A TISSUE BIOMARKER BASED MODEL THAT IDENTIFIES PATIENTS WITH A HIGH RISK OF DISTANT METASTASIS AND DIFFERENTIAL SURVIVAL BY LENGTH OF ANDROGEN DEPRIVATION THERAPY IN RTOG PROTOCOL 92-02

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Running Head: Biomarkers, Radiation and Androgen Deprivation for Prostate Cancer
STATEMENT OF TRANSLATIONAL RELEVANCE:

The association between seven apoptotic/cell proliferation proteins and risk of distant metastasis (DM) is examined in immunohistochemical analysis of tissue from RTOG 92-02 patients. The trial compared external beam radiotherapy (EBRT) to ~70 Gy + short term androgen deprivation therapy (STADT) with EBRT+long term ADT (LTADT). Modeling identified four biomarkers (Ki-67, MDM2, p16 and Cox-2) that were jointly associated with DM. The model predicted for DM and identified a subgroup of patients at a particularly high risk of both DM and prostate cancer specific mortality (PCSM) when EBRT+STADT were used. LTADT resulted in significant gains in DM and PCSM, and there was a suggestion of greater importance in this very high risk subgroup. Our findings suggest that the addition of biomarkers to classical clinical-pathologic factors identifies a group at very high risk of DM after EBRT+ADT which will benefit significantly from LTADT both from the perspective of reduced DM and PCSM.
ABSTRACT

Purpose: To examine the relationship between the expression of 7 promising apoptotic/cell proliferation proteins (Ki-67, p53, MDM2, bcl-2, bax, p16, and Cox-2) and risk of distant metastasis (DM).

Experimental Design: RTOG 92-02 compared external beam radiotherapy (EBRT) to ~70 Gy+short term androgen deprivation therapy (STADT) with EBRT+long term ADT (LTADT). Immunohistochemical analysis was available for ≥4 biomarkers in 616 of 1521 assessable cases. Biomarkers were evaluated individually and jointly via multivariable modeling of DM using competing risks hazards regression, adjusting for age, PSA, Gleason score, T-stage, and treatment.

Results: Modeling identified four biomarkers (Ki-67, MDM2, p16 and Cox-2) that were jointly associated with DM. The c-index was 0.77 for the full model and 0.70 for the model without the biomarkers; a relative improvement of about 10% (likelihood ratio p < 0.001). Subdivision of the patients into quartiles based on predicted DM risk identified a high risk group with 10-year DM risk of 52.5% after EBRT+STADT and 31% with EBRT+LTADT; associated 10-year prostate cancer specific mortality (PCSM) risks were 45.9% and 14.5% with STADT and LTADT.

Conclusion: Four biomarkers were found to contribute significantly to a model that predicted DM and identified a subgroup of patients at a particularly high risk of both DM and PCSM when EBRT+STADT was used. LTADT resulted in significant reductions in DM and improvements in PCSM, and there was a suggestion of greater importance in this very high risk subgroup.
INTRODUCTION

The role of androgen deprivation therapy (ADT) as an adjuvant to external beam radiation therapy (EBRT) for prostate cancer patients has been a focus of study for decades; particularly for patients at a higher risk of distant metastases.\(^1, 2\) RTOG 92-02\(^1, 3\) was launched to compare standard dose (~70 Gy) EBRT plus short term ADT (STADT) versus EBRT plus long term ADT (LTADT). Androgen deprivation therapy consisted of flutamide and goserelin, beginning 2 months before EBRT and continuing until EBRT completion (STADT+EBRT arm) vs. goserelin continued for an additional 2 years after EBRT (LTADT+EBRT arm). A significant benefit was observed in biochemical failure, disease free survival, freedom from distant metastasis and disease specific survival for patients randomized to LTADT+EBRT. These results, and those of EORTC 22961,\(^2\) support the use of LTADT in men with high risk prostate cancer. However, LTADT is associated with significant long term side effects. Better selection of patients for LTADT, as well as for those in need of more aggressive strategies beyond this standard, are needed. Tumor tissue biomarkers have the potential to improve patient selection.

