**B536 HW#3**

Fall 2013

1. **Table 1. Characteristics of men enrolled in clinical trial of hormonal therapy for prostate cancer**

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|  | **Nadir PSA** |
| **<4ng/ml** (n=33) | **≥4ng/ml**(n=17) |
|  Mean (sd) or N (%) |
| **Baseline characteristics** |
| Age (years) | 66.788 (5.527) | 68.706 (6.192) |
| Pre-treatment PSA (ng/ml)+ | 527.368 (1092.678) | 938.40 (1597.985) |
| Performance status\* 80-100 50-70 | 27 (71)5 (50) | 11 (29)5 (50) |
| Tumor grade\*\* Least aggressive Intermediate Most aggressive | 7 (70)10 (67)12 (75) | 3 (30)5 (33)4 (25) |
| Bone scan score# Least disease Intermediate disease Most disease | 5 (100)10 (77)17 (57) | 0 (0)3 (23)13 (43) |
| **Post-treatment characteristics** |
| Nadir PSA (ng/ml) | 0.69 (0.68) | 46.776 (56.805) |
| Duration of remission (months) | 36.273 (16.417) | 13.294 (11.246) |

 +7 missing values \*2 missing values \*\*9 missing values #2 missing values

1. Does distribution of relapse within 24 months differ across groups defined by nadir PSA level after adjustment for bone scan score and performance status?
	1. Perform an adjusted logistic regression comparing the odds of relapse within 24 months across groups defined by the nadir PSA level when modeled as a continuous, untransformed variable.

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| --- | --- | --- | --- | --- |
| **Covariate** | **N** | **Odds Ratio** | **P-value** | **95% CI** |
| Nadir PSA (ng/ml), per unit | 48 | 1.034 | 0.476 | 0.943-1.133 |
| Performance status | 48 | 0.952 | 0.211 | 0.882-1.028 |
| Bone scan score | 48 | 2.624 | 0.064 | 0.994-7.297 |

A logistic regression model adjusting for bone scan score and performance status, with robust standard errors, estimates that when comparing two groups of men with different nadir PSA levels, the odds of prostate cancer relapse within 24 months is estimated to be 1.034 times higher for each 1ng/ml difference in nadir PSA. This observed difference is not statistically significant from an odds ratio of 1 (p=0.476). The 95% confidence interval suggests that the observed odds ratio is not what might be typically observed if the true odds of relapse within 24 months was anywhere between 0.943 lower or 1.133 times higher for each 1ng/ml difference in nadir PSA.

* 1. Perform an adjusted logistic regression comparing the odds of relapse within 24 months across groups defined by the nadir PSA level when modeled as a continuous, log transformed variable.

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| **Covariate** | **N** | **Odds Ratio** | **P-value** | **95% CI** |
| Log nadir (per unit ng/ml) | 48 | 2.363 | 0.007 | 1.268-4.402 |
| Performance status  | 48 | 0.949 | 0.174 | 0.880-1.023 |
| Bone scan score  | 48 | 2.345 | 0.223 | 0.595-9.243 |

A logistic regression model adjusting for bone scan score and performance status, with robust standard errors, estimates that when comparing two groups with different log nadir PSA levels, the odds of relapsing within 24 months is 2.363 times higher for each log difference in nadir PSA level, with men having a higher level of log nadir PSA tending towards a higher odds of relapse within 24 months of hormonal treatment. This observed difference is statistically significant from an odds ratio of 1 (p=0.007), with a 95% confidence interval suggesting that the observed odds ratio is what might be typically observed if the true odds of relapse within 24 months was anywhere between 1.268 and 4.402 times higher for each unit of log nadir PSA level. We reject the null hypothesis of no association between log nadir PSA level and relapse of prostate cancer within 24 months in favor of a trend towards higher odds of relapse among men with higher log nadir PSA levels.

* 1. Perform an adjusted logistic regression comparing the odds of relapse within 24 months across groups defined by the nadir PSA level when modeled as linear splines with knots at 1, 4, and 16 ng/ml.

**Figure 1: Scatterplot of prostate cancer relapse and nadir PSA**



The lowess curve shows a non-linear relationship between relapse within 24 months and nadir PSA. The distribution of nadir PSA is left-skewed.

Fitting linear splines allows nadir PSA to have a non-linear effect on the outcome.

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| --- | --- | --- | --- | --- |
| **Covariate** | **N** | **Odds Ratio** | **P-value** | **95% CI** |
| Nadir0to1, per unit ng/ml | 48 | 29.617 | 0.031 | 1.359-654.633 |
| Nadir1to4, per unit ng/ml | 48 | 0.903 | 0.845 | 0.327-2.496 |
| Nadir4to16, per unit ng/ml | 48 | 1.380 | 0.096 | 0.944-2.017 |
| Nadir16up, per unit ng/ml | 48 | 0.982 | 0.043 | 0.964-0.999 |
| Performance status | 48 | 0.937 | 0.154 | 0.856-1.025 |
| Bone scan score  | 48 | 2.522 | 0.206 | 0.601-10.581 |

After adjustment for differences in bone scan score and performance status across groups defined by nadir PSA and modeled as linear splines, we estimate that the predicted odds of prostate cancer relapse within 24 months increase by 29.617 for each 1 ng/ml increase in nadir PSA from 0 to 1 ng/ml, by 0.903 for each 1 ng/ml increase in nadir PSA from 1 to 4 ng/ml, by 1.380 for each 1 ng/ml increase in nadir PSA from 4 to 16 ng/ml, and by 0.982 for each 1 ng/ml increase in nadir PSA above 16 ng/ml.

