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Predictive Models in External Beam Radiotherapy for Clinically Localized Prostate Cancer

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Abstract

Predictive models are increasingly being used in effort to allow Physician and patient expectations to be aligned with outcomes that are based on available data. Most predictive models for men treated with external beam radiotherapy for clinically localized prostate cancer are based on Gleason Score, clinical T-Stage and prostate specific antigen (PSA) levels. More sophisticated models have also been developed that incorporate treatment related variables such as the dose of radiation and use of androgen deprivation therapy. Most of the predictive models applied to prostate cancer were derived using PSA recurrence rates as the major endpoint but increasingly clinical endpoints have been incorporated into predictive models. Biomarkers are also increasingly being added to predictive models in an effort to strengthen them. The Radiation Therapy Oncology Group (RTOG) have completed studies on a wide range of markers using tissue from two Phase III Trials (RTOG 8610 and 9202). To date preliminary assessments of p53, DNA Ploidy, p16/pRB, Ki-67, MDM2, Bcl-2/Bax, CAG repeats, Cox-2, Stat3, Cyp3A4 and PKA have been completed. Although not ready for wide spread routine use, there are reasons to believe that future models will combine these markers with traditional pretreatment and treatment related variables and improve our ability to predict outcome and select the optimal treatment.

Keywords

prostate cancer; radiotherapy; randomized trials; predictive models

Introduction

Many men are treated with external beam radiotherapy (EBRT) with curative intent for clinically localized prostate cancer. In an effort to give meaningful guidance to these men, a number of models have been developed to guide therapy and predict outcome. Most of these models have been based on standard pretreatment prognostic factors including: Gleason Score, T Stage and when available PSA. In addition, treatment related variables such as radiation dose, and androgen deprivation therapy have been added to predictive models.

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These pretreatment and treatment related factors have been well studied and are the focus of this review. In addition to the standard predictors of outcome alluded to above, a number of biomarkers have been studied in combination with radiotherapy 1⁻3. A comprehensive review of this topic is beyond the scope of this review but the next section summarizes work published (at the time of this writing) by the Radiation Therapy Oncology Group (RTOG) focusing on a number of potential prognostic factors. The latter part of this review will focus on the "state-of-the-art" of predictive models that have been based on pretreatment factors widely available outside of the research setting.

Biomarkers in radiotherapy for prostate cancer: Contributions from the RTOG Trials

The RTOG can be credited with having performed the most extensive studies of biomarkers in men with clinically localized prostate cancer treated with external beam radiotherapy (EBRT) on Phase III Randomized Trials. A partial list of these studies is shown in Table 1. The source of the tissue used for these studies came from two Phase III Trials RTOG 8610 and RTOG 9202. Altogether eleven markers have been studied in 15 manuscripts between 1997 and 2008.

The first biomarker evaluated by the RTOG was p53. The study population consisted of a subset men entered on RTOG protocol 8610, treated with EBRT with or without combined androgen deprivation therapy (ADT) 4. This subset consisted of 129 (27%) of the 471 patients entered in the trial, for whom there was sufficient tumor material for analysis. Abnormal p53 protein expression was detected in 23 (18%) of tumors. Statistically significant associations were noted between abnormal p53 protein expression and increased risk of distant metastases (P=0.04), decreased probability of progression-free survival (p=0.03), and reduction in overall survival (p=0.02). Patients treated with EBRT and ADT, whose tumors exhibited abnormal p53 protein expression had a reduced time to the development of metastases (P = 0.001), however this difference was not seen patients treated with EBRT alone. Based on this preliminary analysis, the RTOG carefully evaluated this endpoint for patients treated on RTOG 9202.

Tumor tissue sufficient for analysis of p53 status was available in 777 cases from RTOG 9202 5. Abnormal p53 was noted in 22% of these cases, and was associated with cause-specific survival (p=0.014) and risk of distant metastasis (p=0.013). In the subgroup of patients treated with short term ADT, there was a correlation between p53 status and cause-specific survival (p=0.004). When patients were divided into subgroups according to p53 status, only the subgroup of patients with abnormal p53 showed significant association between the assigned treatment and cause-specific survival (p<0.01). Unfortunately, because all patients on RTOG 9202 received ADT, the question of a possible unfavorable interaction between abnormal p53 expression and the use of short term ADT compared to EBRT alone (raised in the previous analysis based on RTOG 8610) could not be resolved.

