

Percentage of teratoma in the orchiectomy and risk of retroperitoneal teratoma at the time of post-chemotherapy retroperitoneal lymph node dissection in germ cell tumors

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Introduction:

Presence of teratoma in the orchiectomy and residual retroperitoneal mass size are known predictors of finding teratoma during post-chemotherapy retroperitoneal lymph node dissections (PC-RPLND). We sought to determine if the percentage of teratoma in the orchiectomy specimen could better stratify the risk of teratoma in the retroperitoneum.

Materials and Methods:

The Indiana University testis cancer database was reviewed to identify patients who underwent PC-RPLND for non-seminomatous germ cell tumors from 2010-2018. A logistic regression model was fit to predict the presence of retroperitoneal teratoma using teratoma and yolk sac tumor (YST) in the orchiectomy, residual mass size, and log transformed values of pre-chemotherapy AFP and bHCG. The study cohort was split into 60% training and 40% validation sets using 200 bootstraps. A predictive nomogram was developed for predicting teratoma in the retroperitoneum.

Results:

A total of 422 men were included. Presence of teratoma in the orchiectomy (OR 1.02, $p < 0.001$), residual mass size (OR 1.16, $p < 0.001$) and log transformed pre-chemotherapy AFP (OR 1.12, $p = 0.002$) were predictive factors for having teratoma in the retroperitoneum. The C-statistic using this model demonstrated a predictive ability of 0.77. Training set C-statistic was 0.78 compared to 0.75 for the validation set. A nomogram was developed to aid in clinical utility.

Conclusion:

The model better predicts patients at higher risk of teratoma in the retroperitoneum following chemotherapy which can aid in a more informed referral for surgical resection.

Introduction:

Testis cancer is the most common solid malignancy diagnosed in men aged 18-44¹. Cure rates are exceptional, due to cisplatin-based chemotherapy and surgical resection when appropriate². Therefore, contemporary investigations have focused on attempts to reduce treatment-related morbidity. **Percentage of teratoma in the orchiectomy and risk of retroperitoneal teratoma at the time of post-chemotherapy retroperitoneal lymph node dissection in germ cell tumors** Adam C. Calaway¹, Sean Q. Kern², David Crook², Yan Tong³, Timothy A Masterson², Nabih Adra⁴, Lawrence H. Einhorn⁴, Richard S. Foster^{3,4,2}, Clint Cary²

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Post-chemotherapy retroperitoneal lymph node dissections (PC-RPLND) are advocated in men with NSGCT (nonseminomatous germ cell tumor) with a residual radiographic retroperitoneal mass >1cm and negative serum tumor markers. Pathology may demonstrate active cancer (15%), teratoma (45%) or necrosis (40%)^{5,6}. Men undergoing PC-RPLND for necrosis are subject to the potential complications of surgery with no additional benefit of

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Recently, promising results suggest microRNA-371 is a very accurate biomarker for active cancer; however, it is unable to distinguish between teratoma and necrosis

Key Words: Testicular Cancer, Retroperitoneal Lymph Node Dissection, Teratoma

Our group has previously evaluated predictors of teratoma at the time of PC-RPLND, finding the likelihood of teratoma in the retroperitoneum increased with increasing residual mass size

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and presence of teratoma (yes/no) in the orchiectomy specimen¹⁴. Other studies have

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demonstrated that YST and teratoma in the orchiectomy specimen further increases the odds of

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retroperitoneal mass^{12,15}. However, no studies have combined these risks factors

or utilized teratoma percentage in the orchiectomy specimen to create a better prediction tool.

We sought to determine if the percentage of teratoma in the orchiectomy specimen, along with other risk factors, could better stratify the risk of teratoma in the retroperitoneum.

Materials and Methods:

Patient Selection:

Percentage of teratoma in the orchiectomy and risk of retroperitoneal teratoma at the time of post-chemotherapy retroperitoneal lymph node dissection in germ cell tumors

After Institutional Review Board approval, our prospectively maintained testis cancer database was queried to identify men with NSGCT who underwent PC-RPLND from 2010-2018. Adam C. Calaway¹, Sean Q. Kern², David Crook², Yan Tong³, Timothy A Masterson², Nabih Adra⁴, Lawrence H. Einhorn⁴, Richard S. Foster², Clint Cary²

All men had pre-operative tumor markers at the time of surgery. University Hospitals/Case Western Reserve University¹

Indiana University School of Medicine Department of Urology², Indiana University Department of Biostatistics, Indiana University Melvin and Bren Simon Comprehensive

Cancer Center⁴ systemic chemotherapy prior to orchiectomy were excluded from the analysis. All PC-RPLNDs

were performed in an open fashion. The template performed, as well as nerve-sparing, was

individualized to the patient after the shared decision-making process between the patient and

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orchiectomy specimen, residual mass size, and pre-chemotherapy alpha fetal protein (AFP) and

Key Words: Testicular Cancer, Retroperitoneal Lymph Node Dissection, Teratoma

beta-human chorionic gonadotropin (bHCG).

