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A Competing-Risks Nomogram for Sarcoma-Specific Death Following Local Recurrence

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SUMMARY

The majority of staging systems focus on the definition of stage, and therefore, prediction of prognosis. In the current era of clinical trial research, it has become apparent that the clinical stage alone is not sufficient to assess patient risk of treatment failure. As the number of biological markers increase, our ability to partition the traditional disease classification system and improve our ability to predict patient success continues to increase. One approach to quantifying individual patient risk is through the nomogram. Nomograms are statistical models, which provide the probability of treatment outcome based on patient-specific covariates. We will focus on the use of the nomogram when the response variable is time to failure and there are multiple, possibly dependent, competing causes of failure. In this setting, estimation of the failure probability through direct application of the Cox proportional hazards model provides the probability of failure (e.g., death from cancer) assuming failure from a dependent competing cause will not occur. In many clinical settings, this is an unrealistic assumption. The purpose of this study is to illustrate the use of the conditional cumulative incidence function for providing a patient-specific prediction of the probability of failure in the setting of competing risks. A competing risks nomogram is produced to estimate the probability of death due to sarcoma for patients who have already developed a local recurrence of their initially treated soft-tissue sarcoma.

KEY WORDS: competing risks; conditional cumulative incidence function; nomogram; spline estimation

1. INTRODUCTION

Risk estimation is central to medical decision making. Clearly, treatment selection is driven by the prediction of how well a patient will fare with a given treatment versus some alternative. Obviously, statistical prediction models have the potential to play a major role in daily medical decision making. For example, the Gail model,[1] which predicts the probability that a woman will develop breast cancer, is used as an eligibility criterion in a very large trial in chemoprevention.[2]

A key obstacle to the use of statistical prediction models in the clinic lies in implementation difficulty. It is impractical to have a clinician execute a statistical package routine to obtain a patient's predicted probability. An attractive, paper-based implementation solution is the nomogram. This is a graphical device which implements a regression model in a friendly manner, enabling the user to map the subject-specific covariates to the probability of an event.

For example, consider the situation where the clinician wishes to predict the probability that a patient with soft tissue sarcoma will die of this disease. If that probability is sufficiently high, investigational therapy may be warranted. From a large cohort of these patients, we developed a Cox proportional hazards model for predicting disease-specific survival based on pathologic data for patients who have received surgery and appear to be free of disease.[3] The nomogram, which implements this Cox model, appears in Figure 1. The clinician begins by finding the individual patient's values on each axis, and

drawing a line upwards to determine how many "Points" the patient receives for each variable value. For example, a patient who is 60 years old receives 38 points (determined by drawing a line from 60 on the Age axis straight upwards to the Points scale.) Once all points have been determined, they are summed and located on the Total Points axis. Then, the clinician draws a line straight downwards to determine the predicted probability of a disease-specific death. Interestingly, in this example, Grade violated the proportional hazards assumption, and therefore, separate axes were necessary for low grade and high grade tumors to obtain the probability of a sarcoma-specific death within twelve years of treatment.

Events that take time to develop may be vulnerable to competing events. For example, when following a patient until death from a particular disease, the patient may first die of another cause, which prohibits him or her from dying from the disease of interest. If the incidence rates for multiple causes of failure are significant, and the independence between these failure types cannot be safely assumed, then the statistical methodology for handling competing risks becomes necessary to use. The subject of competing risks and their analytical complexity has been studied quite extensively.[4, 5] However, the derivation of multiple variable nomograms for outcomes in the presence of competing risks has received little attention.

The above example does not account for competing causes of failure and, to the best of our knowledge, no one has presented nomograms derived from models where patients failing from competing risks were not simply censored. Because of the analytic

complexity necessary for appropriate modeling of competing risks, most standard statistical software packages do not provide built-in functions necessary for the computation of a probability in the presence of competing risks (hereafter referred to as a "competing risk probability"). The exception is the S-Plus library function, Competing Risks Regression, written by Fine and Gray.[6] Unfortunately, many nomograms that provide the physician with a patient's probability of surviving the disease of interest actually provide the probability of surviving the disease of interest assuming no death from a competing cause. For the example above, the nomogram provides the probability that a patient will die of sarcoma within 12 years assuming competing causes of death are not associated with the disease. Others have described such predictions as "hypothetical" because neither the patient nor his physician can know with certainty whether death from a competing cause was associated with the disease.[7] Clearly, the hypothetical probabilities of death from the cause of interest are inflated when the competing risks are dependent, since some of these patients will first die of a different cause. Unfortunately, the assumption of independent competing risks cannot be tested empirically.