DNA-Ploidy was evaluated using a cohort of 149 men (33% of the total number) treated on RTOG 8610 3. From this cohort 50% were treated with EBRT alone, and 50% with EBRT and short-term ADT. DNA ploidy was independent of other pretreatment variables. The 5-year overall survival was 70% in those with diploid tumors and 42% for non-diploid tumors. Although, the possession of a non-diploid tumor was associated with a reduced overall survival, there was no correlation with distant metastasis. The investigators postulated that patients with non-diploid tumors might be less responsive to salvage ADT and that the use of short term ADT might not be advisable in patients with non-diploid tumors.

Based on a subset of patients treated on RTOG 8610, loss of p16 expression, was associated with an increased risk of local failure, distant metastasis and disease-specific survival ($p<0.01$; $p<0.03$; and $p<0.01$, respectively) and there was a borderline association with on overall survival of ($p=0.07$) 6. In an analysis of 612 patients from RTOG 9202, reduced expression was associated with an increased rate of distant metastases ($p<0.04$) 7. Among patients with high immunostaining for p16, the use of long term ADT was associated with an increase in cause specific survival and a decreased incidence of distant metastasis compared to short-term ADT ($p<0.001$, $p<0.01$). This may suggest that p16 expression might be associated with increased hormonal sensitivity.

Ki-67 was the next marker evaluated by the RTOG using tissue from RTOG 8610. Diagnostic material from 108 patients was available for Ki-67 analysis with 60 patients treated with EBRT alone, and 48 also receiving short-term ADT 8. Ki-67 staining index </=3.5% and >3.5%, was associated with a 5-year risk of distant metastasis of 13.5% and 50.8% ($p=0.0005$), a 5-year risk of disease specific survival of 97.3% and 67.7% ($p=0.0039$), and a five year overall survival rate of 70 and 55% ($p=0.17$). These trends were confirmed in multivariate analyses. An additional assessment of Ki-67 was also made using tissue from 537 patients treated on RTOG 9202 9. When analyzed as a continuous variable, Ki67 staining index was associated with the risk of distant metastasis ($P <0.0001$), disease specific survival ($p<0.0001$), and overall survival ($p< 0.01$), and was the most significant predictor of the first two endpoints. Based on a subset analysis, the authors hypothesized that there may be a subgroup of patients who do not require long term ADT. This observation suggests that Ki-67 might be useful in selecting patients for short term ADT and stratifying patients placed on future trials.

The RTOG also evaluated the association between MDM2 expression (an oncoprotein that promotes p53 degradation) and outcomes using tissue from RTOG 8610 10. Adequate archival diagnostic tissue specimens from 108 patients with MDM2 overexpression classified as having > 5% nuclear staining was seen in 44% ($n = 47$) of specimens. By multivariate analysis there was trend for a relationship with the risk of distant metastasis at 5 years ($P = 0.06$). A more comprehensive and promising study combining MDM2 with Ki-67 based on patients treated on RTOG 9202 is near completion (but not yet available). The results indicate that MDM2 compliments Ki-67, is much stronger a predictor of outcome than p53 and the combination of MDM2 and Ki-67 has promise in identifying men at a particularly high risk of distant metastases.

Bcl-2 and Bax expression were also evaluated using tissue form RTOG 8610 11. Suitable diagnostic tissue was available from 119 (26%) patients for bcl-2 and 104 (23%) for bax analysis. Bcl-2 over expression was exhibited in 26% ($n = 30$) and abnormal bax expression in 47% ($n = 49$) of cases. Based on this analysis, neither were found to be related to outcomes. A follow-up investigation was carried out using tissue from 502 patients for Bcl-2 and 343 patients for Bax treated on RTOG 9202 12. Bcl-2 was positive in 45.6% cases, and Bax expression altered in 53.9% cases. The combination of negative Bcl-2/normal Bax expression was related to reduced biochemical failure ($p= 0.036$), particularly among those who received short term ADT suggesting that long term ADT might be advised when either Bcl-2 or Bax is abnormally expressed.

A quantitative assessment of CAG base pair repeats on the androgen receptor (AR) gene was also performed on a subset of patients treated on RTOG 8610 13. CAG repeats were measured in 94 tumor specimens and did not significantly influence either local control, the risk of metastasis, cause specific or overall survival. Patients with short repeats who received short term ADT did seem to have a higher local control rate, however.

Cox-2 expression was also evaluated using tissue from 586 men treated on RTOG 9202 who had sufficient tissue for immunohistochemical staining and image analysis 14. The intensity of Cox-2 staining was predictive of the risk of distant metastasis (p=0.0004) and the risk of biochemical failure using both the ASTRO and the Phoenix definitions (p=0.008 and p=0.014), particularly among those who were treated with short term ADT.