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A logistic regression model examined the predictability of teratoma in the

Manuscript word count: 2418 orchiectomy, YST in the orchiectomy, residual mass size, and

pre-chemotherapy AFP and bHCG. The model included both teratoma and YST in the

orchiectomy as continuous variables. A nomogram for the estimated predictive probability for

teratoma in retroperitoneum by pre-surgical variables was created. All statistical tests were

based on a two-sided significance level of 0.05. Analysis was performed using SAS 9.4 (Cary, NC).

Validation Procedures
Percentage of teratoma in the orchiectomy and risk of retroperitoneal teratoma at the time of post-chemotherapy retroperitoneal lymph node dissection in germ cell tumors

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The prediction model was validated internally using the original dataset. The bootstrap split sample validation procedure was utilized for prediction model validation. A bootstrap sample consisted of a training set and a validation set with a 60:40 ratio in size of the original study sample, respectively. Patients were randomly selected into the training or the validation set with replacement. For each bootstrap sample, the selected prediction model was fit based on the training sample. The predicted probability of the outcome for each patient was computed for the validation sample by applying the model parameter estimates obtained from training sample.

Corresponding author:

Clint Cary, MD, MPH (AUC) for the validation sample were then calculated based on the 535 Barnhill Dr
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hence 200 repetitions of validation process were conducted. The mean AUCs of all bootstrap
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AUCs were calculated for training sets and validation sets. The bootstrap confidence bands of

Funding Source: None selecting 2.5th and 97.5th percentiles of the 200 bootstrap AUCs for the

Conflict of Interest: None training sets and the validation sets. The internal bootstrap validation procedure was performed using SAS 9.4 (Cary, NC).

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Results:

Patient Demographics and Clinical Characteristics:

Overall, 422 men were included in the analysis. The median age at the time of surgery was 29 years (Quartiles 23-33). Overall, 294 (69.7%) men had teratoma and 279 (66.1%) had yolk sac components in their orchiectomy specimens. Median values of pre-chemotherapy AFP and post-chemotherapy retroperitoneal lymph node dissection in germ cell tumors

and AJCC were 17.5 (Quartiles 4.9-47.9) and 2.5 (Quartiles 0.7-7.4), respectively. Authors: **Adnan C. Galway¹, Sean Q. Kern², David Crook², Yan Tong³, Timothy A. Masterson², Nabil Adra⁴, Lawrence H. Einhorn⁴, Richard S. Foster², Clint Cary²** received risk-appropriate induction chemotherapy. Most men were treated with bleomycin, etoposide and cisplatin multi-agent chemotherapy (346, 82%). None of the men included in the study received salvage chemotherapy. At the time of PC+RPLND, the median residual

retroperitoneal mass size was 5 cm (Quartiles 3.2-7.7) with the largest mass size being 29 cm.

Demographic and clinical characteristics are summarized in Table 1.

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observed in 28 (6.6%). Of these patients, sixteen (3.8%) had teratoma and cancer while 12

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(2.8%) had cancer only in the retroperitoneum. Of the 294 men with teratoma in the orchiectomy, 236 (80.3%) had teratoma in the retroperitoneum.

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Predictive Model.
Logistic regression for predicting presence of only teratoma in the retroperitoneum was

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performed (Table 2). Presence of teratoma in the orchiectomy (OR 1.02, p<0.001), residual

mass size (OR 1.16, p<0.001) and log transformed pre-chemotherapy AFP (OR 1.12, p=0.002)

were predictive factors for having teratoma in the retroperitoneum. A nomogram was developed

for predicting the probability of finding teratoma in the retroperitoneum at the time of RPLND to give physicians an easy tool to enhance clinical utility (Figure 1).

Percentage of teratoma in the orchiectomy and risk of retroperitoneal teratoma at the time of post-chemotherapy retroperitoneal lymph node dissection in germ cell tumors

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Results from internal validation procedures indicated good predictive accuracy of our prediction model. Results from internal validation procedures indicated good predictive accuracy of our prediction model (AUC=0.743, 95% PI 0.686-0.801). Minimal differences in AUCs between training (AUC=0.775, 95% CI 0.734-0.82) and validation sets (AUC=0.749, 95% CI 0.686-0.815) were observed (Figure 2).

