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A Multi-disciplinary Approach to Optimize Primary Prostate Cancer Biobanking

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Abstract

Purpose: Biobanking tissue of high quality and fidelity is imperative for cancer genomics research. Since it is a challenging process, we sought to develop a protocol that improves the fidelity and quantity of biobanked primary prostate cancer (PCa) tissue.

Materials and Methods: We conducted a pilot study evaluating pathologic concordance of biobanked tissue and the radical prostatectomy specimen using either standard protocol (SP) vs next-generation protocol (NGP).

Results: There were no significant differences in clinical and pathologic characteristics (age, BMI, pre-operative PSA, prostate weight, race, final prostatectomy Gleason score, or pathologic tumor and nodal stages) between the two protocol arms. Utilization of the NGP compared to the SP resulted in a significantly higher rate of pathologic concordance between the biobanked and RP specimens (61.8% vs 37.9%, p=0.0231) as well as a nearly two-fold increase in the amount of biobanked tumor tissue (330 mm^3 vs 174 mm^3, p<0.001). When looking at relevant clinical and

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pathologic characteristics, NGP was associated with pathologic concordance on both univariate [OR 2.65 (95% CI 1.13 – 6.21), p = 0.025] and multivariate analysis [OR 3.11 (95% CI 1.09 – 8.88), p = 0.034].

Conclusions: Our study validates the NGP as a multi-disciplinary approach for improving the fidelity and amount of biobanked primary PCa tissue for future studies. Given the challenges to banking tissue from primary PCa as tumors are often difficult to visualize grossly and are frequently multifocal, optimizing the fidelity and volume of biobanked tissue is an important step forward to improve the generalizability of genomic data as we move towards precision medicine.

Keywords

prostate cancer; biobank; pathology; radical prostatectomy; gross pathology; Gleason score; tumor volume; fresh frozen tissue; molecular subtype; TCGA

1. Introduction

In order to define the genomic landscape of prostate cancer (PCa), investigators have relied on the collection of large tissue biobanks through multi-institutional collaborations, such as The Cancer Genome Atlas (TCGA).[1] We have previously published our approach on how to optimize biobanking based on our experience in these consortiums.[2, 3] However, compared to other malignancies (e.g. lung, pancreas, breast, colorectal), biobanking primary PCa is a unique challenge due to the lack of visualizable lesions on gross pathology, the multifocal nature of the disease, and significant intra- and inter-focal genomic heterogeneity that confounds clinical research.[4, 5]

This challenge can be illustrated by the specimens biobanked through the TCGA consortium, where only 33.0% of the frozen specimens had their Gleason score concordant with the final clinical Gleason score based on the radical prostatectomy specimen.[1] International efforts to standardize biobanking [6, 7] and guidelines released by the National Cancer Institute[8] address ischemia time, optimal temperatures, use of buffers, and methods to optimize downstream yields of DNA, RNA and protein. However, the need to improve procurement of primary PCa tissue for biobanking that accurately reflects the patients' disease has not been addressed. We conducted a pilot trial utilizing clinical correlates with real-time tissue scrapings to target tissue from radical prostatectomy (RP) specimens for biobanking in order to improve the fidelity and quantity of primary PCa tissue in the Weill Cornell Medicine Specialized Program of Research Excellence (SPORE) biobank.

2. Materials and Methods

2.1 Patient Selection

Specimens from patients who underwent RP for PCa performed by two high-volume academic urologic oncologic surgeons (DSS, CEB) were prospectively collected from February 2019 to January 2021. We estimated that with enrollment of at least 27 patients in the next-generation protocol (NGP) cohort, the study would have 80% power at α=0.05 to detect an improvement from the 33% concordance rate seen in the TCGA consortium to an estimated 70% concordance rate with our protocol.

At the time of pre-operative visit, patients scheduled for RP were offered the opportunity to contribute to our tissue biobank for research as part of a protocol approved by the Weill Cornell Medicine Institutional Review Board. After enrolling 100 consecutive patients, we were able to process 34 patients using our NGP while 66 patients were processed using the standard protocol (SP).

