The Association Between Measures of Progression and Survival in Castrate-Metastatic Prostate Cancer

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Abstract

Purpose: To explore the association between progression-free survival and overall survival time in patients with castration-resistant prostate cancer treated with microtubule-targeted therapies.

Experimental Design: We retrospectively studied patients treated in three trials evaluating a taxane or an epothilone for progressive castration-resistant prostate cancer. Study subjects were 98 patients with bone metastases; 63 of them also had soft tissue lesions. All scans were reviewed independently. Associations of radiographic progression-free survival and prostate-specific antigen (PSA) progression-free survival with survival time were measured using Kendall's τ, adjusted for right censoring. A smoothing procedure was applied to estimate Kendall's τ within each neighborhood of the follow-up process.

Results: The overall associations between progression-free survival time and overall survival time were moderate: 0.4 for radiographic progression-free survival and 0.33 for PSA progression-free survival. The association between radiographic progression-free survival and overall survival was weakest early in the follow-up process, whereas the PSA association was weakest when the progression-free survival – related event (PSA progression, death, or censoring) occurred after 6 months from the start of treatment.

Conclusions: Current measures of progression-free survival time for men with castration-resistant prostate cancer are not strongly concordant with survival time. Factors that attenuate the association include interval censoring and the discontinuation of therapy early in the follow-up due to imaging changes that may not reflect true failure of the treatment. For radiographic progression-free survival, the association may be increased by requiring confirmation of progression with a second scan, as is routinely done when assessing response.

Criteria to assess outcomes in therapeutic trials aim to provide objective and reproducible measures which reflect clinical benefit to patients. The difficulties in assessing the response to treatments in prostate cancer are well recognized across the spectrum of the disease. This is because changes in radionuclide bone scan are difficult to quantify objectively and reproducibly (1), and changes in prostate-specific antigen (PSA) may be dissociated from clinical outcomes such that a post-therapy decline may not mean that the drug has "worked", and an increasing value that it has not. The situation is complicated further by the fact that the most widely used criteria, Response Evaluation Criteria in Solid Tumors (2), adapt poorly to the most common clinical manifestations of prostate cancer (3). Although dramatic responses associated with effective therapies can be identified with Response Evaluation Criteria in Solid Tumors, targeted approaches that stabilize or slow tumor growth and which are not cytotoxic, may not. Given these difficulties, we proposed that the outcome measures for prostate cancer clinical trials shift to what is done routinely in clinical practice, focusing less on whether a drug has induced a response to a determination of when it has failed (3).

From the point of view of a clinical trial or clinical practice, the measure that considers when a drug has not worked at all or is no longer effective is represented best by progression-free survival, the time from the start of therapy to progression of disease, death, or last follow-up. Because it is closer to survival time in the follow-up process, one would postulate that progression-free survival would be a more informative (predictive) intermediate end point with a stronger association with survival. In fact, there are few studies that have explored this association in prostate cancer, or for any cancer type. This is in part because the methodology required is nonstandard, as both progression-free survival and overall survival are time to event end points. As a result, any measure of association must account for censoring in progression-free survival and overall survival. Variability is increased because survival times are assessed daily, whereas progression-free survival is assessed at

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Table 1. Distribution of disease in patients with castrate-metastatic prostate cancer

Category	Overall	Memorial Sloan-Kettering Cancer Center
Total no. of patients reviewed	171	116
TEC (1997-1999)	49	40
Hi-TEC (1999-2000)	30	24
Epothilone (2001-2003)	98	52
Median PSA at baseline (all studies)	97.9 (range, 0.52-2,282.2)	91.4 (range, 0.52-2,282.15)
Number of patients with		
bone only	51 (29.8%)	35 (30.2%)
bone and soft tissue	95 (55.6%)	63 (54.3%)
soft tissue only	25 (14.6%)	18 (15.5%)

*Thirty-nine percent to 40% had "measurable disease" (including visceral disease).

intervals. If the intervals between assessments are too long, a measure of progression-free survival can become meaningless.

In this report, we explore the association between progression-free survival and overall survival for patients with progressive castrate-metastatic prostate cancer (4) enrolled in three sequential trials of microtubule-targeted cytotoxic agents. Our goal was to assess whether the common intermediate end points for metastatic prostate cancer, radiographic progression-free survival and PSA progression-free survival, were in concordance with survival time. A close association between progression-free survival time and overall survival would support the use of progression-free survival as an intermediate end point for prostate cancer clinical trials, with the potential to accelerate drug development in this patient population.