We have identified multiple tumor tissue biomarkers that are significantly associated with outcomes of patients after EBRT+ADT, including: Ki-67,\(^4\) p53,\(^5\) MDM2,\(^4\) bcl-2 & bax,\(^6\) p16,\(^7\) and Cox-2.\(^8\) For the most part, these markers have been studied individually or paired with one other marker (i.e., Ki-67 & MDM2,\(^4\) bcl-2 & bax\(^6\)). In this report, we analyze a large clinical trial cohort to develop a statistical model using clinical-pathologic covariates and multiple tissue biomarkers that significantly predicts for distant metastasis (DM), over that achieved by modeling clinical-pathologic factors alone. The primary endpoint of DM was chosen because of the strong relationship of DM to survival, which is born out in the data presented.
PATIENTS AND METHODS

Patient characteristics

The study details of RTOG 92-02 have been described.(1, 3) Briefly, this Phase III trial compared EBRT+STADT vs. EBRT+LTADT in men with high-risk prostate cancer. External beam radiation therapy was administered to a dose of 44-46 Gy (1.8 - 2.0 Gy/day four to five times a week) to the regional lymphatics followed by a field reduction and continued treatment to 20-29 Gy (1.8 - 2.0 Gy/day) for a total of 65-70 Gy to the prostate for stage T2c and 67.5 - 70 Gy for stages T3 and T4. Patients received flutamide (two 125 mg capsules TID PO) and goserelin, (3.6 mg s.c. monthly), beginning 2 months before EBRT and continuing until EBRT was completed. Patients assigned to LTADT received additional goserelin after the completion of EBRT for two years.

The trial underwent institutional review board approval at all participating sites and at the RTOG central coordinating center. Tissue samples to analyze the biomarkers studied were collected from patients after informed consent for protocol participation was obtained.

Biomarker data analysis

The techniques for biomarker staining and analysis of Ki-67,(4) p53,(5) MDM2,(4) bcl-2 & bax,(6) p16,(7) and Cox-2(8) have been described in detail previously. Briefly, archival paraffin-embedded diagnostic prostate biopsy tumor tissues were cut onto poly-L-lysine slides, deparaffinized in xylene, rehydrated and washed before antigen retrieval using a pressure cooker. Primary antibodies were then added at titrated dilutions to optimize staining. The primary antibodies used were MIB-1 for Ki-67 (No. M7240, 1:100 dilution; Dako Corp., Carpinteria, CA), p53 (No. M7001, Clone DO7, 1:100 dilution; Dako Corp.), MDM2 (No. M7146, Clone SMP14, 1:100 dilution; Dako Corp.), Bcl-2 (clone 124, 1:100 dilution; Dako Corp.), Bax (clone 2D2, 1:200 dilution; Zymed Laboratories, Inc., San Francisco, CA), p16 (No. SC-1661, 1:100 dilution; Santa Cruz Biotechnology Inc., Santa Cruz, CA), and Cox-2 (No. 804-112-C050,
1:200 dilution: Alexis Biochemicals, Lausen, Switzerland). Antibody binding was detected by the labeled streptavidin biotin method (Dako LSAB 2 Kit; Dako Corp) for MDM2, Ki-67, Bcl-2, Bax, p16 and Cox-2, and by the ABC method, using 3-amino-9-ethylcarbazole as the chromogen for p53. Bcl-2 & bax,(6) p53(5) and Ki-67(4) were based on manual scoring, whereas p16,(7) MDM2(4) and Cox-2(8) were based on semi-automated image analysis.

**Statistical methods**

Disease end points have been described previously.\textsuperscript{15-17} DM was defined as clinical evidence of distant disease by radiographic or pathologic criteria. Prostate cancer specific mortality (PCSM) was defined as death certified as due to prostate cancer, death due to treatment complications, death from unknown causes with active malignancy (clinical disease relapse), or from another cancer with documented bone metastases attributed to prostate cancer before the appearance of the second independent cancer.

