August 2018 (95% confidence interval [June 2017, February 2019], **Figure 1B**). From 2010 to the estimated changepoint in 2018, the mean number of fractions per treatment course decreased at an average rate of 0.21 per month (95% CI [0.15, 0.28]). After the changepoint in September 2018, the mean number of fractions per treatment course decreased at an average rate of 1.43 per month (95% CI [1.13, 1.74]).

Treatment volume for breast cancer was relatively steady throughout the study period (**Figure 2A**). The mean number of fractions per treatment declined from 28.4±4.3 in 2010 to 18.9±5.9 in 2020. The estimated changepoint in the time trend of monthly number of fractions per treatment course was October 2019 (95% CI [March 2019, December 2019], **Figure 2B**). From 2010 to the estimated changepoint in October 2019, the mean number of fractions per treatment course decreased at an average rate of 0.68 per month (95% CI [0.61, 0.76]). After the

change point in October 2019, the mean number of fractions per treatment course decreased at an average rate of 6.7 per month (95% CI [5.51, 7.92]).

Treatment volume for prostate cancer increased throughout the study period but fell briefly after pandemic onset (**Figure 3A**). The mean number of fractions per treatment declined from  $34.2 \pm 12.0$  in 2010 to  $13.8 \pm 11.6$  in 2020. The estimated change point in the time trend of monthly number of fractions per treatment course was October 2016, 95% CI [April 2016, March 2017], **Figure 3B**. From 2010 to the estimated change point in October 2016, the mean number of fractions per treatment course increased at an average rate of 0.69 per month (95% CI [0.26, 1.12]). After the change point in October 2016, the mean number of fractions per treatment course decreased at an average rate of 5.49 per month (95% CI [4.90, 6.08]).

For bone metastases, treatment volume increased throughout the study period (**Figure 4A**). The mean number of fractions per treatment declined from  $7.1 \pm 4.5$  in 2010 to  $4.9 \pm 3.6$  in 2020. The estimated change point in the time trend of monthly number of fractions per treatment course was January 2015, 95% CI [March 2013, April 2020], **Figure 4B**. From the start date to the estimated change point in January 2015, the mean number of fractions per treatment course decreased at an average rate of 0.04 per month (95% CI [-0.09, 0.18]). After the change point in January 2015 the mean number of fractions per treatment course decreased at an average rate of 0.35 per month (95% CI [0.26, 0.44]).

For all four disease sites, upon visual inspection, the nonparametric model estimated a similar change point to the broken line linear regression and led to qualitatively similar conclusions.

## Discussion

In this study, which we believe is a model for how other institutions might evaluate their own practice patterns, we observed increased adoption of hypofractionation at our institution during the study period for all cancers and specifically for both breast and prostate cancer. For bone metastases, hypofractionation had largely been adopted before the study period. For most disease sites, adoption of hypofractionated treatment courses occurred largely before the onset of the COVID-19 pandemic. Bone metastases was the only disease site where we could not rule out an increase in hypofractionation adoption related to the COVID-19 pandemic.

Understanding patterns of adoption of hypofractionation is important because hypofractionation is a more efficient approach that can, when applied appropriately, increase value. Indeed, when the ABIM Foundation's Choosing Wisely campaign engaged professional organizations in identifying practices that may represent inappropriate use of finite societal resources, ASTRO's first "top five" list of opportunities to improve the quality and value of cancer care included two separate items focused on hypofractionation.<sup>25</sup> Complex factors, including financial incentives and the desire for mature data of equivalence, led to an initially slow adoption of hypofractionated regimens after the initial publication of landmark trials,<sup>26</sup> but the accumulation of evidence and heightened attention from the media, public, and insurers led to increased uptake of hypofractionation even before the COVID-19 pandemic.<sup>27</sup> Ongoing attention to patterns of practice is especially informative now, as the COVID-19 pandemic may have encouraged physicians unfamiliar with these approaches to begin using them. Although our study demonstrated that hypofractionation adoption at our institution had largely occurred before the COVID-19 pandemic, as Thomson et al. note, "There may be novel opportunities to learn from patients treated with nonstandard dose fractionations during the COVID-19 pandemic,

either to set aside certain fractionation practices or to inform future rational clinical trial designs.”<sup>28</sup>

Information about uptake of hypofractionation is also important because this information is directly relevant for the purposes of planning for technology needs. Both oversupply and undersupply of radiation therapy services are suboptimal for society. Undersupply creates access issues; oversupply wastes resources and creates redundancy that reduces patient volume per center to the detriment of quality, to the extent that there are relationships between quality, volume, and specialization. When modeling the level of external beam radiation services anticipated to be needed in a given geographic area in order to inform policy decisions (e.g., issuance of certificates of need), hospital strategists and state policy-makers typically consider data on cancer incidence patterns, the proportion of patients diagnosed with each cancer type who have indications for radiotherapy, and the number of treatments necessary per course of treatment. Information on the last point has been quite limited,<sup>13</sup> and this study provides a framework for how similar evidence might be captured from a diversity of institutions in order to yield data required to plan appropriately for population health needs.

