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Index tumor volume on MRI as a predictor of clinical and pathologic outcomes following radical prostatectomy

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Abstract

Purpose Index tumor volume (ITV) measured on radical prostatectomy (RP) specimens has been shown to be associated with adverse pathologic and oncologic outcomes. We evaluate the value of ITV calculated from prostate multiparametric MRI (mpMRI) in predicting adverse clinical and pathologic outcomes.

Materials and methods Data from a prospectively maintained, single-institution database were analyzed for patients who underwent mpMRI prior to RP (2007–2016). Index tumor was defined as a T2-visible lesion with the longest diameter. Adverse pathologic outcomes were extraprostatic extension (EPE), lymph node invasion (LNI), seminal vesicle invasion (SVI), and positive margins (PM). Logistic and Cox proportional hazard regression were used to assess associations with adverse pathology and biochemical recurrence (BCR), respectively.

Results Of the 455 patients included, EPE, LNI, SVI and PM were present in 23.5%, 6.2%, 5.5% and 15.7% patients, respectively. Patients with adverse pathologic outcomes had larger median ITV. ITV was found to be an independent predictor of EPE (OR 1.22, $p=0.010$), LNI (OR 1.39, $p=0.001$), and SVI (OR 1.28, $p=0.009$), but not PM (OR 1.03, $p=0.522$). Combination of ITV and PSA was found to have predictive ability comparable to that of modified Partin tables (EPE:ITV + $PSA_{AUC}=0.71$ vs. $Partin_{AUC}=0.71$; LNI:ITV + $PSA_{AUC}=0.92$ vs. $Partin_{AUC}=0.90$, SVI:ITV + $PSA_{AUC}=0.78$ vs. $Partin_{AUC}=0.82$). 5 year BCR-free survival (median follow-up 24.9 months) was higher for patients with ITV < 2 cc (84.1% vs. 58.5%, $p=0.001$). However, ITV was not found to be an independent predictor of BCR (HR 1.69, $p=0.130$).

Conclusions We demonstrate that ITV measured on mpMRI is a predictor of adverse pathologic and clinical outcomes and can aid in preoperative risk assessment.

Keywords Biomarkers · Magnetic resonance imaging · Prostatic neoplasms · Tumor volume · PSA

Introduction

Index lesion tumor volume (ITV), measured on radical prostatectomy (RP) whole-mount specimen, has been demonstrated to correlate with adverse clinical and pathologic outcomes. A study by Knoedler et al. found that ITV was significantly associated with systemic progression, prostate cancer (PCa)-specific mortality, and all-cause mortality and that the incorporation of ITV into their model significantly increased its predictive ability of all-cause mortality [1].

However, ITV is difficult to measure on pathology accurately, and since there is currently no preoperative surrogate, it cannot be used for preoperative decision making.

Recent advances in MRI technology have rendered it a powerful tool in directing prostate biopsies, with a sensitivity and specificity of 90% and 88% for clinically significant

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cancers [2]. Prior research has already established that tumor volume (TV) can be measured on MRI [3, 4]. We hypothesized that ITV measured on preoperative MRI could play a role in the prediction of extraprostatic extension (EPE), seminal vesicle invasion (SVI), lymph node invasion (LNI), positive surgical margins (PM), and biochemical recurrence (BCR).

In this study, we analyze the novel approach of measuring ITV on preoperative multiparametric magnetic resonance imaging (mpMRI) for use as a predictive variable.

Materials and methods

Patient selection

Patients undergoing RP for biopsy-proven PCa under various Institutional Review Board-approved protocols were included in the study. Between May' 07 and Jan' 16, 499 patients received RP for localized PCa at the National Cancer Institute following mpMRI. Of these, 22 patients were excluded due to lack of MRI-visible lesions on preoperative mpMRI, and an additional 22 were excluded due to prior radiotherapy or androgen deprivation therapy.

Imaging protocol

All patients underwent a diagnostic mpMRIs of the prostate on a 3.0 T (Achieva, Philips Healthcare) scanner, as previously described [5]. Sequences obtained included triplanar T2-weighted, axial dynamic contrast-enhanced (DCE), axial diffusion weighted imaging (DWI) with apparent diffusion coefficient (ADC) mapping with or without MRI spectroscopy. Lesions assigned internal NIH MRI suspicion scores of low, moderate, or high PIRADS scores were not analyzed, as they were not in use throughout our study period, and a large proportion of our patients did not have PIRADS score calculated.