Patients with soft-tissue sarcoma, who develop a local recurrence, are primarily concerned about what their risks are of dying of sarcoma. Local recurrence is not commonly a cause of death, but the majority of patients who recur systemically will inevitably die of sarcoma.[8, 9] The time from systemic recurrence to demise is 6 months with patients who undergo complete pulmonary resection, and five-year survival estimates range from 20%-36%.[8-10] Local recurrence is not thought to be a cause of systemic recurrence but is associated with it. The patient therefore with a local

recurrence is concerned most about developing systemic recurrence and dying of the disease.

Herein, we illustrate the development of a competing risks nomogram using an example of disease-specific survival following soft tissue sarcoma local recurrence. In this example, the patient has had an operation for his or her soft tissue sarcoma, but has now experienced local disease recurrence, and the physician wishes to predict the patient's probability of death from sarcoma within a fixed time period. We illustrate the construction of the competing risks nomogram, which provides the probability of dying from sarcoma within each year, up to 5 years, in the presence of competing causes of death.

2. DESCRIPTION OF DATA

Soft tissue sarcoma is a relatively rare neoplasm. Approximately 8,000 cases and 4,000 deaths due to this disease are expected in 2002. About 50% of patients treated with surgery alone experience some form of disease recurrence within a decade. Many of these patients will die of their disease, but their course is highly variable. From July 1982 through May 2000, 2,327 adult (>16 years of age) patients underwent surgery for primary soft tissue sarcoma at Memorial Sloan-Kettering Cancer Center. These patients were prospectively entered and continuously followed in a computerized database. As of 2/18/01, 355 of these patients have experienced local disease recurrence following surgery. Many of these patients had large primary tumors, with 44% of patients having tumors > 10cm. High-grade disease was somewhat more common, occurring in 62% of patients. Nearly all patients (87%) had deep rather than superficial primary disease. The sites varied greatly, with the lower extremity being most common (39%), and head and

neck disease being most rare (4%). Many different histopathologic subtypes were present, though liposarcoma was most common (35%). Their median age was 57 (range 17-89).

3. NOMOGRAM DEVELOPMENT

The predicted probability of death due to sarcoma within *t* years of treatment was derived from the cumulative incidence function conditional on a set of disease related characteristics. Specifically, the conditional cumulative incidence function is defined as the probability of death within *t* years, and the death is attributable to the sarcoma (S), for a given set of patient baseline characteristics (z). This is written using the notation Pr(T<*t*, Cause=S|Z= z). Historically,[11] the cumulative incidence function is derived from two components in survival analysis: the conditional survival function G(t|z) and the cause-specific hazard function

$$h_S(t \mid z) = \lim_{\Delta \to 0} \Delta^{-1} \Pr(t \le T < t + \Delta t, Cause = S \mid T \ge t, z)$$

Heuristically, the cause specific hazard function is proportional to the probability of death due to sarcoma at time t given the patient has not died of other causes prior to time t. In addition to being a function of time, the hazard and survival components are functions of the patient covariates. The conditional cause specific hazard and overall survival function are modeled as:

$$h_S(t|z) = h_{0S}(t|z)\exp[CSRI]$$

$$G(t|z) = G_0(t)^{\exp[SRI]}$$

where CSRI and SRI are the cause-specific hazard and overall survival risk indices respectively, that are composed of the patient specific characteristics.

Combining these two functions, the conditional cumulative incidence function is specified as:

$$\Pr(T \le t, Cause = S \mid z) = \int_{u \le t} h_S(u \mid z)\, G(u \mid z)\, du$$

This development of the conditional cumulative incidence function is unsatisfactory for two reasons. First, as has been argued in Fine and Gray,[6] the covariates that compose the cause-specific risk index may be different than the covariates that have the strongest impact on the cumulative incidence function. Second, since there are two risk indices, the construction of the nomogram would require two separate mappings, from covariates values to points, in order to produce the probability of an event.