The study aim was to investigate whether a set of molecular features will add to the prognostic classification in a model with recognized prognostic stratification features, seeking a parsimonious model containing molecular characteristics that enhance prediction over known patient and disease characteristics associated with risk of DM, which include age at diagnosis, initial PSA (iPSA), Gleason score (GLSC), and T-Stage. Treatment group was also included in the model, and potential interaction effects between treatment and biomarkers were formally tested.

From among 1,521 eligible trial participants (763 STADT, 758 LTADT), there were 616 (41\%) patients for whom data was available for at least four of the seven biomarkers. The prognostic significance of these biomarkers was evaluated in a model for cumulative incidence of DM based on the subdistribution hazards regression approach that accounts for the influence of competing risks.\textsuperscript{(9)} Covariates for biomarkers were considered on a continuous linear scale for scaled values ((value – mean)/standard deviation), unless model diagnostics for evaluating
functional form suggested otherwise. Each was examined singly in the presence of clinical covariates, and those found to show an association with DM were examined jointly. Variables that had previously been omitted were examined again for possible inclusion. Likelihood ratio tests and Akaike's information criterion (AIC) were used to contrast models. In the resulting model, four biomarkers (Ki-67, MDM2, Cox-2, and p16) remained important predictors in multivariable analyses, with 372 patients having complete data on all 4 of these biomarkers.

The resulting final model was used to explore risk prediction in several ways. First, the c-index for the competing risks regression model was used to evaluate the contribution of biomarkers to prediction after inclusion of clinical characteristics. Second, the model was used to generate outcomes for hypothetical patients according to covariates; for example, by fixing clinical characteristics at common representative values and varying biomarker values. Finally, as an empirical check on risk prediction, the ‘risk scores’ that each patient had based on their covariate values and the model coefficients were used to partition patients into quartiles of potential failure risk. Nonparametric cumulative incidence estimates were then generated for patients in each quartile to determine if the model appears to segregate risk.

Model robustness was evaluated by several approaches. To evaluate the influence of individual cases on the model estimates, 1000 random samples (with replacement, e.g., bootstrap) of size n = 75% of the total sample were drawn and model parameter estimates with the larger bootstrap variance estimates were examined to determine whether any of the covariates became superfluous in the model. Secondly, it is recognized that the c-index estimate on the same data following model fit is overly optimistic for future prediction. A Monte-Carlo analysis was performed, taking 1000 random subsamples (without replacement) of 50% of the final model cohort, followed by c-index computation for the counterpart of the cohort that was not used to estimate the model. The mean c-index for the validation subcohort is reported.

The median follow-up was 11.6 years (25th percentile= 10.5 years, 75th percentile = 12.3 years). Statistical Analysis System (SAS Institute, Cary, NC), Stata (StataCorp, College Station,
TX), and R (R Foundation for Statistical Computing, Vienna, Austria) software were used for statistical analyses.
RESULTS

Study Cohort and Biomarker Characteristics

Information on the patients in the biomarker cohort relative to all trial participants is shown in Table 1. There are no material differences in patient or disease characteristics between those with and without the marker data; although, there were fewer patients with Gleason score <7 in the final marker set.

Descriptive statistics for individual biomarkers are shown in Table 2. Associations between marker value distributions indicated that Ki-67 has low correlation with other markers. Other pairwise correlations (e.g., between Cox-2 and MDM2) are larger; although, in no case did the correlation exceed 0.35. The overall associations were moderately small. Relationships between biomarkers and other characteristics were also investigated (not shown). Biomarker values did not differ by age or T-stage. Higher values of Ki-67, Cox-2, and MDM2 were more frequent among patients with high GLSC. Patients with low p16 tended to have low iPSA values; but, otherwise iPSA was not related to these markers.

