

Cox-2 Expression Predicts Prostate Cancer Outcome: An Analysis of RTOG 92-02

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ABSTRACT

Purpose: The cyclooxygenase-2 (Cox-2) enzyme, one of two isoenzymes, is responsible for converting arachidonic acid to prostaglandins and other eicosanoids. Apart from its well-characterized role in inflammation, Cox-2 has been found to be expressed in several human cancers, including prostate cancer. In vitro and in vivo studies using Cox-2 inhibitors have highlighted the influence of Cox-2 on angiogenesis and tumorigenesis and also demonstrated a link between Cox-2 overexpression and resistance to chemotherapy and radiation therapy in prostate tumors regardless of androgen-responsiveness.

In this report, we sought to explore the relationship of Cox-2 expression and patient outcome in men enrolled in Radiation Therapy Oncology Group protocol 92-02, who were treated with radiation (RT) and short term or long term androgen deprivation (AD). The endpoints of interest in this study were overall mortality (OM), cause specific mortality (CSM), distant metastasis (DM), local failure (LF) and biochemical failure (BF).

Methods: There were 586 cases in the study cohort from which had available tissue and suitable staining by immunohistochemistry. Median follow-up was 106.9 months. The intensity of Cox-2 staining was quantified by automated image analysis (Clariant Chromavision, San Juan Capistrano, CA). The Cox-2 intensity scores were modeled both as continuous and dichotomized (using the median, 25th and 75th percentiles) covariates. Univariate and multivariate analyses (MVA's) by Cox proportional hazards models were applied using the endpoints OM, CSM, DM, LF, and BF by both the ASTRO consensus (three consecutive rises in PSA or salvage hormones) and Phoenix (PSA > nadir + 2 ng/ml after treatment or salvage hormones) definitions. The MVA's included dichotomized covariates: Age (<70 vs. ≥ 70 years), iPSA (≤30 vs. >30 ng/mL, based on protocol stratification), Gleason score (2-6 vs. 7-10), T-stage (T2 vs. T3/T4) and Assigned Treatment (short term AD+RT vs. long term AD+RT).

Results: There was no statistically significant difference in the distribution of patients by pre-treatment characteristics between those cases with and those without Cox-2 intensity scores, although the distribution by assigned treatment was significant (p=0.0115) (Table 1). Likewise, there was no difference in patient outcome between the Cox-2 available and unavailable groups. In univariate analysis, Cox-2 intensity as a continuous variable was significantly associated with DM and BF by both definitions (Table 2). The higher the intensity, the greater the risk of failure by these endpoints. In the MVA's, Cox-2 as a continuous covariate was an independent predictor of DM, and BF by both definitions (Table 3). All other dichotomized covariates included in the MVA's were also significant.

The Cox-2 intensity score dichotomized at the median cut-point of 134 arbitrary units (range: 69 - 214) was significantly associated with DM and showed borderline significance with BF (Table 4). Dichotomized results by the other cut-points were not significant. The 5 year DM rate was 10.6% for an intensity score of ≤134, versus 14.1% for an intensity score of >134; the 8 year DM rate was 16.4% for an intensity score of ≤134, versus 19.9% for an intensity score of >134. In the MVA's, Cox-2 remained significantly related to DM (Table 5). All other covariates included in the MVA were also significant.

When the patients were subdivided by protocol treatment arm, dichotomized Cox-2 was significantly associated with both BF endpoints for those who received short term AD+RT. Likewise, a trend was seen for DM (p=0.1) in the short term AD+RT patients subdivided by Cox-2; probably this did not reach significance because of proportionally fewer events.

RESULTS

Table 1. Distribution of patients by determined or missing Cox-2 Intensity Score (N=1521)

Characteristics	Determined Cox-2 (n=586)		Missing Cox-2 (n=935)		p-value*
	n	%	n	%	
Age, years					
<70	258	44	423	45	0.6432
≥70	328	56	512	55	
Gleason Score					
Unknown/Missing	43	7	57	6	0.3282
2-6	212	36	370	40	
7-10	331	57	508	54	
Clinical Stage					
T2	268	46	424	45	0.8830
T3 or T4	318	54	511	55	
PSA					
≤ 30	389	66	632	68	0.6248
> 30	197	34	303	32	
Assigned Treatment					
STAD + RT	270	46	493	53	0.0115†
LTAD + RT	316	54	442	47	

Abbreviations: STAD, short-term androgen deprivation; RT, radiotherapy; LTAD, long-term androgen deprivation.
*P-value is from Chi-square statistics.
†Indicates the statistically significant at the significance level of 0.05.

