Treatment Practice Analysis of Intermediate or High Risk Localized Prostate Cancer: A Multi-center Study with Veterans Health Administration Data

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Abstract. Prostate cancer (PCa) is a heterogeneous disease. PCa is stratified into risk groups based on clinical factors such as T-stage, Gleason score, and baseline prostate-specific antigen. Treatments are selected based on these risk groups. However, we hypothesize that non-clinical factors such as the radiation therapy (RT) center may also impact treatment selection, and we investigate the impact of these factors on treatment selection practice and their adherence to recommended guidelines from the national comprehensive cancer network (NCCN). A total of 552 patients with intermediate or high-risk localized PCa related data was collected from 34 radiation therapy centers of the Veterans Health Administration (VHA), who were treated with definitive RT and with or without Androgen Deprivation Therapy (ADT) between 2010 and 2017. Patients' clinical information is extracted by manually reviewing their medical charts. We also extracted treatment intended and treatment administered information from consult and end-of-treatment notes, respectively. The random forest classification algorithm was used to identify the impact of clinical and non-clinical factors in treatment selection, their adherence to the treatment guidelines, and treatment alteration (i.e., change in intended and administered treatments). We created models for predicting treatment intended as well as treatment administered. Our results demonstrated that non-clinical (i.e., treatment center)

The study was funded by the Veterans Affairs (VA) National Radiation Oncology Program (NROP).

I. Măndoiu et al. (Eds.): ICCABS 2019, LNBI 12029, pp. 134–146, 2020.
https://doi.org/10.1007/978-3-030-46165-2_11

factors, along with clinical factors, are significant for predicting the adherence of treatment intended to the NCCN guidelines. Furthermore, the center served as an important factor for prescribing ADT; however, it is not associated with the duration of ADT and is weakly associated with treatment alterations. This presence of center-bias in treatment selection warrants further investigation on details of center-specific barriers for NCCN guideline adherence, and as well as the impact of center-bias on oncological outcomes.

Keywords: Prostate cancer · Radiation therapy · Treatment selection · Machine learning · Clinical informatics

1 Introduction

Prostate cancer (PCa) is the most commonly diagnosed type of cancer after breast and lung cancer. In 2018 alone, over 160,000 new prostate cancer cases and over 29,000 prostate cancer-related deaths were estimated in the United States [1]. PCa is also one of the most heterogeneous type of cancer specifically with respect to intermediate or high-risk PCa [2]. The non-invasive prostate-specific antigen (PSA) test that has led to an increase in early detection of PCa leading to more localized PCa diagnosis in recent years [3].

The National Comprehensive Cancer Network (NCCN) provides clinical practice guidelines that are created by physicians to determine the best way of treating PCa patients (besides other types of cancers), depending on their diagnosis, disease stage, age and other factors. PCa is also treated with monotherapy or polytherapy. Physicians select the treatment modality based on four major criteria - age, race, life expectancy, and NCCN Risk. Factors such as patient preferences, survivorship goals along with tumor biology also play a crucial role in optimizing the treatment modality.

A major consideration during the treatment options for PCa is to check whether the cancer is contained within the prostate gland (localized), or has spread outside the prostate (locally advanced) or has spread to other parts of the body (metastasized). Radical prostatectomy (RP), external beam radiotherapy (EBRT) and brachytherapy (BT) are the common primary treatment options for localized PCa. Hormonal therapeutics such as androgen deprivation therapy (ADT) is also used as neoadjuvant/adjuvant therapy. However, ADT as monotherapy is not recommended for intermediate and high-risk cancer patients by NCCN. Ideally, a treatment option recommendation would be based on the randomized controlled trials (RCT) that compare efficacy and morbidity of alternative treatment methods. There are no randomized trials showing that one treatment is better than the other for the above-mentioned treatment options. Hence, physicians use their personal experience and expertise to predict the outcome of these treatment methods. Physicians also tend to have difficulty weighing the relative importance of each of these factors and inherently possess biases when predicting the treatment outcomes.

Based on the aforementioned considerations, determining an optimal treatment plan for the patient can be a challenging task for the physician. In order to assist the physicians with more accurate prognosis, subsequent treatment outcome prediction, and to make informed decisions, numerous predictive tools have been developed [4]. These include probabilistic models, lookup and propensity scoring tables, risk-stratification tools, classification, and regression tree analysis, nomograms, and artificial neural networks [5,6] However, to the best of our knowledge, no models have been reported that can identify why a prescribed (or administered) treatment plan do not adhere to NCCN guidelines.