ITV assessment on MRI

Index lesion was defined as the largest lesion visible on T2W MRI. Volume was calculated using the ellipsoid formula with the longest diameter as the length, perpendicular diameter as the width, and slice count multiplied by 0.3 mm/slice as the depth of the lesion.

Data collection

Demographic, clinical, and pathologic data were obtained from a prospectively maintained database. All RP procedures were performed by a single surgeon (P.A.P.) using a robotic-assisted laparoscopic technique with concomitant lymphadenectomy. All surgical specimens were processed using the whole-mount technique for EPE, SVI, LNI and PM.

Predicted probabilities of PM, EPE, and LNI were obtained using modified Partin tables [6]. Patients were monitored post-RP with periodic PSA testing. BCR was defined as two consecutive PSA values ≥ 0.2 ng/ml, a single PSA value ≥ 0.4 ng/ml, or receipt of salvage therapy [7].

Statistical analysis

Statistical analysis was performed using SPSS ver21 (Chicago, IL, USA). Pearson Chi-square and Mann–Whitney tests were used to compare the differences between categorical and continuous variables, respectively. Logistic regression analysis was used to assess associations of clinical, imaging, and histopathological variables with adverse pathologic features. Multicollinearity among the predictor variables was evaluated by calculating the variance inflation factors. Significant collinearity among the predictor variables was ruled out if the variance inflation factor of individual predictors was below 10. Receiver-operating characteristic (ROC) curves were used to characterize and compare the predictive ability of ITV with that of Partin tables for PM, EPE, and LN. On BCR analysis, additional two patients were excluded due to persistently elevated PSA after RP, and three were excluded due to distant metastasis at the time of RP. For BCR analysis, ITV was analyzed as a binary variable (<2.0 cc and ≥ 2.0 cc), as analyzed by prior studies [8, 9]. Kaplan–Meier curves were created to determine BCR-free survival, and the log-rank test was used to compare survival between cohorts. Cox proportional hazard analysis was used to analyze predictors of BCR.

Results

Patient demographics

Among the patients considered for eligibility, 455 patients met inclusion criteria. Patient demographics, clinical, imaging and biopsy data are depicted in Table 1. In our cohort, median age and PSA were 60 years (IQR 10) and 6.2 ng/ml (IQR 5.7), and 23.3% were "high-risk" (Gleason 8–10) on biopsy. Median ITV was 0.836 cc (IQR 1.308). Example is in Fig. 1.

EPE analysis

One hundred and two (22.8%) of 455 patients had EPE on pathology. Median ITV was significantly larger in the EPE cohort vs non-EPE: (1.302 cc vs 0.754 cc). In addition, patients with EPE had higher median PSA (8.9 ng/

Table 1 Descriptive characteristics of patients treated with RP from May 2007 to January 2016

Patients, *n* (%)	455
Age (years), median (IQR)	60 (10)
PSA (ng/ml), median (IQR)	6.2 (5.7)
Race, *n* (%)	
White	326 (71.6)
Black	94 (20.7)
Other	35 (7.7)
Clinical stage	
>ct1c	43 (9.6)
Prostate volume on MRI, median (IQR)	37 (19)
NIH score, *n* (%)	
Moderate to high	392 (90.1)
Gleason score, *n* (%)	
<8	349 (76.7)
≥8	106 (23.3)
Tumor volume (cm^3), median (IQR)	0.836 (1.308)
ECE, *n* (%)	102 (22.8)
LNI, *n* (%)	25 (5.5)
SVI, *n* (%)	28 (6.2)
PM, *n* (%)	71 (15.7)

PSA prostate-specific antigen, *ECE* extracapsular extension, *LNI* lymph node invasion, *SVI* seminal vesicle invasion, *PM* positive margins, *BCR* biochemical recurrence

ml vs 5.7 ng/ml, $p<0.001$), and a higher proportion of these patients were clinical stage > T1c (19.0% vs 6.8%, $p<0.001$) and biopsy Gleason Score (bGS) ≥ 8 (45.1% vs 16.8%, $p<0.001$). Multivariate analysis showed that ITV (Odds Ratio (OR) 1.22, $p=0.010$), PSA ($p=0.003$), clinical stage > T1c ($p=0.001$), and bGS ($p=0.001$) were independent predictors of EPE (Table 2).

ROC curves were drawn using the predicted probabilities of ITV and Partin tables for EPE (Fig. 2). The area under the curves (AUCs) for ITV (0.66, $p=0.142$), ITV and PSA combined (0.71, $p=0.912$) and modified Partin tables (0.71) in predicting EPE were comparable.