As a result, we consider an alternative approach to modeling the conditional cumulative incidence function, which does not have these limitations. The approach is based on the subdistribution hazard function

$$h_S(t \mid z) = \lim_{\Delta \to 0}\ \Delta^{-1}\ \Pr(t \le T < t + \Delta t, Cause = S \mid T \ge t \cup (T \le t \cap Cause \ne S), z).$$

Using a proportional hazards specification

$$h_S(t \mid z) = h_{0S}(t) \exp[r(z)]$$

the conditional cumulative incidence function is estimated from the expression

$$1 - \exp\{-\int_{u \le t} h_{0S}(u)\, \exp[r(z)]\, du\}.$$

Thus, the conditional cumulative incidence function is estimated directly from the cumulative baseline hazard subdistribution for cause S, $H_{0s}(t) = \int_{u \le t} h_{0s}(u)\, du$, and the

subject specific relative risk function r(z). Alternative specifications for the conditional cumulative incidence function, using the general class of scale transformation models, are provided in Fine.[12]

For the proposed nomogram, the characteristics used to predict the patient specific cumulative incidence function were the following: age, site, tumor size, tumor grade, depth, and histology. In this variable set, all variables except age were categorical. In an attempt to maximize predictive accuracy,[13] no variable selection was conducted, and a restricted cubic spline was used for the continuous variable age. Separating age from the other covariates $z = (a, z_1)$, the relative risk function may be written as $r(z) = \exp[g(a) + z_1 \beta]$, where g(a) is a nonparameteric function of age.

The partly linear Cox proportional hazards, used to estimate the conditional cumulative incidence function, is specified by $h_S(t;z) = h_{0S}(t) \exp[g(a) + z_1 \beta]$. Estimation of the parameters β and the nonparametric function g, is accomplished through maximization of a penalized weighted partial log-likelihood function.[14]

$$\log \prod_i \left(\frac{\exp[g(a_i) + z_{1i}\beta]}{\sum w_k \exp[g(a_k) + z_{1k}\beta]} \right)^{w_i} - p(g)$$

It is assumed that censoring time is independent of the covariates. The weights (w_j) are a function of the Kaplan-Meier estimate of the censoring time survival function. Cain and Lange also used a weighted partial likelihood to downweight influential observations

when fitting the Cox proportional hazards model, although their use was for efficiency gain whereas here it is to produce an unbiased estimating equation.[15] The product is taken over sarcoma-specific deaths and the summation represents those still at risk when subject *i* fails. The second term above represents the penalty function used to estimate the spline function of age. The risk set in the partial likelihood is unconventional and it is defined as follows. Let X denote the follow-up time for each subject. Then the risk set at failure time t_i is

$$R_i = \{ j : X_j \geq t_i \cup (X_j \leq t_i, Cause \neq S) \}.$$

Thus, the risk set includes subjects that are still being followed when subject i fails, or subjects whose non-sarcoma deaths occurred prior to the time subject i failed.

As a result of estimating the effect of age nonparametrically in the relative risk function, an alternative to the conventional likelihood based method of assessing variability in the finite and infinite dimensional parameter estimates is required. As a result, a bootstrap procedure is applied to compute prediction intervals for the nomogram estimates and the standard errors for the relative risk parameters (b, g).

To estimate the sarcoma specific probability of death within *t* years for an individual with covariate z, we compute

$$\Pr(T < t, \text{Cause}=S \mid Z=z) = 1 - \exp[- \int_{u=0}^{t} h_{0S}(u) \exp\{g(a) + z_1 b\} du]$$

where estimation of the cumulative baseline subdistribution hazard $\int_{u=0}^{t} h_{0S}(u)du$ is

attained through a weighted version of Breslow's estimate, again considering only

sarcoma-specific deaths and using the risk set defined above. [6] All calculations were performed using S-Plus 2000 Professional (Insightful Corp, Seattle) with the `Design`, `Hmisc`, and `cmprsk` libraries added.[16]

To assess the accuracy of our nomogram prediction model, we generated predicted probabilities for each case by leaving it out of the dataset, refitting the model on the N-1 patients, and predicting the probability of failure for the left-out case, conditional on the patient-specific covariate vector. Given the size of the sarcoma dataset, this is comparable to the asymptotic jackknife. Quartiles were then formed from the predicted probability of failure for each year. Subjects within each quartile were used to compute the marginal cumulative incidence of failure by that year and the mean predicted conditional probability of failure by that year. Estimation of the marginal cumulative incidence function Pr(T<*t*, Cause=S), is described in Kalbfleisch and Prentice.[11] A calibration plot was generated to compare the mean predicted conditional probabilities to the non-model based marginal cumulative incidence probability within each quartile. A perfectly accurate nomogram prediction model would result in a plot where the marginal/conditional probability pairs would fall along the 45 degree line through the origin.