Stat-3 expression was evaluated in a subset of 62 patients who had sufficient tissue from RTOG 8610 15. Activated STAT3 was inversely correlated with the development of distant metastasis (p=0.04), but not survival or local control although due to the small sample size this conclusion has to be cautiously interpreted.

Polymorphisms in the androgen receptor CYP3A4 were evaluated for a subset of patients treated on RTOG 9202 to understand how variation polymorphisms in CYP3A4 correlated with outcomes and race 16. Tissue from 56 men African-American origin and 54 of European-American patients was studied. There was a strong association between race and CYP3A4 polymorphisms with 75% of European-Americans having the Wild Type compared to only 25% of African-American men (p<0.0001) but there was no association between CYP3A4 polymorphisms studied and outcomes.

Archival diagnostic tissue samples from 80 patients treated on RTOG 8610 was used to study the predictive value of protein kinase A RI-alpha (PKA) expression 17. On multivariate analyses, there was a correlation between overexpression and increased biochemical failure (p=0.03), increased distant metastasis (p=0.018), and a trend for increased cause specific mortality (p=0.08). The analysis PKA expression to RTOG 9202 patient outcome is nearing completion and validates the findings from RTOG 8610.

Several conclusions can be reached based on these hypothesis-generating studies. Despite these interesting observations taken as a whole the major conclusion remain. Biomarkers as a major predictor of outcome are not yet ready for routine use in clinical practice. However, the relationships observed are promising. A model is being developed that incorporates the key markers identified in cases from RTOG 92-02; preliminary evidence indicates that such a model will add significantly to classic clinical, pathologic and treatment-related covariates in predicting distant metastasis at 10 years. The preliminary findings of these studies support the need for validation studies (which are in progress). As is shown in Table 1., the most robust observations relate to the clinical relevance of p16, Ki-67, MDM2, Cox-2 and PKA, with most of these appearing to be useful in identifying subsets of patients who do not appear to benefit from LTADT.

Predictive Models Using Standard Pretreatment Clinical Features

Predictive models for men with clinically localized prostate cancer have evolved over the last ten years. Ross et al. reported over 40 models that could be used to predict various outcomes for prostate cancer patients 18. They included six models involving pretreatment variables that might be useful for predicting PSA recurrences after External Beam Radiotherapy (EBRT) 18. These models were based on data from retrospective and prospective studies. These algorithms have generally been based on mathematical constructs 19, 20, or simple additive models 21, 22. Some models have helped to provide a rationale for determining what volumes should be selected for irradiation 23, 24. In addition to the variety of sources of the data, and the methods used to create predictive models, these models have also varied in their endpoints. Most predictive models are designed to predict PSA failure (typically at 5 years), while a small number have been use to predict survival 19–22, 25. More recently, surrogate endpoints such as PSA doubling time (PSADT) or time to distant metastasis (DM), have been considered in an attempt to shorten the time required to reach clinical endpoints with a closer association with survival 26, 27.

The shortfalls of each of these models have become more apparent as we have accumulated empirical data and learned more about prostate cancer. For example, it is now known that early nomograms used to determine the risk of lymph node involvement are probably inaccurate. In these early series the type of lymph node dissection was not extensive enough to identify all of the nodes that were involved 23, 28–30. Early predictive models also tended to assume the impact of Gleason score 7 was the same as a PSA (e.g. 10 and 20ng/ml) and ignored the impact of having multiple adverse prognostic features and the impact of the percentage positive biopsies 21, 22. Subsequent updates of these models addressed some but not all of these issues 31.

Kattan and associates have contributed mightily to the area of predictive models with many predictive nomograms encompassing a variety of treatment options including three-dimensional conformal external beam radiotherapy 19. The nomograms have been based on more than 1000 patients and using a combination of statistical methods including eight prediction techniques and Cox proportional hazard regression methods, an artificial neural network and recursive partitioning and later validated. Despite the eloquence of this nomogram and wide-scale adoption it is now clear that there are severe limitations to its use. Among the shortcomings of the first Kattan EBRT nomogram is that it excludes consideration of a number of factors shown to be of prognostic significance. For example this nomogram ignores the potential impact of whole-pelvic radiotherapy and assumes that the benefits of neoadjuvant androgen deprivation therapy are uniform across prognostic subgroups 32. This early Kattan et al nomogram is also problematic because of the relatively short follow-up which compromises the accuracy of predictions when based on the American Society of therapeutic Radiology and Oncology (ASTRO) Consensus Definition) ADT 19, 34, 35. The use of the ASTRO Definition has also been shown to be inappropriate for men treated with ADT 34, 35.