LNI analysis

Twenty-five (5.5%) patients had LNI, with a median ITV over three times higher than that of the non-LNI cohort (19.5 ng/ml vs 5.9 ng/ml, $p<0.001$). As expected, PSA, > cT1c, and bGS ≥ 8 were significantly higher in the LNI cohort ($p<0.001$, $p=0.001$, and $p<0.001$, respectively). On multivariate logistic regression analysis, ITV (OR 1.39, $p=0.001$) and PSA $p=0.001$) and clinical stage > T1c ($p=0.009$) were found to be independent predictors of LNI (Table 2).

As with EPE, the AUC of ITV (0.81, $p=0.151$) and ITV with PSA (0.92, $p=0.614$) were comparable to that of Partin tables (0.90).

SVI analysis

Patients with SVI had more than double the median ITV of patients without SVI (1.902 cc vs 0.801 cc, $p<0.001$). In the case of SVI, only ITV (OR 1.28, $p=0.009$) and bGS ≥ 8 ($p<0.001$) were independent predictors on multivariate analysis (Table 2).

Again, Partin tables had comparable AUC (0.82) to both ITV (0.75, $p=0.283$) and ITV combined with PSA (0.78, $p=0.419$).

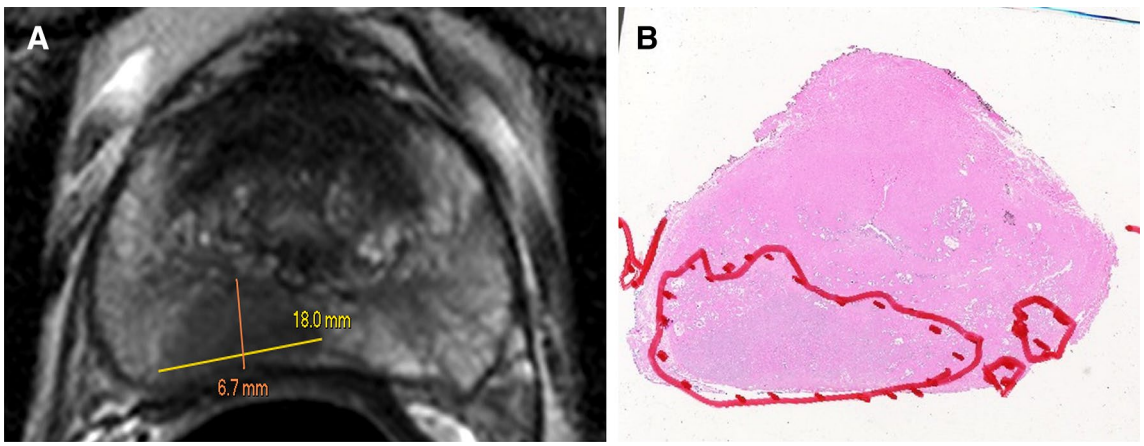

Fig. 1 57 y/o male with PSA 11.47 ng/ml, Gleason 4+4 on biopsy, NIH MRI score = high, and radical prostatectomy on 6/14/2013. On pathology, the patient had Gleason 4+4, positive margins. Index tumor volume was calculated from T2W MRI by the ellipsoid formula, using slice count × 0.3 mm/slice as an estimation for tumor depth

Table 2 Multivariate logistic regression model predicting pathologic outcomes on final pathology after RP

	Extracapsular extension			Positive lymph nodes			Seminal vesicle invasion			Positive margins		
	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value
ITV (cc)	1.208	1.041–1.401	0.013	1.405	1.145–1.725	0.001	1.278	1.067–1.531	0.008	1.030	0.930–1.140	0.573
Age (years)	0.998	0.963–1.034	0.893	1.023	0.949–1.103	0.549	1.016	0.951–1.086	0.641	0.980	0.944–1.018	0.295
PSA (ng/ml)	1.046	1.017–1.076	0.001	1.057	1.019–1.097	0.003	1.034	0.365–2.931	0.949	1.035	1.009–1.061	0.008
Race	0.612	0.338–1.106	0.104	1.530	0.509–4.602	0.449	1.034	0.365–2.931	0.058	1.078	0.602–1.932	0.801
Clinical stage > ct1c	3.158	1.525–6.539	0.002	5.298	1.586–17.696	0.007	2.912	0.963–8.807	0.058	1.035	0.420–2.547	0.941
Gleason ≥ 8	2.552	1.465–4.447	0.001	2.498	0.874–7.140	0.088	7.458	2.778–20.025	< 0.001	1.777	0.953–3.313	0.070