The predictive models for treatment plan (or outcome) prediction have a major disadvantage. Such models do not consider the impact of non-clinical factors associated with the treatment center. The factors associated with the treatment center have shown to play a determining role in the physicians' treatment prescription practices. Non-clinical factors can be patient-related, physician-related or practice-related. These factors include patient's preference/availability, patients' adherence, physician's availability, cost, geographical proximity, treatment centers' equipment condition/availability, treatment centers' cultural aspects, type of practice (private vs. public), availability of health resources [7–10]. However, there have not been many studies which have investigated the extent of the contribution of these factors in the treatment selection process itself. Thus the motivation of this study is two-fold:

1. To use both clinical and non-clinical features for localized and locally advanced PCa patients from multiple VHA centers and use machine learning methods to predict the treatment prescribed; such methods provide a statistical approach for calculating the weight (impact) of these clinical/non-clinical features from an empirical and retrospective point-of-view.
2. To perform quality assurance assessments across the different centers and verify if the prescribed treatments were in concordance with NCCN guidelines.

This study presents a comparative analysis of treatment prescription consistency across multiple VHA centers.

2 Materials and Methods

2.1 Data Source

The study cohort comprised of patients from the United States VHA. The VHA has 40 centers treating cancer patients with radiation therapy (RT) across the US. The patient cohort was generated as a radiation oncology practice assessment (ROPA) initiative, in which clinical data of the most recently treated 20 patients from each center was collected to assess the quality of the treatment. From here on, the generated data set is referred to as the VHA-ROPA data set. The study was approved by the clinical research ethics committee of the VHA.

2.2 Study Population

A maximum of 20 patients from 34 VHA RT centers are selected whose treatment was completed between 2010 to 2017. Patients were included if they had localized intermediate or high-risk PCa. Patients were excluded if they had previous malignancy, M1 disease, or lymph node involvement. The final cohort had 552 patients from the 34 centers with NCCN risk classified as Intermediate or High.

2.3 Definitions of Variables

Definitions of variables used in our study are as follows.

Clinical Variables: We considered pre-treatment PSA count, Gleason score (GS) [primary grade, secondary grade], Gleason Grade, Tumor staging [TNM-stage], NCCN risk group, performance status, and quality of life (QoL) measures. The values for these clinical variables were manually extracted from the consult notes.

Non-clinical Variable: We defined Center-ID as a non-clinical variable. It designates a unique ID to identify the VA radiation treatment center.

ADT Duration: NCCN guidelines define ADT duration as short term (ST) or long term (LT). ST duration is 4–6 months, and LT duration is 2–3 years. We further differentiated ADT duration based on intended and administered duration. The intended duration signifies whether it was mentioned in consult notes during treatment planning, whereas ADT administered duration is calculated based on the dates of ADT injection. Table 2 shows the ADT injection type and their effective period in months depending on the dose. Table 3 shows the distribution of ADT intended and administered duration. A third category of not otherwise specified (NOS) was used to indicate cases where ADT duration was not mentioned in consult as a treatment plan.

NCCN Concordance: We defined the treatment prescribed or administered is concordant with NCCN guidelines if they were as per the NCCN guidelines [12].

2.4 Model Selection

In this section, we present the details of feature-set selection, predictive models, machine learning algorithms, and model evaluation metrics.

We used machine learning algorithms as a statistical tool to find the association between the treatments and clinical and non-clinical features. We used a supervised machine learning algorithm called random forests (RF) [13], to find these associations. The RF algorithm, as the name suggests, is the ensemble of decision trees. The RF algorithm takes the features (clinical and non-clinical variables) and target (treatments) to build the individual trees with randomly selected uncorrelated features set. The majority target predicted from all trees becomes the final model prediction. The model also provides the significance

of features in classifying the targets. The significance of all features sums to 1, where higher the significance of a feature stronger is its association with the treatments, and lower significance indicates the weaker or no association.

Feature Selection. We created two feature sets using the clinical and non-clinical features to highlight the contribution of non-clinical features. The feature sets (FS) are as below

1. FS-1: Clinical features only.
2. FS-2: Clinical and Non-clinical (Center-ID) features.

Table 1. Details of the clinical factors in the VHA ROPA dataset and their frequency distribution, NOS: Not Otherwise Specified.