4. RESULTS

The marginal cumulative incidence functions for this cohort appear in Figure 2. The probability of death due to sarcoma within five years of recurrence in the presence of competing causes of death is 0.44 (se = 0.03); the 5-year probability of a non-sarcoma

death is 0.10 (se = 0.02). As depicted in Figure 2, sarcoma is the primary cause of death in the early follow up period after a recurrence. However, if the patient remains alive for two years after a recurrence, the sarcoma and other causes death rates are approximately equal. To provide a patient-specific estimate of the incidence of sarcoma induced death, the conditional cumulative incidence model was fit. The model based log relative risk (standard errors) for the binary variables Grade and Depth were -0.969 (0.228) and -0.253 (0.382), respectively. Figure 3 illustrates the nonlinear effect of age. The calibration plot of the conditional cumulative incidence function appears in Fig 4. This plot compares the quartiles of model predicted conditional probabilities (via jackknife) for each year with the marginal cumulative incidence function. In general, the conditional cumulative incidence estimates correspond closely to the non-model based marginal cumulative incidence estimates for each quartile, although very high predicted probabilities (>60%) may actually be too low.

The nomogram for computing the probability that an individual patient will die from sarcoma appears in Figure 5. The mechanics of this tool are as follows. First, the user determines the patient-specific index. This is accomplished by calculating how many points the patient receives for values of each of his prognostic factors, and summing these to arrive at his total points. The total points can then be used to determine the patient's probability of death from sarcoma. For example, the 40 year old patient receives 34 points for his age. His $\leq$ 5 cm, high grade deep fibrosarcoma of the trunk contributes 0 + 47 + 13 + 25 + 0 = 85 additional points, for a total of 119 points. He has a 3.3% chance

of dying from sarcoma within 1 year, and a 12% chance of dying within five years, with 95% confidence intervals 0-9% and 2-31%, respectively.

5. **DISCUSSION**

For the patient with soft-tissue sarcoma, a local recurrence, while a frightening event, is seen more by the patient and his physician as a harbinger of "will I die from sarcoma." The ability to translate the risk of dying of sarcoma, in the presence of local recurrence, is a major concern. A second motivation for modeling disease-specific death, besides patient interest, is that this is the endpoint potentially modifiable by the physician and treatment. The patient who is at high risk for disease-specific death is the ideal target for aggressive therapy. A prediction of all-cause, rather than disease-specific, survival dilutes this target. A third motivation is that disease-specific survival can be predicted more precisely for the individual patient. We typically have several good measures of disease aggressiveness and extent, which collectively can do well at predicting disease-specific outcomes. In contrast, predicting death from other causes is considerably more difficult, and we generally have limited predictors for this purpose. However, death from other causes cannot be ignored. In our series, the probability of death from other causes within 5 years for a 40-year-old patient is 5%, rising to 25% for an 80-year old patient. Probabilities like these should be discussed in the decision making process.

The use of the cumulative incidence function in our competing risks nomogram removes the hypothetical nature from the disease-specific death prediction. Rather than providing the patient with his probability of dying from sarcoma assuming other causes of death are

either removed or not associated with the sarcoma, we provide the patient with his probability of dying from sarcoma given that he is also at risk of dying from other causes. These competing causes of death are potentially related to but not directly attributable to the sarcoma.

There are limitations to our analysis. In particular, it is difficult to assess the accuracy of survival models, especially a competing risks nomogram, where traditional measures such as r-squared and area under the receiver operating characteristic curve are problematic due to censoring. Validation is always an issue, and our nomogram needs to be validated on outside datasets. Another limitation lies in the difficulty of accurately representing the predicted probabilities on paper. We plan to rectify this using our Palm and desktop software approach, which we use for several prognostic nomograms (see www.nomograms.org).

It is important to emphasize that our database, while a powerful one, is probably only valid given the timing and number of events, out to five years. So, while projections to ten years are needed, the numbers at ten years for patients at risk are low. In this disease setting, prognosis seems to be remaining stable, as year of local recurrence did not contribute prognostic information when added to the model. In addition, we utilized a cohort primarily of patients treated at a single institution, so they can be expected to be a relatively favorable group.