Also of concern is the fact that it seems to be most accurate for the “average patient”. When applied to patients at extremes it seems to render predictions that do not jive with clinical experience. For example, Figures 1a and 1b provide two such examples. In the first example (Figure 1a), a patient with a PSA of 4 ng/ml, clinical stage T3c disease, a Gleason Score of 10, and is treated to 72 Gy with short-term androgen deprivation therapy. The nomogram predicts a five-year control rate of 70% (figure 1a). In fact such patients usually do very poorly and can be expected to have a very high relapse rate (and mortality rate see discussion below). In the second example (Figure 1b) a patient has a low T-stage, Gleason Score, dose of radiation and no hormonal therapy but a high PSA (25 ng/ml) is predicted to have a worse outcome. In fact however, his survival would be expected to be higher than the patient in the first example. These conclusions are highlighted by the stark contrast between the weighting for this nomogram and a more recent nomogram that was shown to correlate with time to metastasis and death (see discussion below)27, 33 The more recent nomogram that is predictive of the time to metastatic disease following EBRT as shown in Figure 4. This more clinically relevant nomogram has been validated to be predictive of survival as well 27, 33.

Note however, the two nomograms are weighted very differently, even though they were created by the same investigators, include similar variables and presumably similar (or the same) patients as the first nomogram. This means that the true significance of a high PSA (e.g. 25 ng/ml) and a high Gleason Score (e.g. 10) alluded to above are reversed when metastasis and survival are the primary endpoint (as noted above).

The first predictive model for overall and disease specific survival after EBRT for localized prostate cancer was published by the RTOG in 2000, as shown in Figure 3 25. This model was based on data from the largest prospective Phase III Trials evaluated to date and was

also useful for defining who should be prescribed androgen deprivation therapy and whether it should be prescribed short or long term 36. This model was subsequently validated using multi-institutional data and is useful in first elucidating the impact of pretreatment PSA on overall and cause specific survival 37.

With additional follow-up other models, including the popular risk stratification schemes proposed by D'Amico, have been shown to predict survival 31. As a result of these and other similar data, a modification of the current American Joint Commission for Cancer (AJCC) Staging system, has been proposed 38. This revised staging system is shown in Table 2, and would appear to be a relatively simple way for the AJCC system to be improved by incorporating PSA, Gleason and T Stage in a way that reflects current practice habits.

Using the nomogram for predicting the probability of metastatic disease after EBRT developed by Kattan et al. a number of investigators have reported the ability to predict overall and cause specific survival that improved upon the RTOG Risk Groups, as can be seen in Figure 4. The major value of this model is that it can be used not only to predict time to metastatic disease but also as a surrogate for disease specific and ultimately overall survival, thus potentially shorting the time critical endpoints in the setting of clinical trials 27, 33.

Despite the major progress that has been made over the past 10 years or more none of the models proposed to date can be said to completely address the complex array of factors contributing to the outcome of men treated with EBRT. For example, in addition to the biomarkers mentioned earlier (as well others not covered here), socioeconomic factors such as KPS and age have also been shown to impact outcome 39. Thus, with time it is likely that far more comprehensive and accurate models will be made available and allowing us to improve our ability to predict outcomes for men treatment with EBRT for clinically of localized prostate cancer.