Materials and Methods

The relationship between progression-free survival and overall survival was determined from an analysis of outcomes from the subset of men treated at Memorial Sloan-Kettering Cancer Center who were enrolled on three sequential multicenter Institutional Review Board–approved protocols evaluating microtubule-targeted chemotherapy (5–7). Enrollment required histologically confirmed adenocarcinoma of the prostate, a Karnofsky performance status of ≥70%, a testosterone level of <50 ng/mL, and documented disease progression following a trial of antiandrogen withdrawal as appropriate. PSA progression was defined as a minimum of three increasing PSA levels obtained 2 or more weeks apart, in which the range of values was at least 25% (8). The event was recorded on the date of the first PSA increase. If a PSA event did not occur, censoring was defined at the date of the last PSA recorded measure. Radiographic progression was defined as new or progressive (25% bidimensional increase) soft tissue masses on computerized tomography or magnetic resonance imaging, or new lesions on radionuclide bone scan. All imaging studies were reviewed in a blinded fashion by a radiologist. The probability of progressing by time t in the presence of competing causes of death was estimated by the cumulative incidence function.

Association analyses with two time to event variables. In this analysis, the progression-free survival time (S) and overall survival time (T) were subject to censoring. The measure of association was Kendall's τ adjusted for censoring, defined as

$$\tau = 4\Pr(T_i > T_j, S_i > S_j) - 1,$$

where (S_i, T_i) represent the progression-free and overall survival times for the ith subject. The measure varies between -1 and 1, with 1 representing perfect concordance between the time to event variables and -1 representing perfect discordance between the variables; a measure of zero represents no relationship between the two variables. Kendall's τ is estimated through the ranks S and T; it measures the level of concordance and discordance in the ranks of S and T between each pair of subjects. For any pair of subjects i and j, concordance implies that if the progression-free survival of subject i is greater (less) than the progression-free survival of subject j, then the survival time of subject i is greater (less) than the survival time of subject j. Discordance means that if the progression-free survival of subject i is greater (less) than the progression-free survival of subject j, then the survival time of subject i is less (greater) than the survival time of subject j. Kendall's τ provides a measure of the difference between the concordance and discordance outcomes for all pairs of subjects. The SE of this estimate can be derived from U-statistic theory (9).

As a result of censoring, the ranks of the progression-free survival times (S) and the survival times (T) are less certain. For example, suppose subject 1 has a progression-free survival and overall survival time pair, measured in months, equal to $(S_1, T_1) = (7, 12)$, and subject 2 has the failure time pair $(S_2, T_2) = (8, 15)$. Since $(T_2 > T_1)$ and $(S_2 > S_1)$, these two subjects have concordant failure times; subject 2 has the higher survival and progression-free survival times. Suppose, however, that the 12-month survival time for subject 1 represents a censored time, or the last follow-up time. Then the concordance between these two subjects is unknown. It is unclear whether the ultimate survival time for subject 1 would be greater or less than subject 2. All that is known is that the progression-free survival time for subject 2 is greater than the progression-free survival time for subject 1.

The association between time to progression and death as a function of the progression event time. Kendall's τ statistic is a global measure of association that summarizes the association for all the subjects in the analysis. To explore whether the progression-free/overall survival time association changed during the disease process, subsets of the data, using a neighborhood of each progression event time, were employed to obtain a local measure of Kendall's τ. The local estimates of association were based on 67% of the data that were closest to the individual progression event time. The local estimate was used to examine the level of association conditional on the progression-free event time.

Results

A total of 171 men were enrolled in the three studies, of whom 116 were treated and followed at Memorial Sloan-Kettering Cancer Center. This included 40 of the 49 patients treated with docetaxel/estramustine/carboplatin (TEC), 24 of the 30 patients treated with docetaxel/i.v. estramustine and carboplatin (Hi-TEC), and 52 of the 98 patients treated with epothilone B plus or minus estramustine. All of the patients in this group met the enrollment criteria for an increasing PSA set by the Prostate Specific Antigen Working Group (8). The association analysis in this article was based on the 98 men treated at Memorial Sloan-Kettering Cancer Center with either bone or bone and soft tissue lesions. Three of these men were

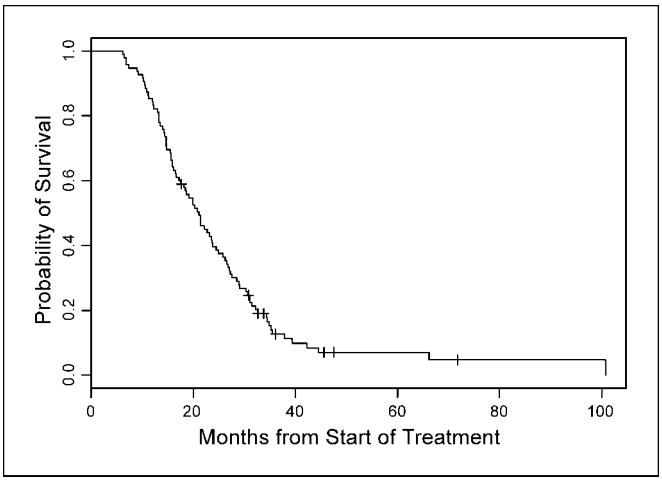

Fig. 1. Kaplan-Meier estimate of survival among all 95 patients in the study.