RP radical prostatectomy, *OR* odds ratio, *CI* confidence interval, *ITV* index tumor volume, *PSA* prostate-specific antigen, *NIH-MSS* NIH MRI suspicion score

PM analysis

Seventy-one patients (15.7%) in our analysis had PM, of whom 45.7% had EPE. Patients with PM had slightly higher median ITV. (0.977 cc vs 0.807 cc, $p = 0.046$). However, unlike with the other adverse pathologic parameters, ITV was not found to be an independent predictor of PM in our cohort (Table 2).

BCR analysis

In total, 49 patients (10.9%) experienced BCR during the median follow-up time of 24.9 months (IQR 28.6). Patients with ITV ≥ 2 cc had a higher incidence of BCR (18.9% vs 8.7%, $p = 0.005$). Estimated 5-year BCR-free survival of the cohort was 78.3% (84.1% for ITV < 2.0 cc, 58.5% for ITV ≥ 2.0 cc, log-rank = 0.001) (Fig. 3). On Cox regression, age ($p < 0.001$), PSA ($p = 0.002$), > cT1c ($p = 0.049$), and Gleason 8–10 on biopsy ($p < 0.001$) were found to be independent predictors of BCR (Table 3). Although ITV was predictive on univariate analysis (HR 2.70, $p = 0.001$), it was not found to be an independent predictor (HR 1.69, $p = 0.130$).

Discussion

The relationship between ITV, measured on post-prostatectomy pathology, and adverse pathologic outcomes has been well established. To the best of our knowledge, this is the first study to evaluate the predictive capacity of preoperative ITV assessment using prostate mpMRI. Although there are several algorithms in use for PCa risk-stratification, there is still a great deal of uncertainty in the prediction of patient outcomes [10]. This is particularly true in intermediate-risk cancers, which often vary widely in rates of adverse pathology and cancer recurrence [11]. We believe that ITV on MRI has the potential to help differentiate patients at higher clinical and pathologic risk.

EPE is a relatively common adverse outcome, with rates of EPE ranging from 10 to 15% in low-risk cancers to as high as 45–50% in higher risk cancers [12]. The ability to predict EPE is valuable in preoperative planning, as the presence or absence of EPE may influence patient selection for nerve-sparing procedures. Gleason score on biopsy, PSA, and clinical stage have all been established as independent predictors of EPE, which is consistent with our results [13, 14]. We found that ITV on MRI was an independent predictor of EPE. We also found that ITV and PSA combined was a comparable predictor of EPE when juxtaposed with Partin tables, one of the most frequently used tools to predict pathologic outcomes. The prognostic value of ITV was previously demonstrated by Chun et al., who showed that both

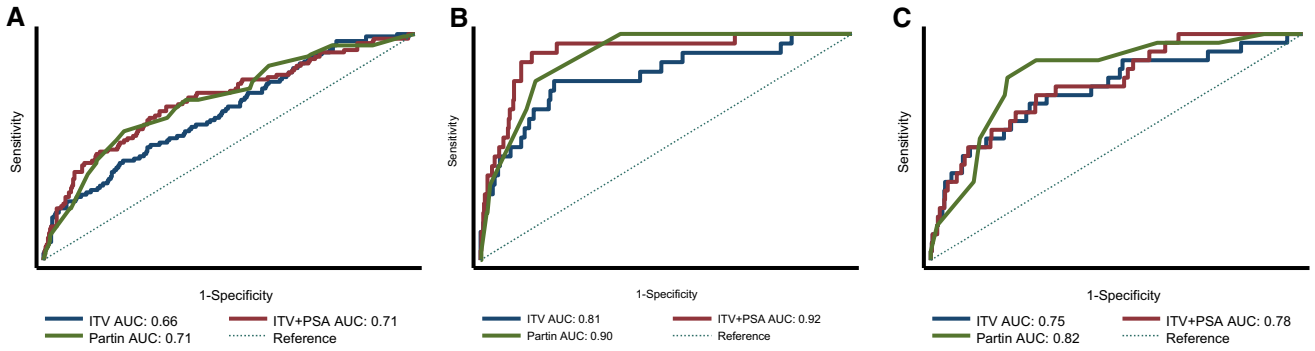

Fig. 2 Receiver-operating curves demonstrating predictive abilities of Index tumor volume (ITV), modified Partin tables, and ITV + PSA for **a** extraprostatic extension, **b** lymph node invasion, and **c** seminal vesicle invasion on final pathology