Table 2. Univariate analysis of Cox-2 Intensity Score as a continuous variable

Endpoint	n	Failures	RR*	p-value**
OM	586	308	1.002	0.5054
CSM	586	91	1.003	0.4815
DM	586	113	1.012	0.0057†
LF	586	68	1.007	0.2282
BF ASTRO	586	350	1.007	0.0068*
BF Phoenix	586	300	1.006	0.0334†

Abbreviations: RR, relative risk; OM, overall mortality; DM, distant metastasis; CSM, cause specific mortality; LF, local failure; BF, biochemical failure.
*Relative risk is for a unit change of 1 percentage in the Cox-2 intensity score.
**P-value from Chi-square test using the Cox proportional hazards model.
†Indicates the statistically significant at the significance level of 0.05.

Table 3. Multivariate analysis of Cox-2 Intensity Score as a continuous variable

Endpoint	Covariate	Group	RR	95% CI	p-value*
DM	Cox-2 intensity	Continuous	1.014	(1.005, 1.023)	0.0026†
	Treatment arm	LTAD + RT	0.599	(0.401, 0.894)	0.0120†
	Age	≥ 70	0.659	(0.442, 0.982)	0.0407†
	Gleason Score**	7-10	2.165	(1.348, 3.476)	0.0014†
	Clinical Stage	T3 or T4	1.612	(1.063, 2.445)	0.0245†
BF ASTRO	Cox-2 intensity	Continuous	1.007	(1.002, 1.012)	0.0098†
	Treatment arm	LTAD + RT	0.466	(0.373, 0.583)	<0.0001†
	Age	≥ 70	0.686	(0.550, 0.856)	0.0009†
	PSA	> 30	1.418	(1.129, 1.781)	0.0027†
BF Phoenix	Cox-2 intensity	Continuous	1.006	(1.000, 1.011)	0.0386†
	Treatment arm	LTAD + RT	0.494	(0.389, 0.628)	<0.0001†
	Age	≥ 70	0.709	(0.560, 0.899)	0.0045†
	PSA	> 30	1.491	(1.170, 1.900)	0.0012†

Abbreviations: RR, relative risk; CI, confidence interval; DM, distant metastasis; LTAD, long-term androgen deprivation; RT, radiotherapy; BF, biochemical failure.
*P-values from Chi-square test using Cox proportional hazards model.
†Indicates the statistically significant at the significance level of 0.05; **43 patients without Gleason score are not included.

Table 4. Univariate analysis of Cox-2 Intensity Score as a dichotomous variable

Endpoint	Cox-2 Cut-point	n	Failures	RR	p-value**
OM	≤ 134	304	150	1.069	0.5648
	> 134	282	158		
DM	≤ 134	304	51	1.500	0.0322†
	> 134	282	62		
LF	≤ 134	304	32	1.236	0.3859
	> 134	282	36		
BF ASTRO	≤ 134	304	177	1.109	0.3329
	> 134	282	173		
BF Phoenix	≤ 134	304	145	1.238	0.0645
	> 134	282	155		

Abbreviations: RR, relative risk; OM, overall mortality; DM, distant metastasis; LF, local failure; BF, biochemical failure.
**P-value is from Chi-square test using the Cox proportional hazards model.
†Indicates the statistically significant at the significance level of 0.05.

Table 5. Multivariate analysis of Cox-2 Intensity Score as a dichotomous variable

Endpoint	Covariate	Group	RR	95% CI	p-value*
DM	Cox-2 intensity	> 134	1.499	(1.010, 2.227)	0.0448†
	Treatment arm	LTAD + RT	0.578	(0.388, 0.862)	0.0072†
	Gleason Score**	7-10	2.107	(1.316, 3.376)	0.0019†
	Clinical Stage	T3 or T4	1.674	(1.105, 2.534)	0.0150†

Abbreviations: RR, relative risk; CI, confidence interval; DM, distant metastasis; LTAD, long-term androgen deprivation; RT, radiotherapy.
*P-values from Chi-square test using Cox proportional hazards model.
†Indicates the statistically significant at the significance level of 0.05; **43 patients without Gleason score are not included.