Data element	Count	Percentage
Total patients	552	
Centers	34	
Gleason score		
Primary + Secondary	549	99.50
3 + 3	17	3.00
3 + 4	219	39.67
4 + 3	128	23.18
3 + 5	18	3.26
4 + 4	79	14.31
5 + 3	2	0.36
4 + 5	61	11.05
5 + 4	19	3.44
5 + 5	3	0.54
NOS + NOS	2	0.36
PSA	549	99.50
T Stage	549	99.50
T1a - T2a	457	82.79
T2b - T2c	64	11.59
T3a -T3b	20	3.63
TX	1	0.18
NOS	7	1.26
Risk	545	98.73
Intermediate	304	55.60
High	241	44.40
Performance Status	523	94.75
Quality of Life	400	72.46
Treatment Prescribed	552	100.0
BT	24	3.07
BT-ADT	1	0.13
EBRT	132	20.23
EBRT-ADT	382	59.28
EBRT-BT	2	0.27
EBRT-BT-ADT	11	2.00

Table 2. ADT injection effective period based on the injection type and dose

ADT injection	Dose	Effective period
Leuprolide	3.75 mg	1 month
	7.50 mg	1 month
	22.50 mg	3 months
	30.00 mg	4 month
	45.00 mg	6 months
Goserelin/Zoladex	3.60 mg	1 month
	10.80 mg	3 months

Table 3. Treatment concordance with NCCN guidelines. ST: Short Term, LT: Long Term, and NS: Not Specified

NCCN risk	Treatment	ADT Duration	Intended	Administered	Concordance with NCCN
Intermediate	ADT-BT	NS	1	–	No
		LT	–	1	Yes
	BT		24	24	Yes
	EBRT		115	115	Yes
	EBRT-ADT	LT	8	15	No
		NS	11	–	No
		ST	142	146	Yes
	EBRT-ADT-BT	ST	1	1	Yes
	EBRT-BT		2	2	Yes
High	EBRT		17	17	No
	EBRT-ADT-BT	LT	9	4	Yes
		ST	1	6	Yes
	EBRT-ADT	LT	185	145	Yes
		NS	18	–	No
		ST	12	70	No

Statistical Models. VHA-ROPA dataset has patients treated with six different treatment methods (Table 1): BT, BT-ADT, EBRT, EBRT-ADT, EBRT-BT, and EBRT-BT-ADT. Based on the available treatment plans, we built the following two models.

1. Model-1: Initial Treatment (EBRT-ADT vs EBRT): This model predicts whether the patients will be treated with EBRT and ADT (EBRT-ADT), or EBRT alone. A total of 514 patients were treated with these two techniques, among which 382 patients were treated with EBRT-ADT, and 132 patients were treated with EBRT alone.
2. Model-2: ADT Duration (EBRT-ADT-ST vs EBRT-ADT-LT): This model predicts whether the ADT prescribed duration is *short term* or *long term*. Model-2 is further divided into 2 A and 2B. Where 2 A is EBRT with ADT intended duration and 2B is EBRT with ADT administered duration.

382 patients were treated with EBRT and ADT. Table 3 shows the treatment with intended and administered ADT duration.

These models will use machine learning techniques to serve the dual purpose of (i) creating a predictive model of initial treatment selection or ADT duration based on the clinical and non-clinical features and (ii) showing the statistical correlation of the individual features in terms of impacting the treatment selection or ADT duration process.

For each of the above mentioned models, the data set was split 80 : 20 ratio into training and test sets. We used random forest algorithm for building predictive models. Models are evaluated with macro-average precision, recall, and F1-Score.

3 Results

Here, we report the results from our proposed models. We observed that treatment non-concordance with NCCN guidelines can be due to the following two reasons:

Firstly, overall treatment may not be in concordance with NCCN guidelines. For example, high-risk cancer patients treated with EBRT alone are not in concordance with NCCN. Figure 1(A) & (B) shows the center wise all non-concordant treatment counts based on ADT intended duration (i.e., prescribed ADT) and ADT administered duration treatments respectively.

Secondly, overall treatment is in concordance with NCCN however the treatment guidelines may be partially not followed. For example, a high-risk cancer patient is treated with EBRT and ADT, but ADT duration is for short-term instead of long-term. Figure 2 (A) & (B) shows the partially non-concordant patient count of each center when patients are treated with EBRT and ADT; the counts are again based on the ADT intended and administered duration respectively.