These limitations aside, our nomograms may be useful to the patient and his clinician when predictions are necessary. Our nomogram in Figure 5 provides the probability of death from sarcoma in the presence of competing risks. Although considerable error in these predictions remains, they may be the best currently available.

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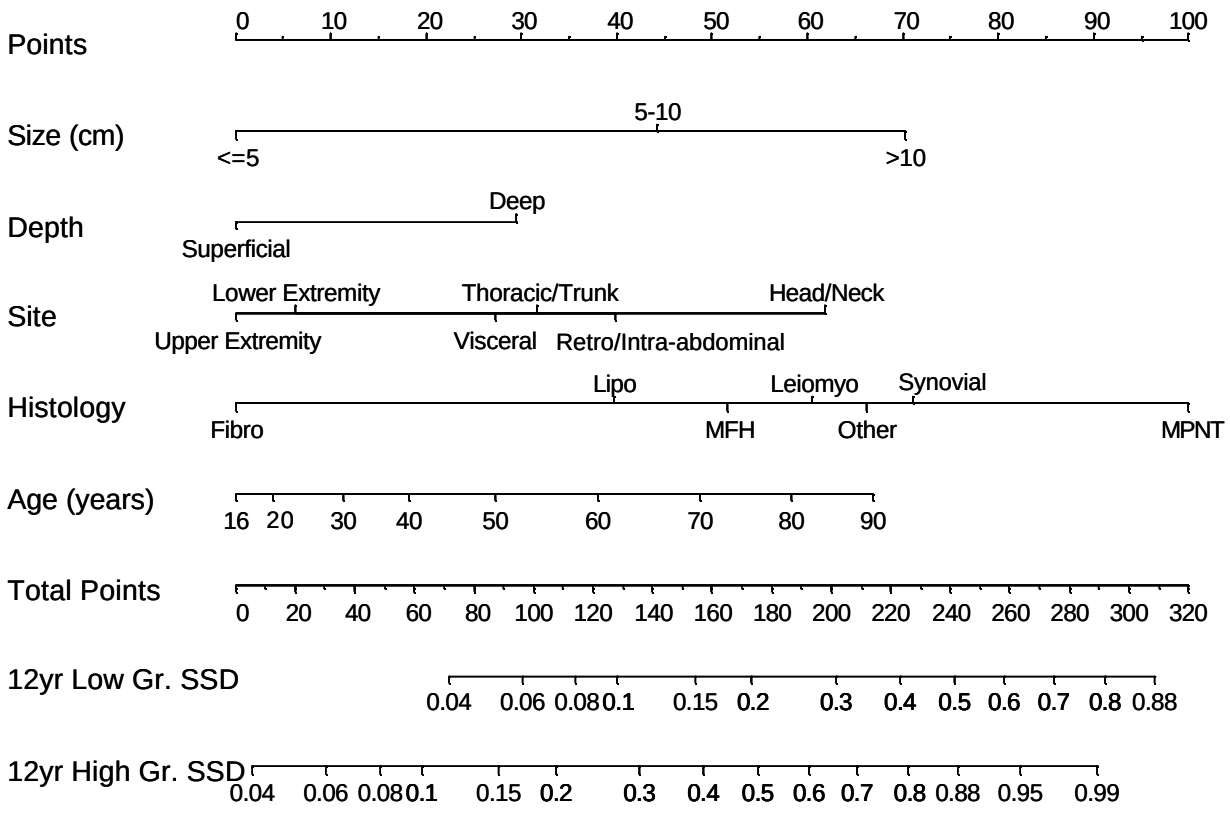
Postoperative Nomogram for 12-Year Sarcoma-Specific Death



Instructions for Physician: Locate the patient's tumor size on the Size axis. Draw a line straight upwards to the **Points** axis to determine how many points towards sarcoma-specific death the patient receives for his tumor size. Repeat this process for the other axes, each time drawing straight upward to the **Points** axis. Sum the points achieved for each predictor and locate this sum on the **Total Points** axis. Draw a line straight down to either the Low Grade or High Grade axis to find the patient's probability of dying from sarcoma within 12 years assuming he or she does not die of another cause first.

Instruction to Patient: "If we had 100 patients exactly like you, we would expect between <predicted percentage from nomogram – 8%> and <predicted percentage + 8%> to die of sarcoma within 12 years if they did not die of another cause first, and death from sarcoma after 12 years is still possible."