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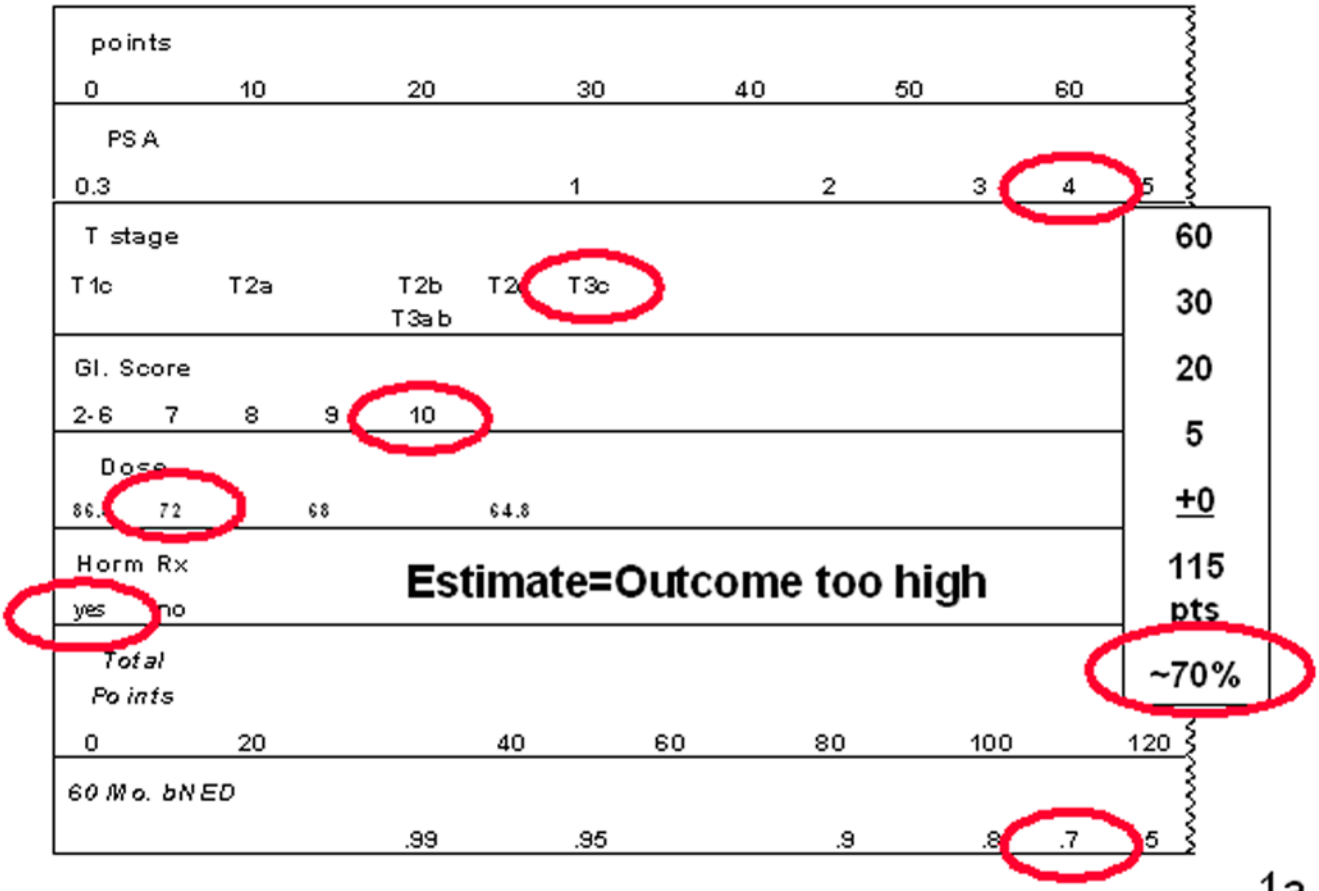
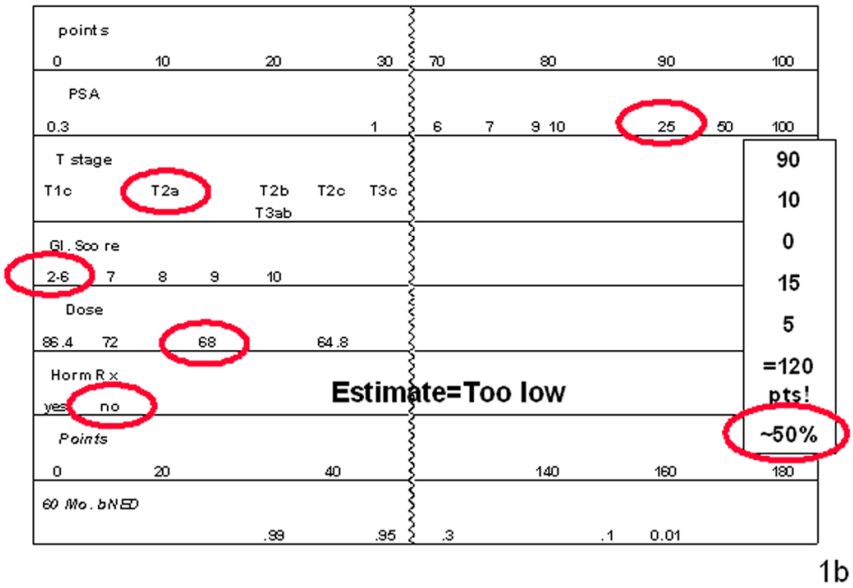


1a



1b

Figure 1.

Figures 1a and 1b

Two examples of outcomes predicted by Kattan nomogram for men with clinically localized prostate cancer treated with three-dimensional conformal external beam radiotherapy 19. In

the first example (Figure 1a), a patient with a PSA of 4 ng/ml, clinical stage T3c disease, a Gleason Score of 10, and is treated to 72 Gy with short-term androgen deprivation therapy. The nomogram predicts a five-year control rate of 70%. Such patients usually do very poorly and can be expected to have a very high relapse rate. In the second example (Figure 1b) a patient is has a low T-stage, Gleason Score, dose of radiation and no hormonal therapy but a high PSA (25 ng/ml) is predicted to have a worse outcome. His survival would be expected to be higher than the patient in the first example however.