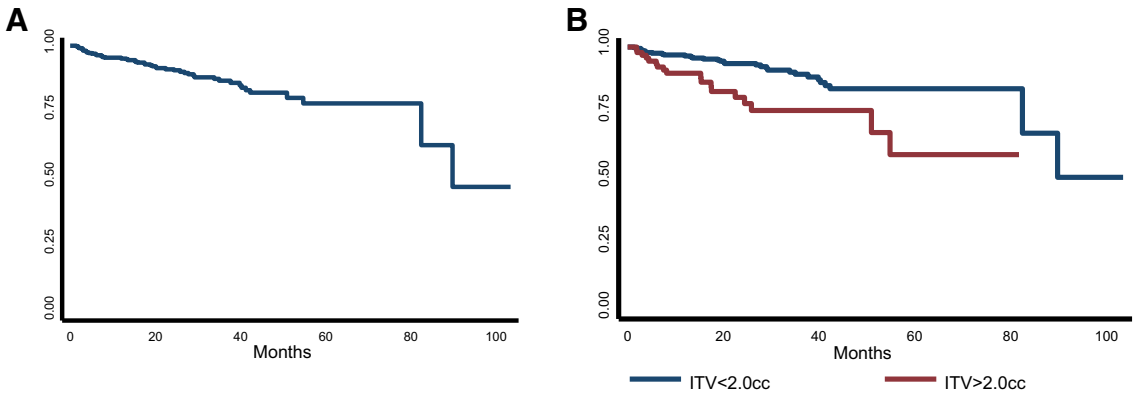

Fig. 3 Kaplan–Meier plots demonstrating overall survival for the entire cohort (median survival 78.3% at 5 years) and comparing survival for Index tumor volume (ITV) ≥ 2 cc vs ITV < 2 cc. 5-year biochemical recurrence-free survival was 58.5% for ITV ≥ 2 cc and 84.1% for ITV < 2, log-rank = 0.001

Table 3 Cox regression model predicting BCR after RP

	HR	95% CI	*p* value
ITV ≥ 2 cc	1.685	0.857–3.315	0.130
Age (years)	0.925	0.885–0.966	< 0.001
PSA (ng/ml)	1.034	1.012–1.056	0.002
Race	1.309	0.702–2.441	0.397
Clinical Stage > ct1c	2.111	1.004–4.439	0.049
Gleason ≥ 8	4.043	2.121–7.709	< 0.001

BCR biochemical recurrence, *RP* radical prostatectomy, *HR* hazard ratio, *CI* confidence interval, *ITV* index tumor volume, *PSA* prostate-specific antigen

pathologic total TV and percentage of high-grade TV were predictors of EPE [15]. As index lesions tend to be higher grade tumors, our results are aligned with their study. EPE itself can also be measured on MRI; however, its detection continues to present a challenge, and a study by Kongnyuy et al. found the sensitivity and specificity of mpMRI for EPE to be only 56% and 72%, respectively [16]. This is because EPE can be quite subtle and is often a microscopic diagnosis. Therefore, a surrogate indicator of EPE may be needed. ITV thus represents an additional, more-easily-measured preoperative predictor of EPE than direct visualization on MRI.

Prediction of LNI and SVI is also important in preoperative planning, as patients with LNI and SVI tend to have poorer outcomes than their counterparts [17]. The sensitivity of preoperative mpMRI for detecting SVI is approximately 40%, and it is even less effective for the detection of LNI, particularly in nodes < 5 mm [17, 18]. mpMRI is limited to detection of enlarged lymph nodes which often does not occur in PCa. In particular, detection of LNI is applicable when determining the extent of pelvic lymph node dissection (PLND) required, which is recommended in the majority of patients who undergo RP, based on nomogram-calculated preoperative risk of LNI. In our analysis, ITV on MRI was an independent predictor of LNI and SVI and produced results comparable to Partin tables. This is consistent with data from Knoedler et al. which found that ITV on pathology was an independent predictor of both LNI and SVI [1].

Of note, there were no patients with Gleason 6 disease who were found to have LNI on pathology, which may contribute to the argument against LN dissection in a lower risk population. As the current predictive capacity for SVI and LNI is still evolving, ITV on MRI may provide another preoperative metric by which to determine the risk of LNI and SVI and, therefore, aid in preoperative decision making.