2.2 Weill Cornell Medicine Next-Generation Biobank Protocol

The workflow utilized in our pilot trial is described in detail in Figure 1. In summary, patients scheduled for surgery were discussed the week prior by a multi-disciplinary team (including representatives from the Pathology and Urology departments as well as the Meyer Cancer Center). This team determined which cases are most suitable for biobanking and ongoing experiments requiring fresh tissue, such as 3D organoid cultures or single-cell sequencing analyses. Relevant clinical information including age, pre-operative prostate-specific antigen (PSA), biopsy Gleason score (GS) with % core involvement, location of positive cores, adverse pathologic features, prostate multi-parametric magnetic resonance imaging (MRI), and any genomic tests (e.g. Decipher, Oncotype Dx) were discussed to coordinate targeted tissue sampling and biobanking priorities. On the day of surgery, the specimen was retrieved by a member from the biobank team immediately after extraction and processed by our institutional biorepository's pathologists' assistant (CL).

For patients in both protocols, the specimen was initially serially sectioned from apex to base (3 to 5 mm slices), and the apical side of each section was placed face-down. In the SP, a representative cross-sectional slice was submitted for biobanking as per published protocol[2,3]. For NGP, a #22 blade was used to collect scrapings from areas suspected to be malignant based on multidisciplinary review, and the scrapings were smeared onto slides and stained using standard hematoxylin and eosin (H&E) staining protocol. A genitourinary pathologist (JJT, FK, JMM, BDR) reviewed the scrape slides to confirm presence of malignant cells and determine which cross sections were frozen for biobanking and/or punched for fresh tissue experiments. The remaining non-biobanked RP tissue was entirely submitted for routine clinical processing in both SP and NGP.

All biobanked tissue had H&E slides cut from the frozen tissue blocks for histopathologic evaluation and review at the time of final diagnosis to ensure clinical care (e.g. Gleason score, stage, margin status) was not compromised by either of the biobank protocols. Biobank frozen tissue slides were re-reviewed by a single genitourinary pathologist (BDR) for Gleason score and tumor volume, which was calculated using a modified "grid method" that removed the correction for formalin fixation since these were fresh frozen tissue samples.[9] The biobank slides were also compared to the routine formalin-fixed and paraffin-embedded clinical slides for correlation with dominant and secondary tumor nodule Gleason scores and locations.

2.3 Statistical Analysis

Clinical and pathologic data were extracted from patient charts and pathology reports. Tumor volume was categorized as low (<5% of total prostate volume), intermediate (5 to

15%), or high (>15%). Biobank GS was compared to final pathology reports to determine pathologic concordance.

Clinical data from the TCGA PCa cohort was extracted from the publicly available resource (https://www.cancer.gov/tcga) in order to determine concordance between biobank tissue and prostatectomy Gleason score. Differences in patient characteristics were assessed using nonparametric t-test for continuous variables (age, PSA) and chi-square test for categorical variables (Gleason score, molecular subtype) with $p<0.05$ set as level of statistical significance.

Differences in patient characteristics recruited for the pilot trial were analyzed by non-parametric t-test for continuous variables [age, body mass index (BMI), PSA, prostate weight] and biobank tumor volume and Fisher's exact test for categorical variables (race, GS, molecular subtype) and rate of concordance. Binary outcome univariate and multivariate logistic regression analyses were performed to assess the independent effect of clinical and pathologic variables on odds for pathologic concordance using IBM SPSS Statistics version 27 (Armonk, NY: IBM Corp).

3. Results

3.1 TCGA Biobank Pathologic Concordance

Of the 333 primary PCa specimens biobanked through TCGA, 279 (84%) reported Gleason score and 92 (33.0%) of these had Gleason score concordant with the final pathologic Gleason score on RP [1]. Although there were no differences in age, PSA, race, or molecular subtype, patients with discordant samples were more likely to have Gleason pattern 5 disease ($p<0.001$) (Table 1). When examining patients with Gleason score 9 or 10 (n=76) at final prostatectomy pathology, we discovered that 69.7% (n=53) did not capture any Gleason score pattern 5 disease in the biobank sample used for molecular analysis.