Multivariable Model

The influence of the four biomarkers that had statistically significant associations with risk of DM after inclusion of other patient/disease characteristics and treatment arm are shown in Table 3. In this model, stage and iPSA were retained, even though they no longer reached conventional statistical significance, because these factors are important prognostic covariates in the cohort as a whole and are well recognized clinical prognostic factors in other studies. For the model in Table 3, the c-index, (13) which provides a measure of model discrimination according to probability of failure, was 0.770 (95% confidence interval (CI) (0.718,0.822)). This value represents a relative improvement of about 10% over a model on the same cohort that included only the patient/disease characteristics (c-index = 0.702, 95% CI (0.658, 0.759)). The likelihood ratio test contrasting models with and without the four biomarker covariates indicated
a statistically significant contribution of the latter to the model ($\chi^2 = 22.2$, 4 df, $p < 0.001$), and the AIC was smaller (825.0 with biomarker covariates vs. 861.3 without). There was no evidence of statistically significant differential effects (e.g., interactions) between biomarkers and treatment (STADT vs. LTADT) in this final model cohort and thus only main effects were included. However, when examining markers individually, there was some indication that Ki-67 and p16 effects are quantitatively larger in patients receiving LTADT, while MDM2 may exert greater prognostic influence among patients receiving STADT.

Because the markers shown all exert significant influence on the risk of DM in the presence of clinical characteristics, patients with specific combinations of biomarker values will have greater or lesser predicted risk for DM for given values of other characteristics. To explore this, the model was used to generate predicted cumulative risks of DM based on covariate profiles. Using the contribution of biomarkers to DM risk suggested by the model in Table 3, predicted risk over time was calculated, contrasting different values for the biomarkers while fixing other covariates at a common value. For a hypothetical 65-year old patient with iPSA of 35, GLSC below 8, and T2 disease, the cumulative probability of DM was contrasted between a favorable biomarker profile (first quartile values for Ki-67 and Cox-2, third quartile value for p16, and MDM2 <184 intensity units) & an unfavorable profile (third quartile value for Ki-67 and Cox-2, first quartile value for p16, & MDM2 $\geq$184). For patients receiving STADT, the 10-year predicted risk increased from 6.7% for those with a favorable marker profile, to 33.2% for those with an unfavorable profile; while, for patients receiving LTADT, the 10-year predicted risk increased from 2.7% to 14.8% (Figure 1).

Model Evaluation

The statistical model in Table 3 indicates that numerous covariates, including tumor biomarkers, will differentiate risk for DM. To evaluate robustness of the above model in absence of an independent validation cohort, several steps were taken. First, bootstrap subsampling of
75% samples and re-estimating the coefficients confirmed that the biomarker covariates selected remained statistically significant predictors of DM risk. Second, prediction computations based on estimation of the model (1000 random samples) on samples of 50% of the cohort and the c-index then computed on the complement of the cohort resulted in average c-index of 0.737 for the proposed model and 0.675 for the model with clinical-pathologic covariates only. While the predictive ability in novel cases diminished as expected, the value still indicated clinical utility and the relative gain over the model omitting biomarkers was the same.

To demonstrate risk classification based on the model empirically, we calculated each patient’s ‘risk score’ as determined by the cumulative sum of covariate values multiplied by the associated coefficients in the model. Patients were then grouped by quartile of scores (overall and then separately within each treatment group because treatment itself is strongly associated with outcome) and nonparametric (i.e., not model-predicted as in Figure 1) cumulative incidence of DM calculated. When subdivided by length of ADT, a gradient of failure risk is clearly observed (Figure 2). For patients receiving STADT, among those in the highest risk quartile, 10-year cumulative incidence of DM was 52.5%, compared to 9.4% for patients in the first risk score quartile (Fig 2, Top). For patients receiving LTADT, those in the highest quartile had a 31.0% 10-year cumulative incidence, compared to no failures (0%) in the first quartile (Fig 2, Bottom). These findings were then related to the risk of dying from prostate cancer. Those who received STAD (Fig. 3, Top) and were in risk group 4 had a 45.9% cumulative probability of PCSM at 10 years; while, those in risk group 3 and below had a 14.5% cumulative probability of PCSM. When LTADT was used (Fig. 3, Middle) there was a significant delay in DM in all risk groups, with separation of risk group 4 from the others not suggested until 12 years. The timing of PCSM after DM was further investigated in group 4 by calculating the cumulative incidence of PCSM from the initial DM event (Fig. 3, Bottom). Those treated with LTAD had a longer time to PCSM that is most obvious at 3-5 years after DM (absolute difference in PCSM of around 20%); however, this difference was not statistically significant (p=0.18).
DISCUSSION