Table 4 shows the Precision, Recall, F1-Score for model-1 (EBRT-ADT vs EBRT). The goal in this model was to classify patients with treatment intent being either EBRT or a combination of EBRT and ADT (EBRT-ADT). Model 1 with FS-2 performed better in all metrics when compared to FS-1. We observed that model-1 has F1-Score of 74% with FS-1 and 82% with FS-2. These results clearly demonstrate the significance of non-clinical feature (Center-ID) in improving the overall classification performance.

Table 4 also shows the results of model-2 (EBRT-ADT-ST vs EBRT-ADT-LT). Interestingly, in this case, FS-1 and FS-2 perform quite similarly with 94% F1-Score for models with ADT intent labels (with FS-1), while F1-Score is decreased when the ADT administered labels were used. This may mean that some external factors (not considered in our feature sets) play a role for causing the alteration from treatment from the prescribed to administered. Also, non-clinical feature (Center-ID) found to have no affect on predicting the ADT duration type as opposed to Model-1 (EBRT-ADT vs EBRT). Based on these

observations, we hypothesize that while centers do play a role in determining whether to prescribe ADT or not, they do not impact the actual ADT duration, in case it was administered; in other words, all centers follow similar practice in administering ADT for localized intermediate or high-risk PCa treatment.

We next evaluated the individual significance (i.e., contributions) of each of the features from FS-1 and FS-2 in our models; the feature significance were generated using the RF algorithm. Table 5 shows the feature importance of all features in all models.

For both FS-1 and FS-2, PSA and Risk consistently ranked as significant features in all the models. Specifically, for FS-1, PSA was ranked as the top feature for Models 1, 2B. For Model-2A (ADT duration intended), Risk was ranked as the top feature. This suggests that decisions on ST or LT ADT duration depend primarily on the Risk with PSA being a secondary feature of importance; these two features are primarily responsible in deciding the ADT course at the initial treatment level; however, decisions in altering the treatment intent (as captured in Model-2B with treatment administered) are impacted by the PSA and Total Gleason score (which is the third ranked feature in this model). For Model-1, PSA was ranked as the top feature with Risk as the secondary feature and T_stage as the third significant feature suggesting that decisions on treating the patients with EBRT alone or a combination of EBRT and ADT depend primarily on the Risk, PSA, and T_stage values.

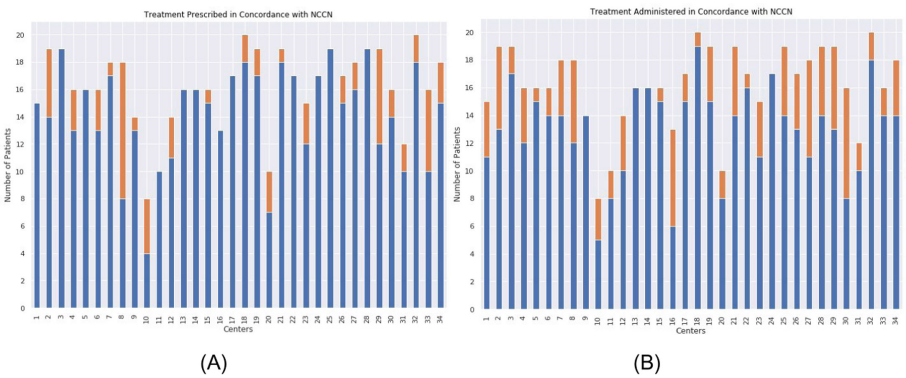

Fig. 1. Treatments in concordance with NCCN when all treatments are considered at each center. Blue: treatments in concordance, Orange: not in concordance. (A): Treatments prescribed at each center when ADT intent course is considered along with all other treatments; (B): Treatments administered at each center when ADT administered course is considered along with all other treatments (Color figure online)