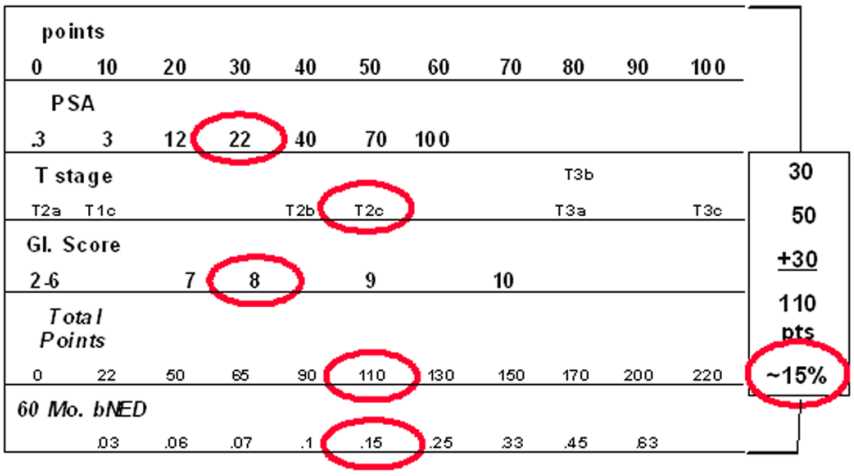


Figure 2.

Example of use of Kattan nomogram for predicting risk of metastasis at 5 years following three-dimensional conformal radiotherapy 27, 33. This nomogram was subsequently validated as predictive of cause specific and overall survival in patients treated at UCSF and University of Michigan as shown in Figure 4 27, 33.