Our main objective was to determine if the addition of multiple biomarkers to standard clinical and pathologic covariates would significantly enhance the prediction of prostate cancer patient outcome based on DM after EBRT+ADT such that patients at the favorable and high risk ends of the spectrum would be better identified. Multiple models have been described, most using classical clinical-pathologic factors (including PSA) and biochemical failure as the endpoint; few models have used DM as the endpoint. We chose DM because there were a greater number of events, and hence greater power for modeling, than PCSM and it is a robust predictor of death due to prostate cancer. To our knowledge, none of the prior models have systematically explored tissue biomarkers using the platform or analytic approach described herein. The platform was that of a randomized trial in which the effects of the length of ADT were investigated in an otherwise homogeneously treated group. The recovery of tissue for biomarker studies was rather typical of such studies and there were no substantive differences between the study cohort and the parent protocol cohort (Table 1).

For this investigation, we chose to model on the cumulative incidence scale using the subdistribution hazards competing risks model. Covariate effects were similar when we used the more familiar cause-specific hazard regression model, a result not uncommonly seen if a relatively large proportion of patients are event-free (e.g., censored). However, the competing risks regression model is likely more appropriate for covariate effect estimation and risk prediction when failures for the event of interest are less frequent than competing events as is the case here (Table 1). This competing risks model has been advocated in similar settings modeling recurrence after prostate cancer using clinical characteristics.

We investigated the potential of seven promising biomarkers to contribute significantly to clinical-pathologic factors in estimating DM risk. Of these, four biomarkers, Ki-67, MDM2, p16 and Cox-2 were selected by multivariable modeling that included relevant clinical prognostic variables. All four of these markers had been identified previously as being associated with
DM.(4, 7, 8) Ki-67 is a proliferation marker and, notably, is the most consistent prognostic tissue biomarker for prostate cancer outcome after radiotherapy(4) or surgery(19) described thus far. Although p53 is also associated with prostate cancer outcome independently of clinical-pathologic factors in our prior experience,(5) in the model described herein (Table 3), MDM2, which is a key regulator of p53, was more significant. The loss of p16, a CDK inhibitor, results in increased phosphorylation of retinoblastoma protein (pRB), dissociation of pRB from E2F1, and greater free E2F1 to promote proliferation from G1 to S phase. The inter-relationship between the p19ARF-MDM-p53 and p16-pRB-E2F1 signaling pathways(20) and the balance between proliferation and apoptosis in response to genotoxic stress provide a rationale for why these biomarkers contribute to the model described herein. Cox-2 overexpression has cell cycle modulatory effects, as well as a number of other actions likely mediated mainly through prostaglandin E2, such as increased proliferation, invasion, and angiogenesis, with blunted apoptosis and reduced radiation response.(21)

Our selection of biomarkers was based on a systematic approach to explore the relationships of biomarkers associated with cell cycle, cell death and angiogenesis pathways. Other potential markers not included, but which have shown promise include markers of hypoxia (e.g., HIF-1α) or other markers of angiogenesis (e.g., VEGF). (22) We have never examined HIF-1α and further biomarker studies in the remaining tissue from the RTOG 92-02 cohort is complicated by the number of missing cases. Of note, VEGF was examined in tissue from RTOG 86-10 and was not predictive of outcome.(23)

The biomarkers tested added significantly to the DM model described here. When patients were divided into quartiles based on model DM risk, there was a subgroup identified with a very high rate of DM (highest DM quartile, group 4) randomized to the STADT arm (>50% at 10 years); this high risk group also had a >45% risk of death due to prostate cancer at 10 years. While group 4 also had a high rate of DM at 10 years in patients randomized to LTADT (>30%), there was less concordance in the translation to PCSM (<20% at 10 years) and the
fourth quartile group had a 10 year PCSM rate that was similar to that of quartile groups 3 and 2 (Fig. 3). To better characterize this unexpected result, we examined the time to PCSM from metastasis with the hypothesis that after LTADT the time from DM to PCSM was longer than after STADT. There may be conditions in which the rate of growth, i.e., biology of prostate cancer changes based on the timing,(24) type,(25) or duration of ADT (suggested in present analysis). While the pattern seen (Fig. 3, bottom) is intriguing because patients exposed to LTAD would be expected to respond for a shorter duration upon reinstitution of ADT (salvage ADT) for DM and the opposite is suggested, the differences were not significant. Larger numbers of patients are needed to understand the mechanisms involved.