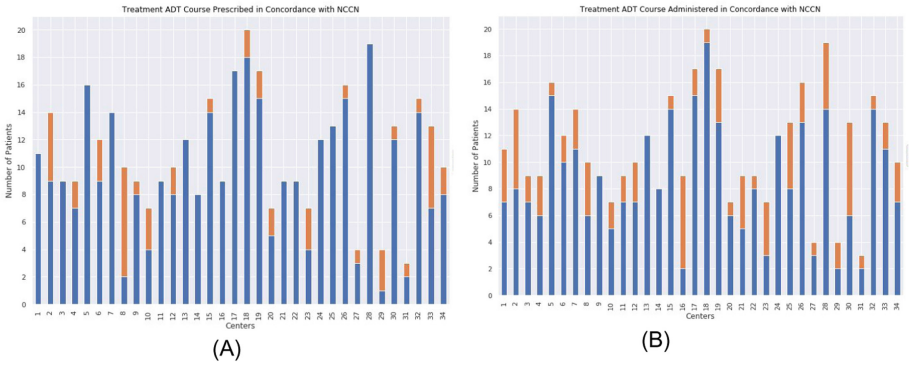

Fig. 2. Patients treated with EBRT and ADT (short term or long term). Blue: number of patients whose treatments are in concordance with NCCN, Orange: number of patients whose treatments are partially not in concordance with NCCN. (A): Treatments prescribed at each center when ADT intent course is considered (B): Treatments administered at each center when ADT administered course is considered (Color figure online)

Table 4. Precision, Recall, F1-Score, for Model-1:(EBRT-ADT vs. EBRT), Model-2: (EBRT-ADT-ST vs. EBRT-ADT-LT) 2A:ADT Intended Duration, 2B:ADT Administered Duration

Model	ADT duration	F-set	Precision	Recall	F1-score
Model 1	–	FS-1	0.75	0.73	**0.74**
		FS-2	0.82	0.82	0.82
Model 2A	Intended	FS-1	0.95	0.94	**0.94**
		FS-2	0.92	0.92	0.92
Model 2B	Administered	FS-1	0.74	0.73	**0.73**
		FS-2	0.72	0.71	0.71

When we considered FS-2, PSA and Risk show similar significance. In this case however, Center-ID plays a crucial role and shows up specifically as the top ranked feature in Model-1 (EBRT-ADT vs. EBRT); this reconfirms our earlier hypothesis that nonclinical factors like the center play a significant role in determining whether patients undergo ADT treatment or not. However, it's significance is much lower in Model-2A (EBRT-ADT-ST vs. EBRT-ADT-LT) with ADT intended duration. Center-ID also shows up as the fourth ranked feature in Model-2B (EBRT-ADT-ST vs. EBRT-ADT-LT) for ADT duration administered; thus we can hypothesize that nonclinical factors may have a role to play in altering the treatment intent.

Table 5. Feature importance in each model. Model 1:EBRT-ADT vs. EBRT, Model 2A: ADT course intended, Model 2B: ADT course Administered

FS	Features	Model 1	Model 2A ADT Intent	Model 2B ADT Administered
FS-1	PSA	**0.52**	0.14	**0.39**
	Risk	0.25	**0.79**	0.30
	Total GS	0.03	0.04	0.14
	T_stage	0.09	0.02	0.07
	Primary GS	0.06	0.01	0.05
	Secondary GS	0.05	0.01	0.05
FS-2	PSA	0.23	0.08	0.24
	Risk	0.28	**0.79**	**0.27**
	Total GS	0.02	0.03	0.19
	T_stage	0.07	0.02	0.05
	Primary GS	0.13	0.02	0.04
	Secondary GS	0.04	0.02	0.04
	Center-ID	**0.29**	0.06	0.17

4 Discussion

In this study, we present an exploratory analysis of localized or locally advanced PCa patients from 34 different VHA treatment centers. We compared the treatments prescribed against the NCCN guideline recommendations and observed that most of the treatment plans (prescribed or administered) matched with the NCCN guidelines. We built machine learning based models to predict the treatment plans for patients and also the likelihood of NCCN concordance of their treatment plans. We observed that PSA and Risk were the top-ranked features in determining the treatment plans for PCa patients.

Center-ID improved the performance of the model that predicts if the selected treatment plan has ADT or not; however, it did not impact the models that predict if the prescribed ADT duration was ST or LT. We also observed some variability in ADT treatments prescribed versus actual ADT treatments administered; the Center-ID, however, had a negligible role to play in such alterations and instead PSA and total Gleason score had significant roles to play in such decisions. We also noticed that the performance status measure had a negative effect on model predictability and hence we dropped it from our feature set. We feel that performance status will be a critical feature in treatment outcome predictions in the future, currently which is outside the scope of this work. Additionally, Risk showed up as the primary feature in predicting ST vs. LT ADT duration. We also observed that the primary reason for treatment plans to be non-concordant with NCCN is due to the ADT course duration not following the guidelines.