Discussion:

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Clint Cary, MD, MPH sought to determine if the percentage of teratoma in the primary orchiectomy, in addition to other known predictors, could accurately predict the presence of retroperitoneal mass. The predictive modeling confirmed that presence of teratoma in the orchiectomy and increasing size of the residual retroperitoneal mass after induction chemotherapy were associated with an elevated risk of retroperitoneal disease at the time of PC-RPLND. Uniquely, we also observed that increasing percentages of teratoma in the orchiectomy specimen conferred additional risk of teratoma in the retroperitoneum. Our model demonstrated a high discriminative ability with a C statistic of 0.74 which was confirmed with validation techniques. A nomogram was developed to provide clinical utility. It is our practice to observe patients who have radiographic normalization of retroperitoneal disease with normal tumor markers after induction chemotherapy while those with > 1cm residual disease are recommended for resection. However, patients who harbor

Key Words: Testicular Cancer, Retroperitoneal Lymph Node Dissection, Teratoma

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necrosis in the residual retroperitoneal mass garner no oncological benefit from surgical resection while being subjected to the surgical risks and recovery of a PC-RPLND. In this clinical paradigm lies the utility and relevance of the findings and clinical nomogram we present. **Percentage of teratoma in the orchiectomy and risk of retroperitoneal teratoma at the time of post-chemotherapy retroperitoneal lymph node dissection in germ cell tumors**

Our prediction model can better identify patients who have a high probability of having teratoma in the retroperitoneum, and a surgeon would want to perform post-chemotherapy retroperitoneal lymph node dissection (RPLND) in these patients. We feel having an adequate instrument for predicting teratoma (or conversely, predicting necrosis) not only aids in pre-surgical patient counseling, but also may benefit the surgeon intraoperatively while resecting adherent retroperitoneal masses away from the great vessels and adjacent organs. Conversely, patients with a low predictive estimate of retroperitoneal teratoma, in conjunction with emerging data regarding the high sensitivity of mi-

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associated with a 48% risk of teratoma in the retroperitoneal mass, while those harboring retroperitoneal mass conferred an 86% risk. In addition, increasing size of the retroperitoneal mass correlated with a higher likelihood of teratoma in the tumor¹⁴. A follow-up paper by Mosharafa et al. in 2004 found that yolk sac tumor in the primary orchiectomy was associated with teratoma in the retroperitoneum¹⁵. These findings were further corroborated by a retrospective study completed at Memorial Sloan Kettering Cancer Center¹². To our knowledge, no other previous study has examined the effect of percentage of teratoma in the orchiectomy when assessing the risk of teratoma at the time of PC-RPLND. We hypothesized

that using this readily obtainable data from pathology reports may provide additional discriminative ability which may aid in operative decision making.

These initial studies were followed by attempts to create statistical models to predict **Percentage of teratoma in the orchiectomy and risk of retroperitoneal teratoma at the time of post-chemotherapy retroperitoneal lymph node dissection in germ cell tumors**

between benign and malignant histology. Our group, using prechemotherapy primary orchiectomy, prechemotherapy serum tumor markers (AFP, HCG, and LDH), size of the mass, and change in mass size from prechemotherapy imaging. The model had high discriminative ability (C-statistic 0.79). The model was further assessed in a multi-institutional validation study and found to have slight improved discriminative ability which confirmed this model as an effective tool to predict histology across numerous clinical settings¹¹. However, this model has not been widely accepted into practice, possibly due to the number of variables

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validation study and found to have slight improved discriminative ability which confirmed this model as an effective tool to predict histology across numerous clinical settings¹¹. However,

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prechemotherapy mass size, and change in mass size to predict benign versus malignant pathology. The model performed reasonably well (C-statistic 0.82) and was validated in two

Key Words: Testicular Cancer, Retroperitoneal Lymph Node Dissection, Teratoma

Funding Source: None¹⁰. Our current predictive model has notable differences to the above

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referenced studies. First, we sought to predict the presence of teratoma only in the residual mass,

not benign versus malignant (active cancer and teratoma) disease. If further studies using micro-