3.2 Weill Cornell Medicine Next Generation Biobank Protocol

The SP (n=66) and NGP (n=34) cohorts had similar age, BMI, pre-operative PSA, prostate weight, race, final GS, tumor volume, and pathologic tumor and nodal stages (Table 2). Patients in the NGP cohort had significantly higher rate of pathologic GS concordance between the biobanked and RP specimen compared to patients in the SP cohort (61.8% vs. 37.9%, $p=0.0231$) and the amount of biobanked dominant tumor nodule was significantly higher in the NGP as compared to the SP group of patients (330 mm^3 vs 174 mm^3, $p<0.001$) (Table 3). Figure 2A shows an SP sample where biobanked tissue did not capture the patient's Gleason 4+5=9 disease. In contrast, Figure 2B demonstrates an NGP sample with biobank and final RP Gleason score 3+5=8 concordance. Thus, Figure 2B highlights one of the many cases where multidisciplinary pre-operative review and biobank planning along with tissue scrapings reviewed at the time of tissue harvesting helped guide more accurate and robust tissue collection.

On univariate analysis, only use of NGP was associated with pathologic concordance [OR 2.65 (95% CI 1.13 – 6.21), $p = 0.025$] (Table 4). Age, BMI, pre-operative PSA, prostate volume, MRI PIRADS score, lesion size on MRI, final Gleason score, tumor volume, and

pathologic T and N stage were not associated with the rate of pathologic concordance. Multivariate analysis was then performed using the same variables excluding age, BMI and pathologic N stage as these should not have an effect on our ability to harvest tumor tissue. This analysis also showed that use of NGP was the only factor that was associated with higher rate of pathologic concordance [OR 3.11 (95% CI 1.09 – 8.88), p = 0.034] (Table 5).

4. Discussion

By utilizing a multi-disciplinary team and incorporating imaging findings as well as real-time tissue scrapings for malignant cells, specimens processed using our NGP had significantly greater percentage of pathologic concordance between biobanked tissue and final prostatectomy specimen when compared to the SP (61.8% vs 37.9%, p=0.0231). Utilization of our NGP was associated with pathologic concordance on both univariate [OR 2.65 (95% CI 1.13 – 6.21), p = 0.025] and multivariate analysis [OR 3.11 (95% CI 1.09 – 8.88), p = 0.034]. Further, the amount of tumor tissue that was biobanked was nearly two-fold greater in NGP as opposed to SP cases with NGP cases yielding an average of 330 mm^3 of dominant tumor nodule tissue compared to 174 mm^3 of dominant tumor nodule tissue in SP cases ($p<0.001$).

Because studies such as TCGA have utilized biobanks to characterize the genomic landscape of cancer,[1] it is important to optimize the fidelity of banked tissue with patient disease pathology. Studies on neuroendocrine and advanced PCa have relied on biopsies of distinct lymph nodes or metastatic lesions to successfully characterize the genomic landscape and identify clinical drivers that may help guide effective treatments.[10, 11] However, primary PCa has demonstrated unique challenges due to the lack of visualizable lesions, multifocality and genomic heterogeneity of the disease.[4, 5] Our analysis demonstrated that two-thirds of specimens in the TCGA primary PCa biobank did not fully represent the patient's RP index lesion. Not only does our next-generation biobanking protocol improve fidelity between the biobanked tissue and the patient's dominant tumor nodule, it also augments the volume of index lesion tissue that is biobanked for research.

Our pilot trial also has implications for assays on fresh tissue that are harvested at the time of RP. In addition to banking frozen tissue, fresh tissue can be harvested and grown in 3D organoid cultures in order to model the lineage specificity of an individual's cancer and perform drug screening to investigate therapeutic sensitivities.[12] Our institution has previously published on patient-derived organoids from metastatic lesions of advanced and neuroendocrine PCa.[13, 14] However, the same challenges mentioned above exist for selecting tissue for primary PCa organoids and have not been addressed in published protocols.[15, 16]

There are several limitations to our data. First, protocol enrollment was not randomized. However, there were no significant differences in any clinical or pathologic characteristics between the two protocol arms. We have also not tested the DNA or RNA quality of the tissue banked, although we have previously published on the robustness of our standard protocol[3], and the extra time for tissue scraping and review during NGP should add only a few minutes to the ischemic time and not affect nucleic acid quality.