Table 6. The predictive value of Cox-2 expression by length of AD (assigned treatment)

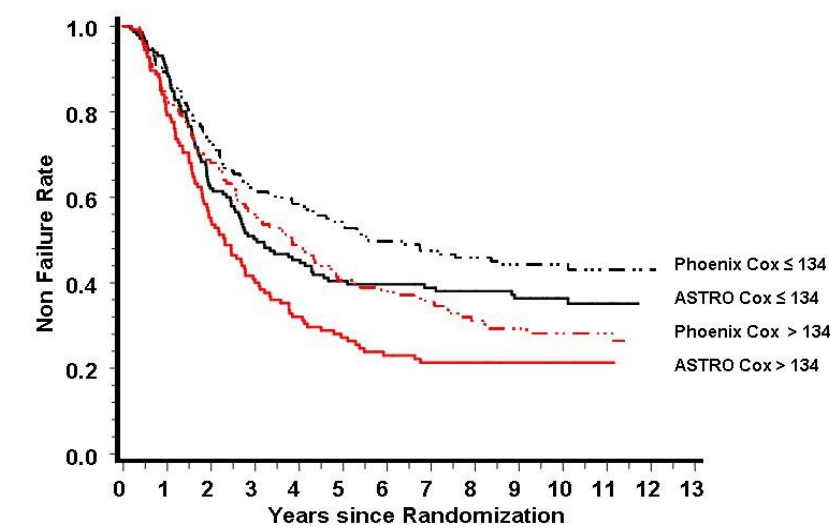
Endpoint	Assigned Treatment	Cox-2 Cut-point	n	Failures	Rate	HR*	p-value**
OM	STAD + RT	≤ 134	145	75	0.4895	RL	
		> 134	125	71	0.4732	1.050	0.7687
	LTAD + RT	≤ 134	159	75	0.5469	RL	
		> 134	157	87	0.5211	1.098	0.5576
DM	STAD + RT	≤ 134	145	30	0.2440	RL	
		> 134	125	37	0.3366	1.496	0.1016
	LTAD + RT	≤ 134	159	21	0.1671	RL	
		> 134	157	25	0.1952	1.490	0.1785
LF	STAD + RT	≤ 134	145	20	0.1580	RL	
		> 134	125	24	0.2102	1.458	0.2134
	LTAD + RT	≤ 134	159	12	0.0793	RL	
		> 134	157	12	0.1418	0.967	0.9364
BF ASTRO	STAD + RT	≤ 134	145	92	0.6494	RL	
		> 134	125	98	0.7872	1.575	0.0019†
	LTAD + RT	≤ 134	159	85	0.5439	RL	
		> 134	157	75	0.5020	0.846	0.2909
BF Phoenix	STAD + RT	≤ 134	145	80	0.5701	RL	
		> 134	125	89	0.7355	1.489	0.0100†
	LTAD + RT	≤ 134	159	65	0.4355	RL	
		> 134	157	66	0.4602	1.071	0.6948

Abbreviations: HR, hazard ratio; RL, reference level; OM, overall mortality; DM, distant mortality; LF, local failure; BF, biochemical failure; STAD, short-term androgen deprivation; LTAD, long-term androgen deprivation.
*Hazard Ratio: a risk ratio of 1 indicates no difference between the two subgroups.
** Actuarial estimates for OM were calculated using the Kaplan-Meier method and the cumulative incidence method was used to estimate DM, LF and BF rates.
†Indicates the statistically significant at the significance level of 0.05.

Figure 1. Survival curve of DM by Cox-2 intensity



Figure 2. Survival curve of BF for the STAD+RT patients by dichotomized Cox-2 intensity



CONCLUSIONS

- Increasing Cox-2 expression was significantly associated with BF and DM.
- Patients in the STAD+RT arm had worse outcome when Cox-2 intensity was high based on the median cut-point.
- Cox-2 inhibitors are potentially useful in high risk prostate cancer patients and this study provides further support for their testing in future clinical trials.