Figure 1. Postoperative nomogram for 12-Year sarcoma-specific death based on 2,163 patients treated at MSKCC. Abbreviations: Fibro=Fibrosarcoma, Lipo=Liposarcoma, Leiomyo=Leiomyosarcoma, MFH=Malignant Fibrous Histiocytoma, MPNT=Malignant Peripheral-Nerve Tumor, Gr=Grade, SSD=Sarcoma-Specific Death.
Reprinted with permission from Kattan et al. [3]

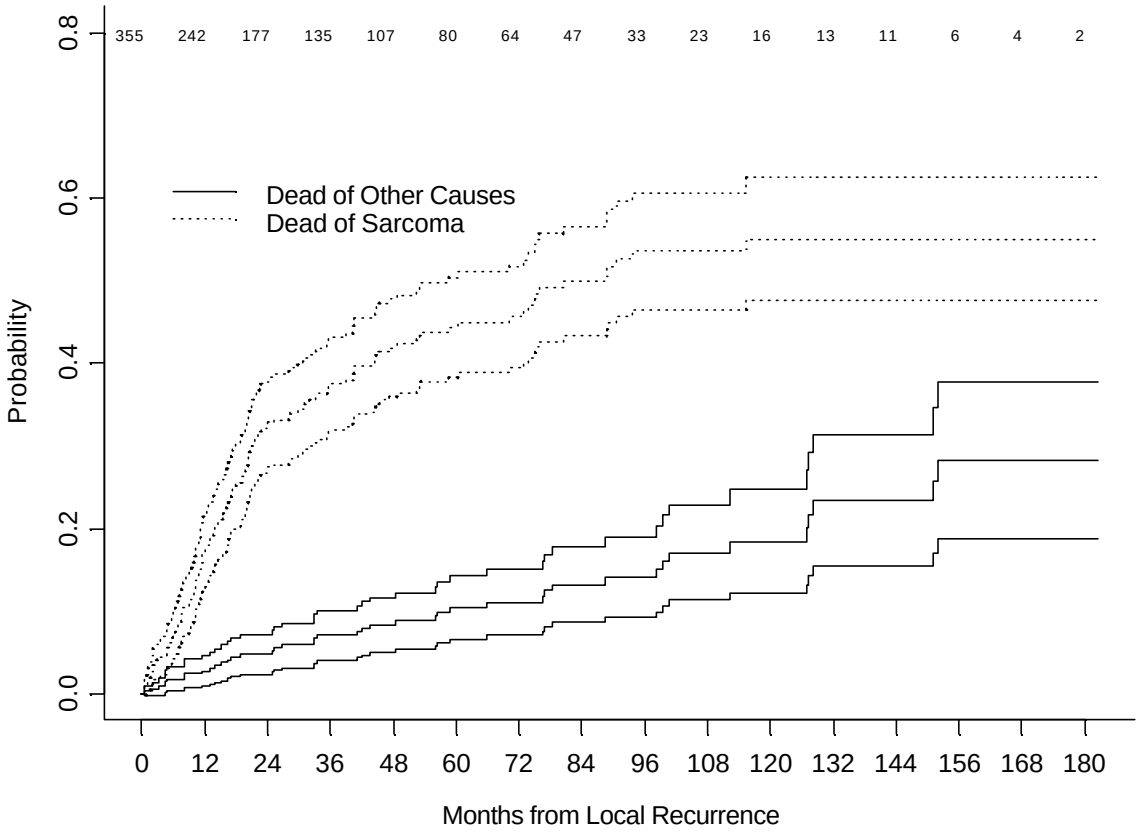


Figure 2. Marginal cumulative incidence functions for death from sarcoma and other causes, with 95% confidence intervals. Figures at the top of plot indicate the number of patients at risk for death.