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RNA 371 continue to show the ability to distinguish between active cancer and necrosis/teratoma

at the time of PC-RPLND, we believe that a tool to differentiate between teratoma and necrosis

may be most beneficial in efforts to reduce the number of invasive surgeries performed for

necrosis¹⁶. Second, our model variables differed as we used percentage of teratoma and

presence of yolk sac tumor in orchiectomy due to their known association with retroperitoneal teratoma^{12,14,15}. We also did not use % change of retroperitoneal mass as this variable may be

hard to estimate and possibly not as clinically relevant or available as the size of the mass at the time of PC-RPLND. **Percentage of teratoma in the orchiectomy and risk of retroperitoneal teratoma at the time of post-chemotherapy retroperitoneal lymph node dissection in germ cell tumors**

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bias of retrospective studies is well characterized. In addition, external validation of our predictive model could be considered prior to routine clinical use to ensure generalizability. However, external validation may be best performed in a multi-institutional effort which would require significant organization and collaboration. To that end, we performed an internal validation to confirm predictive accuracy. Second, many of the variables included in our model are dependent upon accurate pathologic interpretation. In this regard, we only included patients whose pathology was reviewed by experienced genitourinary pathologists at our institution. Prior studies have documented a high discrepancy in interpretation of pathology between hospitals and tertiary referral centers for germ cell tumors which further emphasizes the need to externally validate our model¹⁷. Third, at our institution, we only offer PC-RPLND for men with > 1 cm residual disease. We acknowledge that other centers may offer

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use in that population. In addition, data on induction chemotherapy dose reduction was not collected; however, dose reductions likely would not impact the presence of chemo-resistant teratoma in the retroperitoneum. Finally, based on our findings, the lowest risk of teratoma in the retroperitoneum occurs in men with small residual masses whose primary tumor did not demonstrate teratomatous elements. For example, for a small <2cm residual mass without teratoma or yolk sac tumor elements in the orchiectomy and normal prechemotherapy serum

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tumor markers, the risk of teratoma in the retroperitoneum is approximately 20% (but lower than the 48% as demonstrated in our previous study)¹⁴. Using our model alone may ultimately not be

sufficient to recommend against performing post-chemotherapy surgery; however, it may allow

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of post-chemotherapy retroperitoneal lymph node dissection in germ cell tumors
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how predictive models such as this interplay with emerging molecular studies such as mi-RNA
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as a percentage of the orchiectomy specimen better stratifies the risk of teratoma in the

retroperitoneum. Our model is the first to attempt to specifically predict presence of teratoma in

the retroperitoneum at the time of PC-RPLND. With high discriminative ability, we believe that

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retroperitoneal histology in effort to minimize the morbidity of surgery in men who may only
Key Words: Testicular Cancer, Retroperitoneal Lymph Node Dissection, Teratoma

harbor necrosis in the retroperitoneum. We envision a future in which this predictive model is

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decisions regarding the need to perform post-chemotherapy surgery in men with non-

seminomatous germ cell tumors.

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Conclusion:

The model yields a better understanding of those patients at higher risk of residual teratoma in the retroperitoneum following platinum-based chemotherapy. Conversely, those

without teratoma in the orchiectomy with small residual masses could perhaps be more accurately selected for observation.

Percentage of teratoma in the orchiectomy and risk of retroperitoneal teratoma at the time of post-chemotherapy retroperitoneal lymph node dissection in germ cell tumors

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Key Definitions of Abbreviations

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NSGCT- nonseminomatous germ cell tumor

AFP- alpha fetal protein

bHCG- beta-human chorionic gonadotropin

YST- Yolk Sac Tumor

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AUC- Area under the curve
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Figure Legends:

Figure 1: Nomogram of predicting teratoma in the retroperitoneum.

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Figure 2. Distribution of the AUC's from training and validation samples using 200

bootstrapped samples.

Key Words: Testicular Cancer, Retroperitoneal Lymph Node Dissection, Teratoma

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Table 1: Patient Demographics and Clinical Characteristics