This study has certain limitations. Chief among these is the derivation of information from a single academic institution. Although this center includes several physicians treating each disease site, their practices may not be representative of those elsewhere. Nevertheless, this study illuminates trends in radiation fractionation that may generalize to similar academic centers, suggests that it is possible to deliver radiation oncology care in the modern era with fewer total fractions per treatment course than was typical in the past, and provides a model for studies of hypofractionation adoption at other radiation oncology treatment centers. This study and others

similar will merit consideration by policy-makers seeking to make appropriate plans for future needs.

In conclusion, this study reveals increasing use of hypofractionated regimens for a variety of cancers throughout the study period, which largely occurred before the onset of the COVID-19 pandemic at our institution. Future research is necessary to evaluate patterns in other settings in order to provide the evidence base upon which hospital and state policymakers can ground decisions about capital investments in technology to best promote the health of the public.

**IRB Approval:** This study was determined exempt from review by our university's Institutional Review Board.

#### **Declaration of interests**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Reshma Jagsi reports reports stock options as compensation for her advisory board role in Equity Quotient, a company that evaluates culture in health care companies; she has received personal fees from the Greenwall Foundation, Doris Duke Foundation, and the National Institutes of Health and grants or contracts for unrelated work from the National Institutes of Health, the Doris Duke Foundation, the Greenwall Foundation, the Komen Foundation, Genentech, and Blue Cross Blue Shield of Michigan for the Michigan Radiation Oncology Quality Consortium. She has served as an expert witness for Sherinian and Hasso, Dressman Benzinger LaVelle, and Kleinbard, LLC. RJ is a former member of the Board of Directors of the American Society of Clinical Oncology and chair of the American Society for Radiation Oncology Ethics Committee.

BAYC, MD, CW, MS, JH and CM have no conflicts of interests to declare.

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Table 1: Number of fractions per treatment course for all cancers, breast cancer, prostate cancer, and bone metastases, 2010-2020

Figure 1: Monthly total of radiation treatment courses (A) and mean number of fractions per treatment course (B) for all cancers, 2010-2020

Figure 2: Monthly total of radiation treatment courses (A) and mean number of fractions per treatment course (B) for breast cancer, 2010-2020

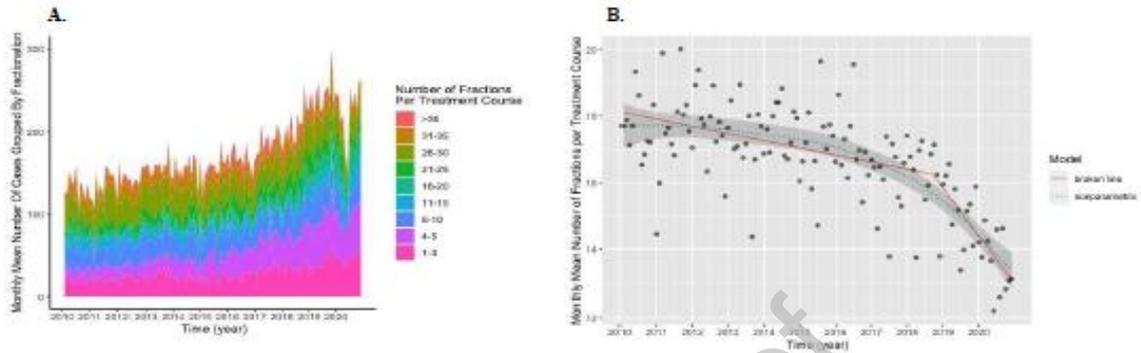
Figure 3: Monthly total of radiation treatment courses (A) and mean number of fractions per treatment course (B) for prostate cancer, 2010-2020

Figure 4: Monthly total of radiation treatment courses (A) and mean number of fractions per treatment course (B) for bone metastases, 2010-2020

**Table 1: Number of fractions per treatment course for all cancers, breast cancer, prostate cancer, and bone metastases, 2010-2020**