In summary, our findings suggest that the addition of biomarkers to classical clinical-pathologic factors identifies a group of prostate cancer patients at very high risk of DM after EBRT+ADT. The results indicate LTADT is particularly important in this group both from the perspective of reduced DM and an even more pronounced reduction in PCSM. The integration of biomarkers into risk classification schemes among patients with clinical characteristics indicating a specific risk (e.g., high risk) may allow re-classification into other risk groups (e.g., intermediate or even low risk) who can then be selected for clinical trials or treatment accordingly. Validation of the biomarker-based model in an independent data set is needed before broader application of this approach.
REFERENCES


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Figure legends

Figure 1. Risk prediction from the model in Table 3: For a hypothetical 65-year old patient with initial PSA of 35, Gleason score below 8, and T2 disease, outcomes are predicted separately by treatment group according to a favorable biomarker profile (low Ki-67, low Cox-2, high p16, & low MDM2) versus an unfavorable profile (high Ki-67, high Cox-2, low p16, & high MDM2). Top: estimated results for EBRT + STADT; Bottom: estimated results for EBRT + LTADT.

Figure 2. Observed cumulative incidence of distant metastasis by model predicted risk. Patients were grouped by quartiles of predicted risk from the model in Table 3, and nonparametric cumulative incidence then computed by quartile group. Top: patients undergoing EBRT+STADT, Bottom: patients undergoing EBRT+LTADT.

Figure 3. Observed cumulative incidence of death due to prostate cancer by model predicted risk based on DM. Patients were grouped by quartiles of predicted DM risk from the model in Table 3, and nonparametric cumulative incidence for PCSM computed. Top: patients by DM model quartile group after EBRT+STADT with cumulative incidence calculated from enrollment in study; Middle: patients by DM model quartile group after EBRT+LTADT with cumulative incidence calculated from enrollment in study; Bottom. Patients in the highest risk DM model quartile subdivided by STADT vs LTADT with cumulative incidence calculated from the first DM event.
### Table 1. Distribution of Patient and Disease Characteristics

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<th>Patients not in Final Marker Set Cohort (n=1149)</th>
<th>Final Marker Set Cohort (n=372)</th>
<th>All Patients (n =1521)</th>
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<td>Freq (Percent)</td>
<td>Freq (Percent)</td>
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<td>LTAD + RT</td>
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<td>100</td>
<td>513 (44.7%)</td>
<td>159 (42.7%)</td>
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<td>Freq (Percent)</td>
<td>Freq (Percent)</td>
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<td>135 (36.3%)</td>
<td>587 (38.6%)</td>
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<td>Freq (Percent)</td>
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<td>Alive</td>
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<td>171 (46.0%)</td>
<td>695 (45.7%)</td>
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<td>Death - prostate cancer</td>
<td>166 (14.5%)</td>
<td>62 (16.7%)</td>
<td>228 (15.0%)</td>
<td></td>
</tr>
<tr>
<td>Death – other cause</td>
<td>459 (40.0%)</td>
<td>139 (37.4%)</td>
<td>598 (39.3%)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Abbreviations: STAD = short term androgen deprivation therapy; LTADT = long term androgen deprivation therapy; RT = radiotherapy; KPS = Karnofsky performance status; DM = distant metastasis; PCSM = prostate cancer specific mortality
Table 2. Descriptive Summary of Tumor Biomarkers in Analysis Cohort (N=372)