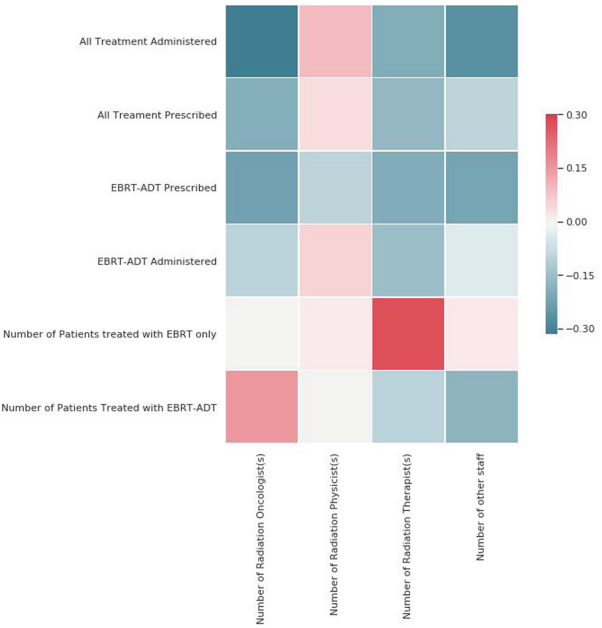

Fig. 3. Pearson correlation between center details (Number of radiation oncologists, radiation physicists, radiation therapists and Other staff) vs. treatment non-concordance (number of non-concordant patients considering all treatments prescribed, all treatments administered, EBRT-ADT prescribed, and EBRT-ADT administered), and treatment selections (number of patients treated with EBRT-only or with EBRT-ADT).

To better understand the impact of non-clinical features like Center-ID in predicting whether the treatment plans were concordant with NCCN guidelines or not, we computed the Pearson correlation between center-specific details (such as staffing details) and the number of non-concordant patients undergoing EBRT-ADT or EBRT-only treatments (either prescribed or administered). Figure 3 shows a small negative correlation between staff details and non-concordance; specifically fewer number of radiation oncologists or radiation therapists led to higher number of non-concordant patients in all cases; while the number of radiation physicists or other staff members did not show any worthwhile correlation. This can be potentially attributed to higher workloads and scheduling conflicts for radiation oncologists/therapists leading to non-adherence to ADT treatment duration requirements from NCCN.

Figure 3 also shows the impact of Center-ID in predicting whether a patient will undergo EBRT-only or EBRT-ADT treatment. We can observe a strong positive correlation between EBRT-only treatment selection and the number of radiation therapists and a less pronounced positive correlation between EBRT-ADT treatment selection and the number of radiation oncologists. While this

positive correlation was expected as more radiation oncologists or therapists will lead to more patients being treated with EBRT-ADT or EBRT-only respectively, it is however not clear why the number of radiation physicists or other staff members correlates poorly with these treatment types. It can arise from the bias of the selected patient cohort.

Our findings corroborate previous studies showing the impact of non-clinical factors on prostate cancer treatment patterns. For example, a recent study done on SEERs data reported that prostate cancer treatment patterns were not strictly influenced by outcomes data and varied significantly by patient age, insurance status, financial model, regional bias and socioeconomic factors [11]. An earlier survey on factors influencing treatment selection for localized prostate cancer suggests that recognizing the beliefs that patients hold about their cancer and its treatment could guide the counseling of patients about the treatments available to them and ultimately, help patients make more informed decisions about both their treatments and subsequent adjustments [14]. Prior work on NCCN non-concordance was conducted on elderly patients with high-risk prostate cancer from SEERs was reported that NCCN concordance in elderly patients with aggressive prostate cancer is low [15]. These findings underline the importance of non-clinical factors in treatment decisions, however, reported results were based on single center data; hence they could not identify the center-specific bias as reported in this paper. However, such non-clinical factors can vary appreciably between multiple centers and result in the bias; our future work will include such non-clinical features from the VHA centers to identify the proper reasons behind such center-specific bias.

The VHA ROPA dataset was extracted from recently treated patients having very little to no follow-up data for oncological outcome analysis. Similar predictive models will be built in the future for treatment outcome analysis considering a patient cohort that was treated at earlier dates. Additionally, the ADT duration is generally dependent on the type of drugs used. In this study, we calculated ADT administered duration based on the ADT injection dates; the calculated ADT duration may slightly change considering the ADT injection types. Finally, our study depicts the importance of non-clinical factors, such as Center-ID, in predictive models for treatment selection or concordance to NCCN guidelines. In the future, we will investigate the effects of other types of non-clinical factors (not limited to staffing) pertinent to the specific VHA centers considered here.

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