Disease site	Number of fractions per treatment course (mean $\pm$ S.D.)										
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
All cancers (n=22,865)	17.5 $\pm$ 1	17.9 $\pm$ 1	17.7 $\pm$ 1	17.3 $\pm$ 1	17.6 $\pm$ 1	17.1 $\pm$ 1	17.1 $\pm$ 1	17.0 $\pm$ 1	16.0 $\pm$ 1	15.0 $\pm$ 1	13.6 $\pm$ 1
Breast (n=2,023)	28.4 $\pm$ 4	29.0 $\pm$ 3	28.6 $\pm$ 4	28.3 $\pm$ 4	27.4 $\pm$ 4	26.9 $\pm$ 5	26.6 $\pm$ 5	25.1 $\pm$ 5	23.8 $\pm$ 5	22.8 $\pm$ 5	18.9 $\pm$ 5
Prostate (n=1,807)	34.2 $\pm$ 1	28.8 $\pm$ 1	25.8 $\pm$ 1	31.5 $\pm$ 1	32.6 $\pm$ 1	32.4 $\pm$ 1	35 $\pm$ 13	29.3 $\pm$ 1	24.4 $\pm$ 1	17.9 $\pm$ 1	13.8 $\pm$ 1
Bone metastases (n=2,748)	7.1 $\pm$ 4.5	6.7 $\pm$ 4.2	6.8 $\pm$ 4.3	6.8 $\pm$ 4	6.8 $\pm$ 3.9	6.8 $\pm$ 3.7	6.0 $\pm$ 3.6	5.2 $\pm$ 3.5	5.7 $\pm$ 3.6	5.3 $\pm$ 3.3	4.9 $\pm$ 3.6

**Figure 1: Monthly total of radiation treatment courses (A) and mean number of fractions per treatment course (B) for all cancers, 2010-2020**



**Figure 2: Monthly total of radiation treatment courses (A) and mean number of fractions per treatment course (B) for breast cancer, 2010-2020**

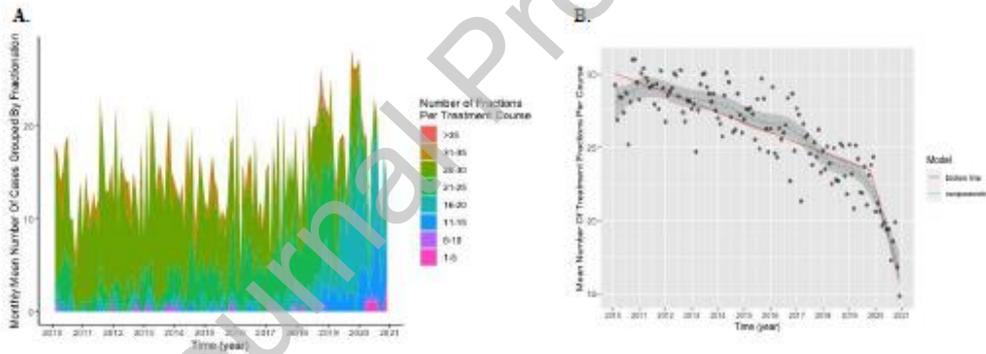


Figure 3: Monthly total of radiation treatment courses (A) and mean number of fractions per treatment course (B) for prostate cancer, 2010-2020

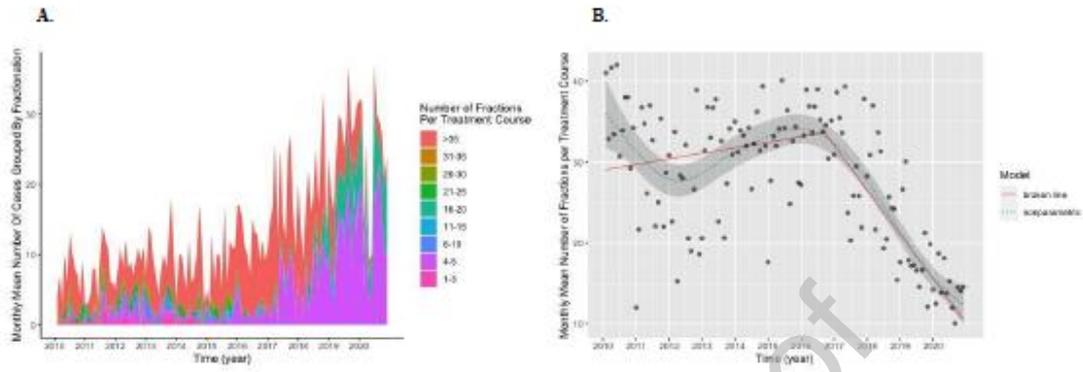


Figure 4: Monthly total of radiation treatment courses (A) and mean number of fractions per treatment course (B) for bone metastases, 2010-2020