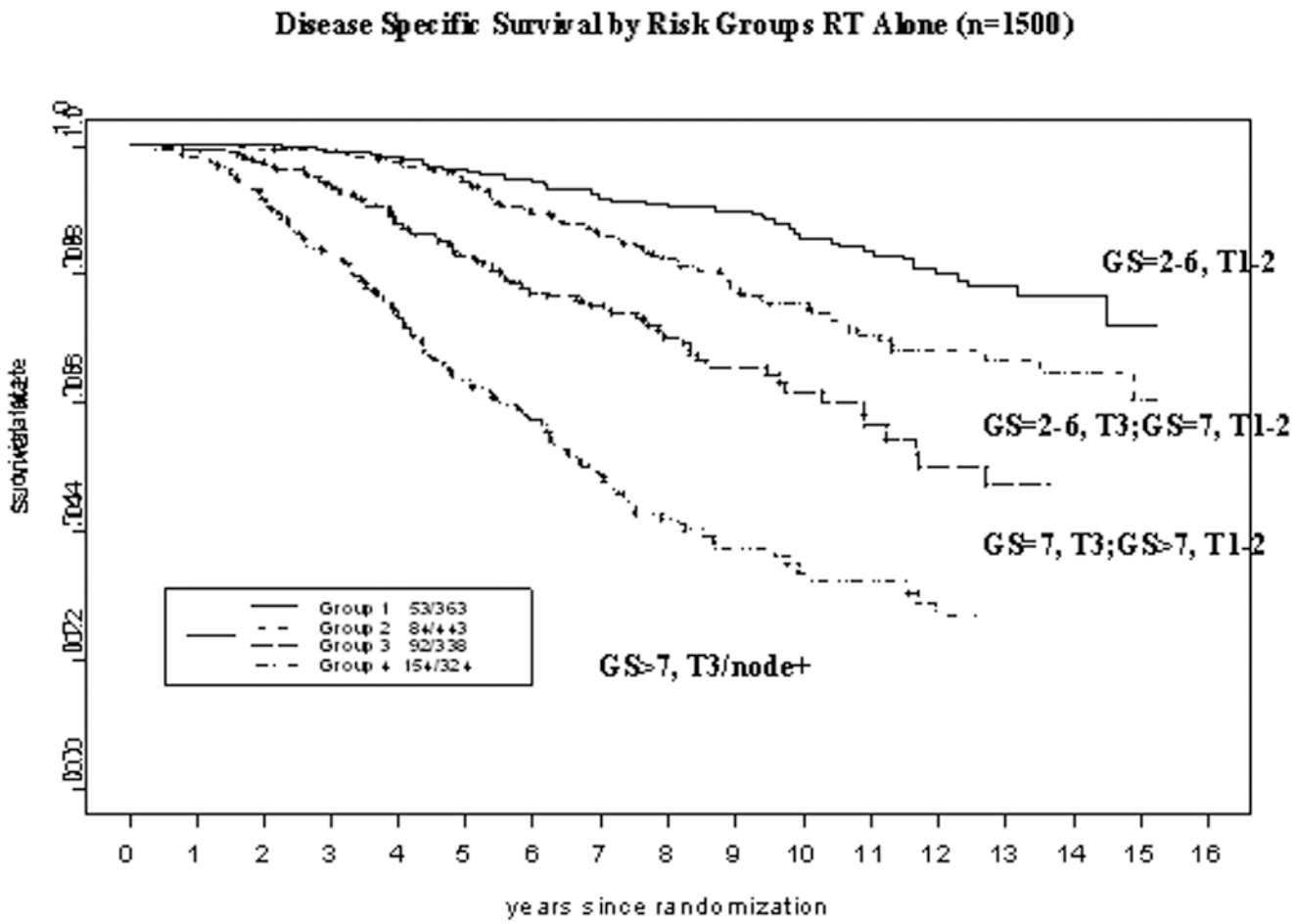


Figure 3.

Disease Specific Survival (DSS) is shown by RTOG Risk Group. Analysis is based on 1500 patients treated with external beam radiotherapy alone on RTOG 8531 and 8610. From top to bottom, *Risk Group 1* defined as: Stages T1-2, Nx, Gleason 2–6; *Risk Group 2* defined as: Stages Gleason 2–6 and T3Nx or N+ or Gleason score=7, T1-2 Nx; *Risk Group 3* defined as: T3Nx with Gleason Score=7 or N+ and Gleason score=7 or Stages T1-2, Nx, Gleason 8; *Risk Group 4* defined as: T3Nx with Gleason Score=8–10 or N+ Gleason score=8–10.