Of particular interest is the relationship between ITV and PM. The presence of positive surgical margins is an established independent predictor of BCR [19]. In some studies, it has also been associated with metastatic progression [20] and PCa-specific mortality [21]. The location and size of prostate tumors on MRI have been increasingly incorporated into operative decision making, allowing surgeons to balance preservation of the bladder neck and neurovascular bundles with adequate cancer control. However, even with the superior imaging, the rate of PM can be as high as 30–50% in high-stage cancers, PM EPE [22]. In our analysis, preoperative PSA was the only independent predictor of PM. This is consistent with a meta-analysis by Novara et al., which demonstrated that although PSA and pathology GS were generally found to be predictive of PM, bGS was not a predictor [23]. Several analyses have also demonstrated an association between TV measured on pathology and PM following RP, although we did not find this to be the case [1, 15]. Chun et al. suggested that total TV, rather than high-grade TV, was predictive of PM [15]. They found that total pathologic tumor volume significantly increased the predictive accuracy of their PM model, while high-grade tumor volume had no effect. As this study, in measuring index lesion, focuses on higher grade tumors, it is possible that future studies will find total TV measured on MRI to be an independent predictor of PM.

Biochemical recurrence is a commonly accepted intermediate metric for the success or failure of PCa treatment. Standard preoperative nomograms use PSA, clinical stage, and bGS to predict the likelihood of BCR. Recently, the use of mpMRI has been considered as an additional predictor of BCR [24]. As an easily measured variable, ITV would be a helpful addition to predictive models of BCR. Numerous studies have determined a correlation between TV on pathology and BCR. A meta-analysis by Meng et al. found that both TV and % TV were independent predictors of BCR [25]. However, in our analysis, we did not find ITV on MRI to be an independent predictor of BCR, although patients with ITV < 2 cc had a significantly longer BCR-free survival compared to those with larger ITVs. Due to a small number of events, our BCR analysis may be underpowered to identify ITV as an independent predictor. It is possible that future studies analyzing a greater number of patients with BCR will reveal an association with ITV.

The additional prognostic information obtained from ITV on MRI may also provide valuable insight while planning prostate interventions. ITV in combination with other clinical predictors can help in risk-stratifying patients with intermediate and high-risk cancer to determine which patients would be suitable candidates for focal therapy and RP, respectively, thus achieving more accurate selection of focal candidates. However, to utilize ITV in this fashion, larger studies will be needed to validate this preoperative variable and to find ITV cutoffs for appropriately risk-stratifying PCa patients.

We recognize the limitations inherent to retrospective design study. All results are from a single institution with a higher risk patient population (26.4% D'Amico high risk), compared to 4–15% in other contemporary cohorts [26, 27]. Therefore, the results cannot necessarily be generalized to populations with a larger percentage of lower risk cancers, although as non-operative interventions such as active surveillance gain traction [28], there may be a trend towards higher risk cancer at the time of prostatectomy. The other limitation is the lack of PIRADS scores for the majority of our patients, and our inability to analyze this more standardized MRI metric. There were also a relatively small number of patients with poor outcomes. This might have reduced the power of the study and may have rendered it more difficult to determine statistical associations. In addition, as our study focused on the tumor volume of the index lesion specifically, we cannot comment on the role that secondary tumor volumes play in the prediction of outcomes. As PCa has a tendency to be multifocal in nature, it is possible that the sum of TV from all lesions could have additional predictive ability.

There is also a concern that MRI falls short for the precise estimation of prostate TV. Although a recent study by Turkbey et al. indicated that MRI may be adequate for accurate estimation of ITV specifically [3]. Finally, as we did not have a second dataset available on which to perform an external validation of the predictive ability of ITV and ITV + PSA, it will be necessary to validate this model in other large cohorts.

We demonstrate that ITV measured on preoperative MRI is a novel factor that has comparable predictive ability for pathologic outcomes when compared to pathologic ITV. We believe that the strength of the association between ITV and EPE, SVI, and LNI merits further investigation as a potential predictive factor for consideration prior to surgery and radiation therapy. If validated, ITV on MRI may provide an easily obtained biomarker for nomogram prediction of PCa staging and surgical planning.

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Compliance with ethical standards

Conflict of interest The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript. NIH, Philips Healthcare have a cooperative research, NIH and Philips share intellectual property in the field and development agreement.

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