<table>
<thead>
<tr>
<th>Marker</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Q1</th>
<th>Median</th>
<th>Q3</th>
<th>Max</th>
<th>Spearman Rank Correlation among markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki-67</td>
<td>10.6</td>
<td>8.2</td>
<td>0.0</td>
<td>5.0</td>
<td>8.5</td>
<td>13.9</td>
<td>51.8</td>
<td>-</td>
</tr>
<tr>
<td>MDM2</td>
<td>155.2</td>
<td>53.8</td>
<td>0.0</td>
<td>148.0</td>
<td>169.0</td>
<td>186.0</td>
<td>223.0</td>
<td>0.196</td>
</tr>
<tr>
<td>Cox-2</td>
<td>132.6</td>
<td>20.5</td>
<td>75.0</td>
<td>118.5</td>
<td>132.0</td>
<td>146.0</td>
<td>214.0</td>
<td>0.063</td>
</tr>
<tr>
<td>p16</td>
<td>71.2</td>
<td>24.0</td>
<td>0.0</td>
<td>60.9</td>
<td>79.7</td>
<td>88.5</td>
<td>100.0</td>
<td>-0.096</td>
</tr>
</tbody>
</table>

Abbreviations: SD = standard deviation; Min = minimum; Q1 = first quartile; Q3 = third quartile; Max = maximum
Table 3: Multivariable model for distant metastasis including clinical and biomarker covariates (N=372)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Subdistribution Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki-67*</td>
<td>1.53</td>
<td>1.28 - 1.82</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Cox-2*</td>
<td>1.37</td>
<td>1.01 - 1.84</td>
<td>0.040</td>
</tr>
<tr>
<td>p16*</td>
<td>0.74</td>
<td>0.60 - 0.92</td>
<td>0.0065</td>
</tr>
<tr>
<td>MDM2 (≥184 vs. &lt;184)</td>
<td>1.73</td>
<td>1.04 - 2.84</td>
<td>0.036</td>
</tr>
<tr>
<td>Treatment (LTADT vs. STADT)</td>
<td>2.53</td>
<td>1.58 - 4.04</td>
<td>0.0001</td>
</tr>
<tr>
<td>Gleason Score (≥8 vs. &lt; 8)</td>
<td>3.11</td>
<td>1.99 - 4.85</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Stage (T3/4 vs. T2)</td>
<td>1.48</td>
<td>0.93 - 2.36</td>
<td>0.098</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>0.96</td>
<td>0.93 - 1.00</td>
<td>0.026</td>
</tr>
<tr>
<td>Initial PSA (per 10 units)</td>
<td>1.003</td>
<td>0.98 - 1.09</td>
<td>0.21</td>
</tr>
</tbody>
</table>

* continuous scale, standardized

Abbreviations: STAD = short term androgen deprivation therapy; LTADT = long term androgen deprivation therapy
Figure 1.

**Predicted Cumulative Incidence of Distant Metastasis - STADT**

- **Favorable Biomarker Profile**
- **Unfavorable Biomarker Profile**

**Predicted Cumulative Incidence of Distant Metastasis - LTADT**

- **Favorable Biomarker Profile**
- **Unfavorable Biomarker Profile**
Figure 2.

Cumulative Incidence of Distant Metastasis by Predicted Risk – STADT

Cumulative Incidence of Distant Metastasis by Predicted Risk – LTADT
Figure 3.
Figure 3, bottom

Cumulative Incidence of Prostate Cancer Specific Mortality after Distant Metastasis in High-Risk Patients

<table>
<thead>
<tr>
<th>Patients at Risk</th>
<th>Years after Distant Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>STADT</td>
<td>12 6 5 2 1 0 0</td>
</tr>
<tr>
<td>LTADT</td>
<td>32 10 9 4 2 1 0</td>
</tr>
</tbody>
</table>
A TISSUE BIOMARKER BASED MODEL THAT IDENTIFIES PATIENTS WITH A HIGH RISK OF DISTANT METASTASIS AND DIFFERENTIAL SURVIVAL BY LENGTH OF ANDROGEN DEPRIVATION THERAPY IN RTOG PROTOCOL 92-02

Alan Pollack, James J Dignam, Dayssy A Diaz, et al.

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