At some institutions, the availability of 1) a physician team to evaluate the patient's clinical data pre-operatively to determine the best anatomical location for biobanking, 2) a biobank team on the day of surgery to coordinate rapid specimen pick-up and processing, and 3) a genitourinary pathologist for slide review at the time of radical prostatectomy may be prohibitive from implementing our next-generation protocol. However, our study did not specifically address which component of the NGP was most useful in improving biobanking outcomes, so we cannot determine whether tissue scrapings, for instance, are necessary or sufficient to obtain higher quality biobank samples since tissue scrapings only allow for determination of the presence or absence of neoplastic cells without distinguishing between various Gleason patterns. As such, modifications to our next-generation protocol, such as omitting the tissue scrapings, may allow for flexibility in its implementation at institutions with limited resources while still improving biobank fidelity, quality, and quantity.

Finally, we have not demonstrated that capturing the highest Gleason score and/or dominant tumor nodule is important for downstream genomic analysis. Previous studies have suggested that there is significant intratumoral heterogeneity when taking different regions from the same tumor focus, but evaluating genomic profiles in different Gleason patterns of the same tumor nodule is beyond the scope of our study.[17]

5. Conclusions

Our research group developed a multi-disciplinary biobank protocol and demonstrated in this pilot study a significant improvement in the pathologic concordance between the biobanked tissue and the radical prostatectomy specimens, as well as an increased amount of dominant tumor nodule tissue that was biobanked. As we increasingly rely on genomic data to evaluate patients and guide therapeutic options in the era of precision medicine, it is important to optimize the fidelity of our banked tissue to the patients' disease as well as efficiently increase the amount of biobanked tumor tissue without compromising patient care.

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Highlights

- Banking primary prostate cancer is challenging because the tumors are often difficult to visualize in the gross specimens and are frequently multifocal.
- Analyzing how well our biobanks represent patients' disease is important to understanding how genomic studies can guide clinical management.
- Biobanked specimens used in TCGA primary prostate cancer analysis had low fidelity to the patient's final prostatectomy Gleason score.
- Multi-disciplinary teamwork and discussions significantly improve the fidelity and quantity of biobanked prostate cancer tissue.

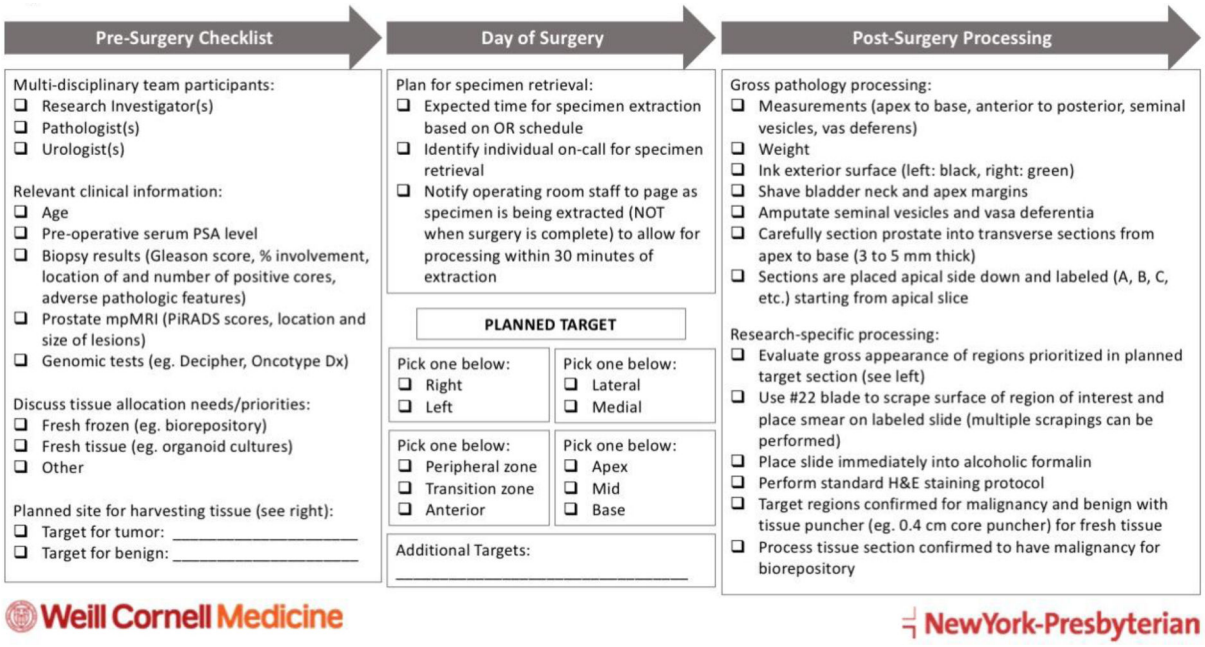

Figure 1. Next Generation Biobank Protocol Workflow.