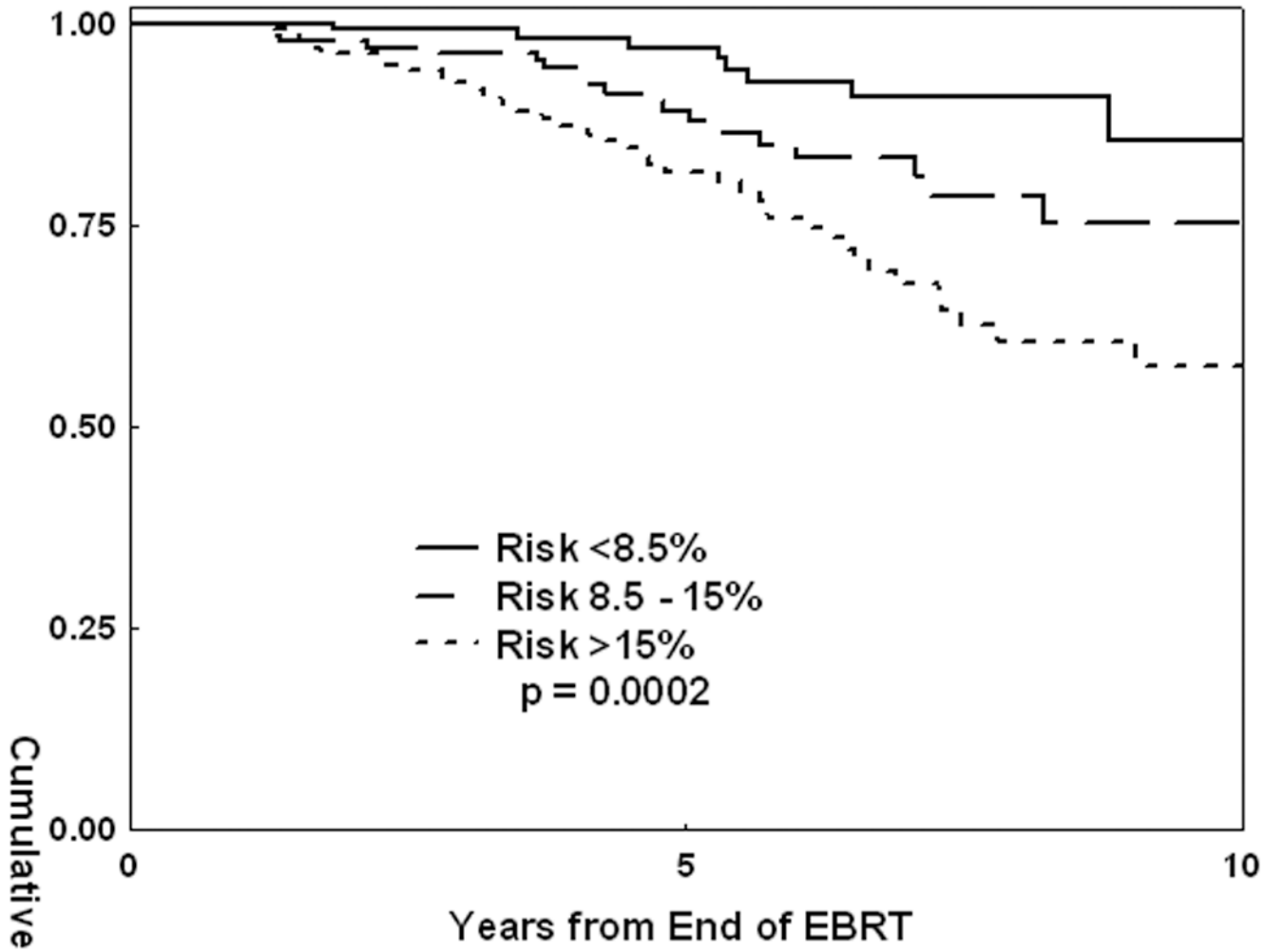


Figure 4.

Disease Specific Survival (DSS) is shown by estimated risk of distant metastases using the Kattan Nomogram 27, 33. Note highly significant differences are observed in DSS among the 3 tertiles created by the nomogram (cut-points: <8.5%, 8.5% – 15%, and > 15%) ($p < 0.001$).

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Table 1

Selected Series of Biomarker studies performed by the RTOG

Marker	**RTOG 8610**			**RTOG 9202**		
	Distant Mets	Cause Specific survival	Overall survival	Distant Mets	Cause Specific survival	Overall survival
p53[*] 4, 5	+	+	+[*]	+	+	+ (among patients treated with STADT)
DNA-Ploidy 3	-	Not reported	+	NYA	NYA	NYA
p16/pRB[†] 6, 7	+	+	+/− (borderline significance, p=0.07)	+	+	-[#]
Ki-67 8, 9	+	+	− (70 vs 55%, p=0.17)	+	+	+[#]
MDM2 10	+/− (borderline significant, p=0.06)	-	-	Work in progress	Work in progress	Work in progress
Bcl-2 / Bax 11, 12	-	-	-	-	-	-
Androgen receptor CAG repeats 13	-	-	-	NYA	NYA	NYA
Cox-2 14	ND	ND	ND	+	-	-
Stat3 15	+	- (inadequate sample size?)	- (inadequate sample size?)	NYA	NYA	NYA
Cyp3A4 16	ND	ND	ND	-	-	-
PKA 17	+	+/− (borderline significant, p=0.08)	-	NYA	NYA	NYA

EBRT=External Beam radiotherapy, ADT=Androgen Deprivation Therapy; STADT=Short Term Androgen Deprivation Therapy;

[*] worse outcome for patients receiving STADT compared to EBRT alone if abnormal p53.

[*†] pRB was only done for RTOG 86–10.

***LTADT=long term ADT; Not yet available = NYA, Not done=ND.

#Survival advantage for those with high levels of immunostaining for use of LTADT.

Table 2

Proposed “New” Prostate Cancer Staging System

Tx	tumor cannot be assessed
T0	no evidence of tumor
Tis	Carcinoma in situ (PIN)
New Stage 1	T1-2 and GS ≤ 6 and PSA < 10 ng/ml
New Stage 2	(T1-2 and GS ≤ 6 and PSA <10–20ng/ml) or (T1-2 and GS=7 and PSA <20ng/ml)
Stage 2a	T1-2 and GS ≤ 6 and PSA 10-<20
Stage 2b	T1-2 and GS 7 and PSA <20
New Stage 3	T1-2 and GS ≤6 and PSA ≥ 20ng/ml or T1-2 and GS 7 and: PSA ≥20 ng/ml or or T1-2 and GS=8–10 or clinical T3 disease
Stage 3a	T1-2, GS ≤6 and PSA ≥ 20 or T1-2, GS 8–10 and PSA <20
Stage 3b	T1-2, GS ≥ 7 and: PSA ≥ 20
Stage 3c	Clinical T3, Seminal Vesicle or Bladder Neck invasion
Nx	lymph nodes cannot be assessed
N0	no regional lymph node involved
N1	metastases, regional lymph node(s)

Modified from Roach et al. 38