Age, years, median (Quartiles)	29 (23-33)
Race (%)	
White	397 (94)
Other	21 (5)
Unknown	4 (<1)
Percentage of teratoma in the orchiectomy and risk of retroperitoneal teratoma at the time of post-chemotherapy retroperitoneal lymph node dissection in germ cell tumors	
% Composition of Teratoma	Yan Tong³, Timothy A Masterson², Nabil Adra⁴, Lawrence H. Einhorn⁴, Richard S. Foster², Clint Cary²
Yolk Sac Tumor	University Hospitals/Case Western Reserve University¹, Indiana University School of Medicine Department of Urology², Indiana University Department of Biostatistics³, Indiana University Melvin and Bren Simon Comprehensive Cancer Center⁴
Prechemotherapy STMs (%)	
hCG	
Normal	106 (25)
<5,000	216 (51)
5,000-50,000	20 (5)
>50,000	22 (5)
Unknown	58 (14)
AFP	
Normal	119 (28)
<1,000	175 (41)
1,000-10,000	51 (12)
>10,000	18 (4)
Unknown	59 (14)
Stage at Presentation (%)	
Stage I	93 (22)
Stage II	158 (37)
Stage III	17 (4)
Key Words: Testicular Cancer, Retroperitoneal Lymph Node Dissection, Teratoma	
IGCCCG Risk Category (%)	
Good Risk	288 (68)
Intermediate Risk	75 (18)
Poor Risk	58 (14)
Unknown	1
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Conflict of Interest: None	
Induction Chemotherapy Regimen (%)	
BEP	346 (82)
EP	66 (15)
Other	10 (3)
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PC- RPLND Surgical Field (%)	
Bilateral Template	111 (26.3)
Right Modified Template	179 (42.4)
Left Modified Template	132 (31.3)

Table 2: Logistic regression for predictive model for presence of teratoma in the RPLND specimen

Model	OR (95%CI)	p-value	C statistics (Area under the Curve)
Percentage of teratoma in the orchiectomy and risk of retroperitoneal lymph node dissection at the time of post-chemotherapy retroperitoneal lymph node dissection	1.02 (1.01 - 1.03)	<.001	0.749
% Teratoma in Orchiectomy	1.02 (1.01 - 1.03)	<.001	0.749
% YST in Orchiectomy	1.01 (0.99 - 1.02)	0.429	0.749
Prechemotherapy AFP	1.12 (1.04 - 1.20)	0.002	0.749
Prechemotherapy HCG	1.03 (0.98 - 1.09)	0.221	0.749

Yolk Sac Tumor (YST), Retroperitoneal (RP), alpha-fetoprotein (AFP), Human Chorionic Gonadotropin (HCG)

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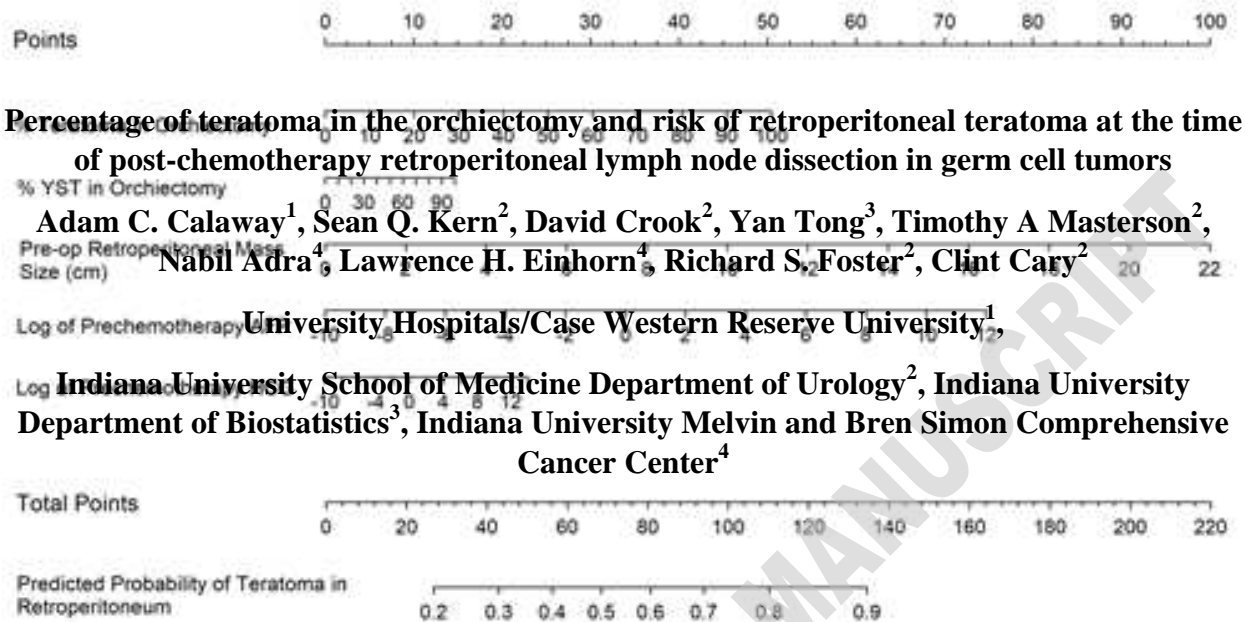
Key Words: Testicular Cancer, Retroperitoneal Lymph Node Dissection, Teratoma

Funding Source: None

Conflict of Interest: None

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Figure 1: Nomogram of predicting teratoma in the retroperitoneum.