Detailed checklist of information to review before surgery (left), steps to coordinate on the day of surgery (center), and instructions for gross pathology and research-specific processing (right).

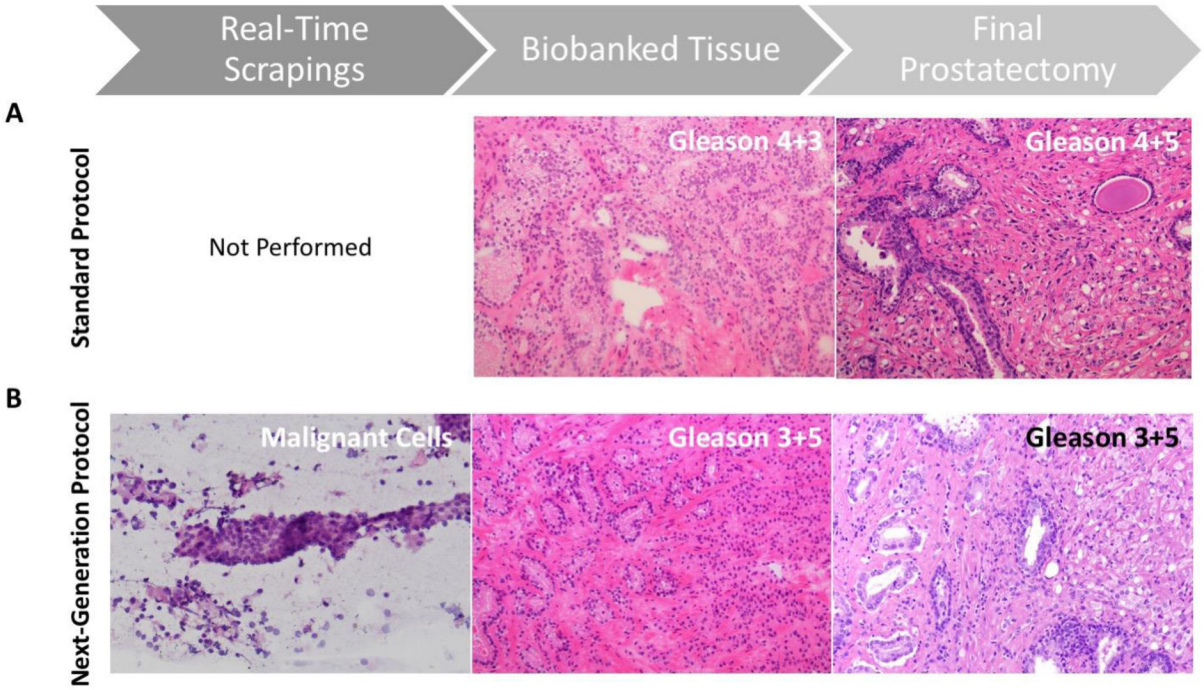

Figure 2. Comparison of Standard Protocol vs Next-Generation Protocol.

(A) Representative pathology from Standard Protocol showing Gleason 4+3=7 in biobanked tissue despite Gleason 4+5=9 in the final prostatectomy specimen versus (B) Next-Generation Protocol demonstrating malignant cells on real-time tissue scrapings and Gleason 3+5=8 on both biobanked tissue and final prostatectomy specimen.

Table 1.

TCGA Patient Characteristics by Pathologic Concordance

	Concordant		**Discordant**		**p-value**
No. pts	92		187		
Median Age - yrs (IQR)	59.5	(54 – 66)	62	(56.5 – 66)	0.151
Median PSA - ng/mL (IQR)	6.6	(4.83 – 12)	7.7	(5.2 – 11.9)	0.288
	N	**%**	**N**	**%**	
Race					0.725
White	56	60.9	107	44.4	
Black	8	8.7	13	5.4	
Asian	1	1.1	5	2.1	
Declined	27	29.3	61	25.3	
Final Gleason Grade Group					<0.001
1	15	16.3	7	3.7	
2	40	43.5	57	30.5	
3	17	18.5	37	19.8	
4	7	7.6	23	12.3	
5	13	14.1	63	33.7	
Molecular Subtype					0.136
ERG	53	57.6	78	41.7	
ETV1	6	6.5	17	9.1	
ETV4	4	4.3	5	2.7	
FL1	1	1.1	2	1.1	
SPOP	10	10.9	25	13.4	
FOXA1	0	0	7	3.7	
IDH1	0	0	3	1.6	
Other	18	19.6	50	26.7	

Table 2.