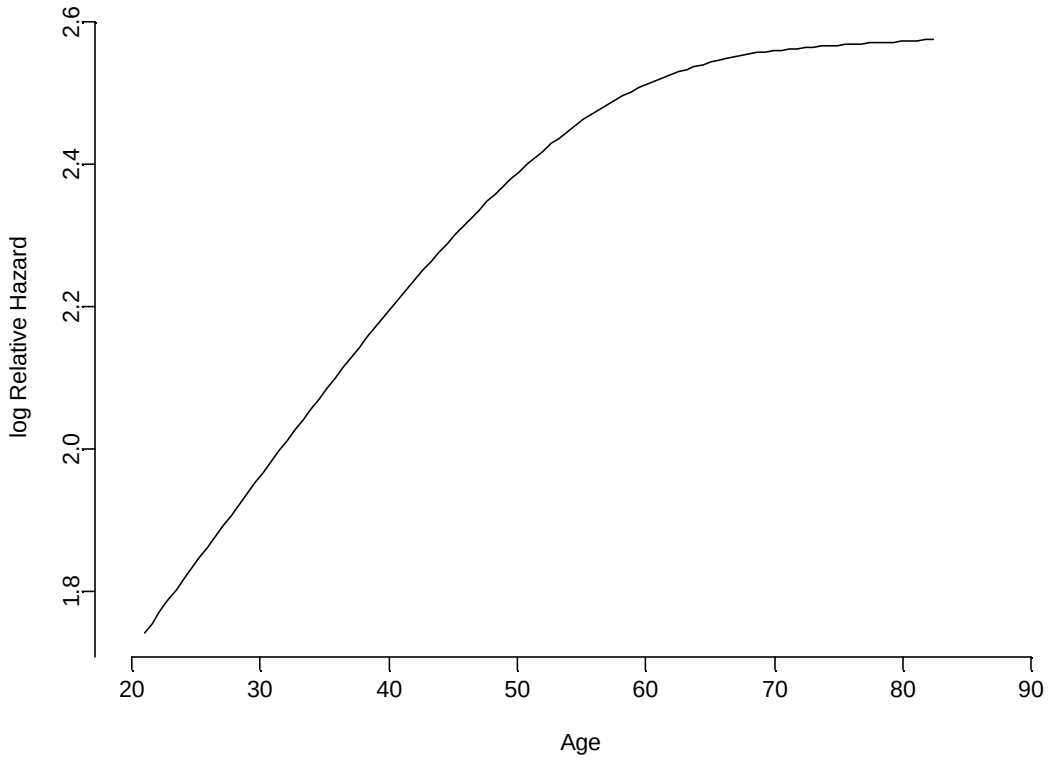


Figure 3. Association of Age with disease-specific survival.