The Wald-test with 4 degrees of freedom in the linear spline fit indicates there is strong evidence that the linearity assumption does not hold (p= 0.0143).

**Figure 2: Linear splines**



* 1. Interpretation of intercepts:
		1. In the model with nadir PSA level as a continuous variable, the estimated intercept 2.072 is the odds of prostate cancer relapse within 24 months for men not in remission at last follow up, with zero performance status and bone scan score. This is not clinically meaningful.
		2. In the model with nadir PSA as a continuous log transformed variable, the estimated intercept 3.061 is the odds of relapse within 24 months among men not in remission and having zero lognadir PSA, bone scan score, and performance score.
		3. In the model with linear splines, the estimated intercept 0.507 is the odds of relapse within 24 months among men not in remission, when all modeled parameters are set to zero.
1. Model using nadir PSA as the response variable, and relapse within 24 months as the predictor.
2. Perform linear regression analyses to determine whether there is an association between mean nadir PSA level and relapse within 24 months after adjustment for bone scan score and performance status.

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| **Covariate** | **N** | **Coefficient** | **P-value** | **95% CI** |
| Relap24 (per unit, ng/ml) | 48 | 23.518 | 0.046 | 0.476-46.559 |
| Bone scan score | 48 | 6.846 | 0.151 | -2.604-16.295 |
| Performance status | 48 | -0.510 | 0.414 | -1.756-0.736 |

From a simple linear regression model with robust standard errors, with adjustment for bone scan score and performance status, we estimate that mean nadir PSA level differs by 23.518 ng/ml when comparing groups of men who relapsed within 24 months after hormonal therapy and those who did not, with men who relapsed tending towards higher mean nadir PSA level. This finding is significantly different from 0 (p=0.046), suggesting the observed results would not be unusual if the true difference in mean nadir PSA level were between 0.476 and 46.559 ng/ml.

1. Perform linear regression analyses to determine whether there is an association between geometric mean nadir PSA level and relapse within 24 months after adjustment for bone scan score and performance status.

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| **Covariate** | **N** | **Coefficient** | **P-value** | **95% CI** |
| Relap24 (per unit, ng/ml) | 48 | 2.614 | <0.001 | 1.418-3.810 |
| Bone scan score  | 48 | 0.482 | 0.113 | -0.118-1.082 |
| Performance status | 48 | -0.007 | 0.795 | -0.063-0.049 |

exp(2.614) = 13.653, exp(1.418)=4.129, exp(3.810)=45.150

From a simple linear regression model with robust standard errors, with adjustment for bone scan score and performance status, we estimate the geometric mean nadir PSA to differ by 13.653 ng/ml (on average) between men who relapsed within 24 months and men who didn’t relapse. This finding is significantly different from 0 (p<0.001), suggesting the observed results would not be unusual if the true difference in geometric mean nadir PSA level were between 4.129 and 45.150 ng/ml, with the group that relapsed tending towards higher average PSA. We reject the null hypothesis that geometric mean nadir PSA does not differ across groups defined by 24-month relapse free survival.

1. What are the relative merits of the five analyses. Which might you prefer *a priori*? Why?
2. Model 1 estimates a common odds ratio for each additive difference in nadir PSA, permitting an estimate of the odds of relapse per unit increase in nadir PSA.

Model 2 estimates a common odds ratio for each multiplicative difference in nadir PSA level. This model uses log transformation to reduce skewness, prevents a few observations from being influential, and is easier to interpret than Model 1.

Model 3 involves linear spline modeling which is useful when there is evidence of non-linearity, but is difficult to interpret.

Model 4 estimates the difference in mean nadir PSA levels across groups defined by prostate cancer relapse within 24 months, permitting a direct comparison of relapse rates.

Model 5 estimates the log difference in mean nadir PSA levels across groups defined by prostate cancer relapse within 24 months. The regression coefficients can be interpreted in terms of multiplicative effects.

*A priori* I would choose model 2, since the distribution of nadir PSA is highly skewed and therefore prone to act multiplicatively in this diseased population. Therefore the model with log transformation is preferable, and easier to interpret using multiplicative effects. Men with prostate cancer would be most interested in knowing whether or not their cancer would relapse. Using nadir PSA to predict the probability of relapse has clinical utility.

1. The definitional problem relates to how the exposure (hormonal therapy) is defined. It involves two different types of treatment: surgical castration (orchiectomy) and medical castration (diethylstilbestrol). Orchiectomy is a once-off treatment. The efficacy of DES depends on patient adherence, and side effects may require discontinuing therapy. These treatments are not directly equivalent. The study should have compared the efficacy of each treatment separately.