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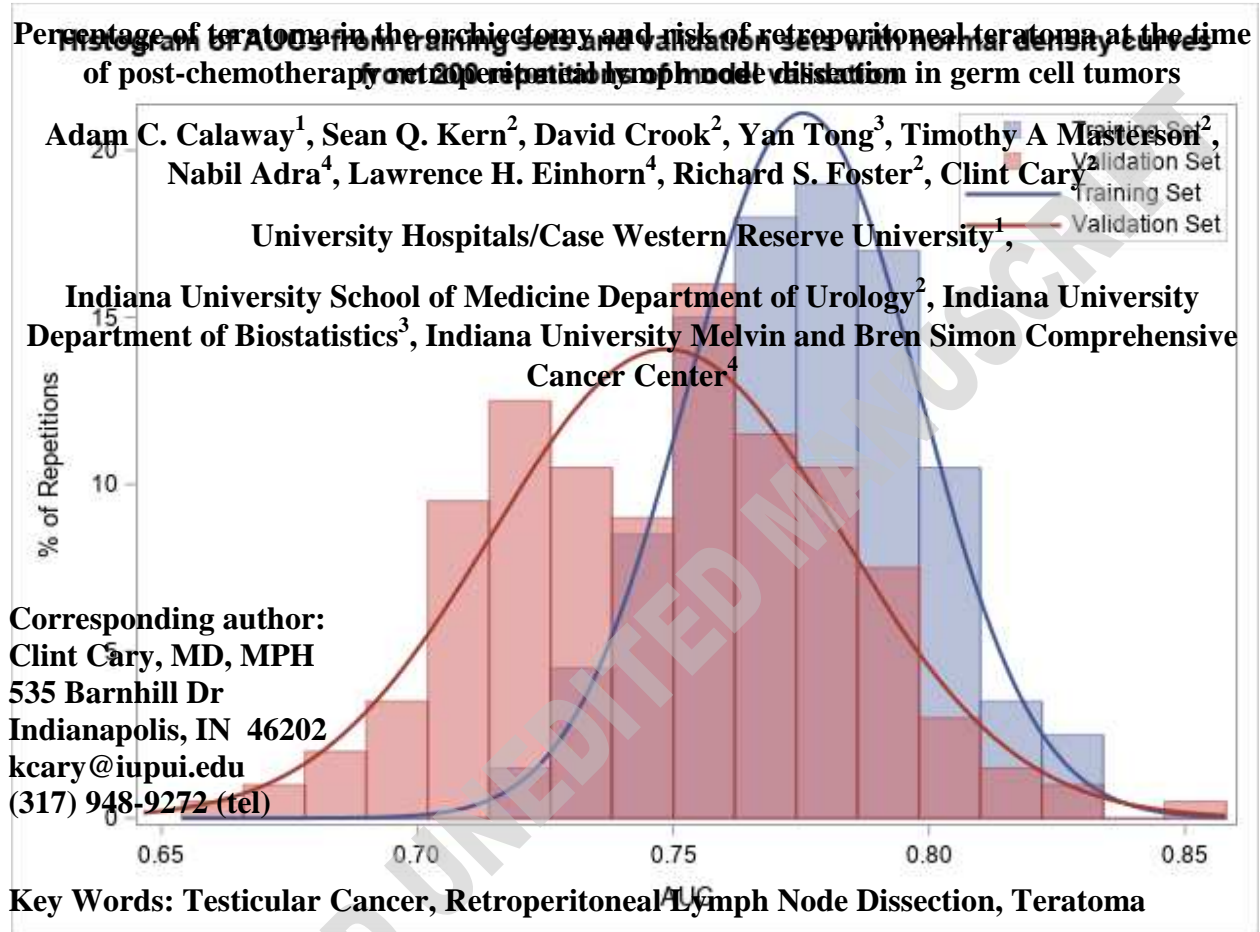
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Figure 2. Distribution of the AUC's from training and validation samples using 200 bootstrapped samples.



Funding Source: None

Conflict of Interest	Mean AUC	95% Confidence Band
Training Set	0.775	0.734 - 0.820
Validation Set	0.749	0.686 - 0.815

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