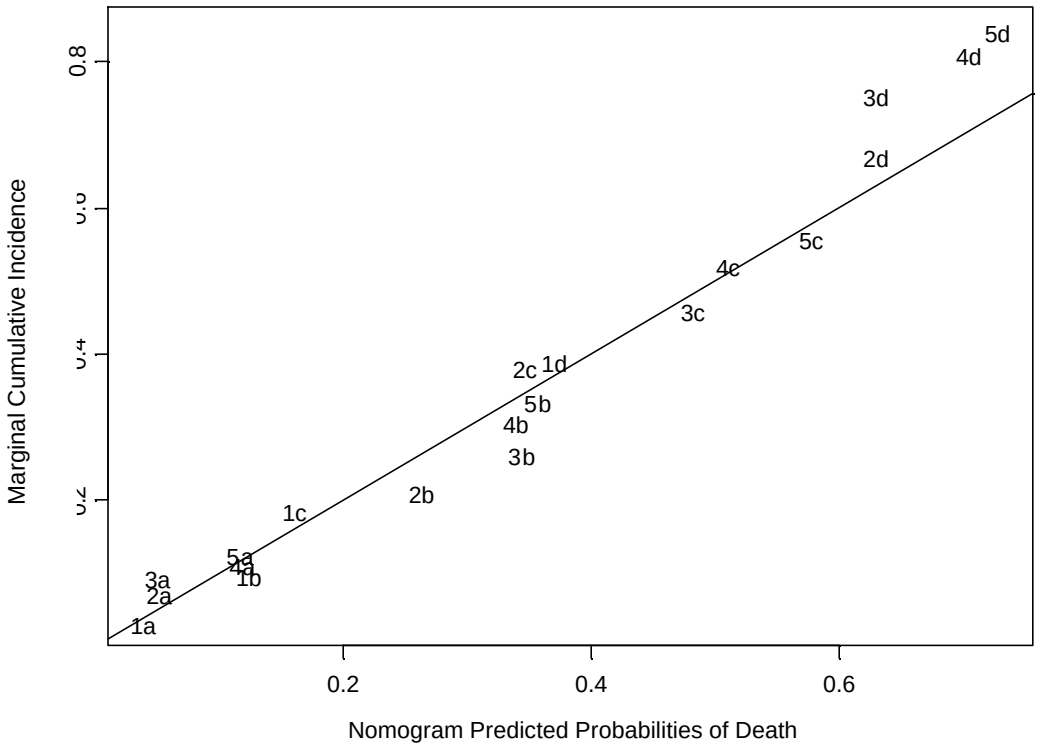
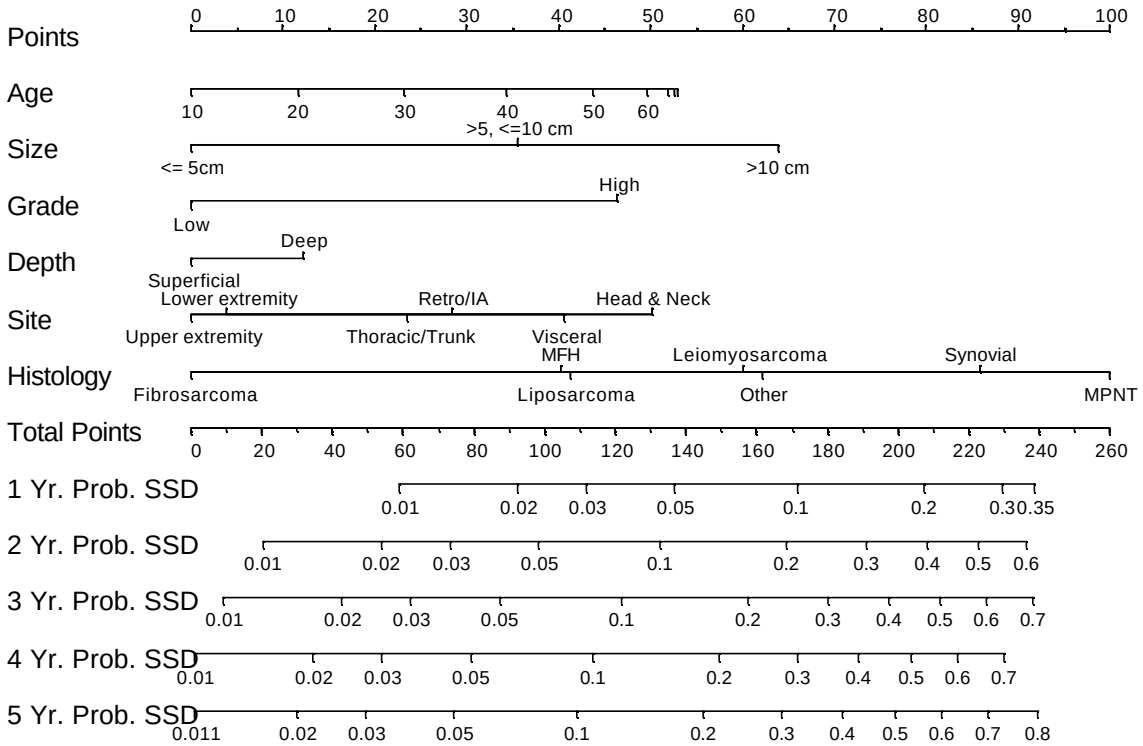


Figure 4. Calibration Plot. X-axis is mean predicted probabilities of the conditional cumulative incidence model. Y-axis is the marginal cumulative incidence probability for the respective cohort. Plotting symbol is year of prediction (numeric) combined with quartile (a letter). For example, point "2c" is the 3rd quartile of the 2-year nomogram predictions. Solid line represents equality between predicted (conditional cumulative incidence from nomogram) and observed marginal cumulative incidence.



Instructions for Physician: Locate the patient's age on the Age axis. Draw a line straight upwards to the **Points** axis to determine how many points towards sarcoma-specific death the patient receives for his age. Repeat this process for the other axes, each time drawing straight upward to the **Points** axis. Sum the points achieved for each predictor and locate this sum on the **Total Points** axis. Draw a line straight down to find the patient's probability of dying from sarcoma each year within 5 years.

Instruction to Patient: "If we had 100 patients exactly like you, we would expect <predicted percentage from nomogram> to die of sarcoma within X years."

Figure 5. Nomogram for probability of death from sarcoma following local recurrence in the presence of competing risks.

Abbreviations: MFH=Malignant Fibrous Histiocytoma, MPNT=Malignant Peripheral-Nerve Tumor, SSD=Sarcoma-Specific Death. Age is age at time of primary surgery. Size refers to primary tumor. Note that comorbidities should be taken into account.