Patient Characteristics by Study Protocol

	Standard Protocol		Next Generation Protocol		p-value
	N=66		N=34		
Median Age - yrs (Range)	64.5	(43 - 80)	67.5	(45 - 78)	0.673
Median BMI - kg/m2 (IQR)	26.3	(19.4 - 33.8)	26.2	(21.5 - 36.3)	0.549
Median PSA - ng/mL (IQR)	6.4	(1.9 - 54.1)	6.2	(2.2 - 52.4)	0.155
Median Prostate Weight - g (IQR)	47.4	(22.6 - 144.1)	44.1	(25.7 - 98)	0.879
	N	%	N	%	
Race					0.108
White	20	30.3	3	8.82	
Black	7	10.6	2	5.88	
Hispanic	4	6.1	3	8.82	
Asian	1	1.5	1	2.94	
Jewish	2	3	0	0	
Unknown	32	48.5	25	73.53	
Prostatectomy Gleason Grade Group					0.067
1	6	9.1	3	8.82	
2	31	47	16	47.06	
3	20	30.3	4	11.76	
4	0	0	0	0	
5	9	13.6	11	32.35	
Tumor Volume					0.501
Low (<5%)	12	18.2	5	14.71	
Intermediate (5 to 15%)	43	65.2	20	58.82	

Table 3.

Pathologic Concordance and Biobank Tissue Volume

	Standard Protocol		Next Generation Protocol		p-value
Number Enrolled	66		34		
Pathologic Concordance	**N**	**%**	**N**	**%**	
Yes	25	37.9	21	61.8	0.0231
No	41	62.1	13	38.2	
Mean Volume of Biobanked Tumor Tissue	174 mm^3		330 mm^3		<0.001

Table 4.

Univariate analysis predicting pathologic concordance

	Univariate Analysis	
	OR (95% CI)	**p-value**
Age	1.02 [0.97 – 1.08]	0.365
BMI	1.10 [0.96 – 1.26]	0.156
Pre-operative PSA	1.01 [0.96 – 1.06]	0.799
Prostate Volume	1.02 [0.99 – 1.04]	0.206
MRI PiRADS Score		
PiRADS 5	Reference	
PiRADS 4	1.89 [0.72 – 4.92]	0.195
PiRADS 3	0.57 [0.15 – 2.15]	0.408
No MRI lesion	3.93 [0.67 – 23.10]	0.13
MRI Lesion Size	0.99 [0.61 - 1.60]	0.955
Final Gleason Score	0.84 [0.61 – 1.16]	0.3
Tumor Volume	0.69 [0.36 – 1.33]	0.267
Pathologic T stage	0.87 [0.52 – 1.45]	0.595
Pathologic N stage	1.26 [0.24 – 6.57]	0.787
Next-Generation Protocol	2.65 [1.13 – 6.21]	0.025*

Table 5.

Multivariate analysis predicting pathologic concordance

	Multivariate Analysis	
	OR (95% CI)	**p-value**
Pre-operative PSA	1.00 [0.95 – 1.07]	0.885
Prostate Volume	1.02 [0.99 – 1.06]	0.139
MRI PiRADS Score		
PiRADS 5	Reference	
PiRADS 4	1.63 [0.42 – 6.38]	0.485
PiRADS 3	0.461 [0.08 – 2.71]	0.391
MRI Lesion Size	1.33 [0.54 – 3.24]	0.535
Final Gleason Score	0.69 [0.41 – 1.16]	0.157
Tumor Volume	0.63 [0.23 – 1.71]	0.36
Pathologic T stage	1.09 [0.52 – 2.29]	0.819
Next-Generation Protocol	3.11 [1.09 – 8.88]	0.034*