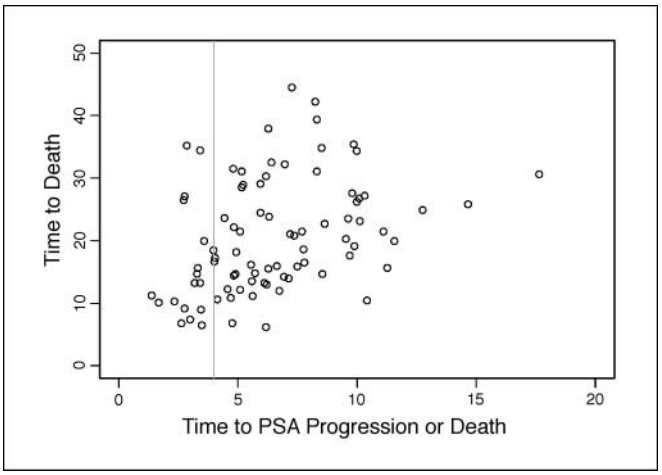

Fig. 3. Time of PSA progression-free survival plotted against the time to death, among patients for whom both PSA progression and death were recorded.

removed from this subset; two for lack of follow-up bone scan data and one for lack of follow-up PSA data. The remaining 95 patients constitute the data set used in this analysis. Eighty-seven of the 95 treated patients died, 94 had a radiographic progression or died, and all 95 met the criteria for PSA progression or death at the time of this analysis. Table 1 shows the distribution of sites of disease. The Kaplan-Meier estimate of survival is provided in Fig. 1.

Relationship between time to bone or PSA progression. The relationship between progression-free survival time (using either imaging or PSA) and survival time was moderate. Neither progression-free survival end point strongly tracked survival time. Kendall's τ statistic, which measured the concordance between progression-free survival time and survival time, was 0.40 (95% confidence interval, 0.32-0.47) when using radiographic progression-free survival and 0.33 (95% confidence interval, 0.25-0.40) for the PSA progression-free survival.

The inadequate relationship between progression-free survival and overall survival is illustrated in Figs. 2 and 3. Figure 2 depicts a scatter plot of the time to radiographic progression-free events and the time to death among patients in whom both failure end points were observed. Figure 3 portrays a similar plot using PSA progression-free events. These figures represent the best possible concordance for the progression-free/survival relationship because only the failure times for each end point were depicted. It is noted, however, that the proportion censored for each end point was small (survival time, 8%; radiographic progression-free survival, 1%; PSA progression-free survival, 0%). Figure 2 shows little association between the time to radiographic progression event and the time to death within the first 4 months after the start of treatment. After the 4-month follow-up period, the scatter plot shows a positive association between these two end points. In Fig. 3, the positive association, although not as strong, occurs earlier in the follow-up process. In the 6- to 10-month follow-up period, a long vertical band of data points indicates significant variability in survival time for a narrow interval of PSA progression event times. This results in an attenuation of the association between PSA progression-free survival and overall survival. A stronger association for either plot would have produced a tighter band of points throughout the horizontal time axis.

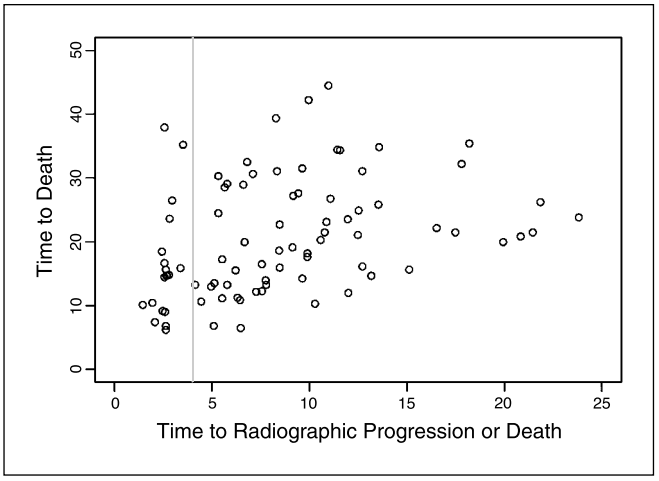

Fig. 2. Time of radiographic progression-free survival plotted against the time to death, among patients for whom both radiographic progression and death were recorded.

Two additional factors that can negatively influence Kendall's τ statistic are the degree of censoring and the interval censoring of the progression times. The reliability of Kendall's τ statistic decreases as the proportion of censoring increases. For this data set, the censoring proportion for each end point was low and should not significantly affect the magnitude of these associations.

Interval censorship will, however, attenuate the association measure. The time to progression was derived from the recorded progression time and not when the progression was detectable. For example, imaging scans were scheduled at months 3, 6, 9, 12, and yearly thereafter. Theoretically, if surveillance was continuous, and a progression was detectable at month 7, it would not be recorded as a progression until the scheduled scan between months 7 and 9. Thus, if the actual progression time strongly tracked the patient survival time, the measurement error that occurred from using the scheduled scan time would dilute the association measure. To date, there is no consensus methodology on how to incorporate interval censoring into an association measure. The effect of interval censoring on the magnitude of the association measure is a positive function of the length of the interval width, but we are unable to quantify its impact.

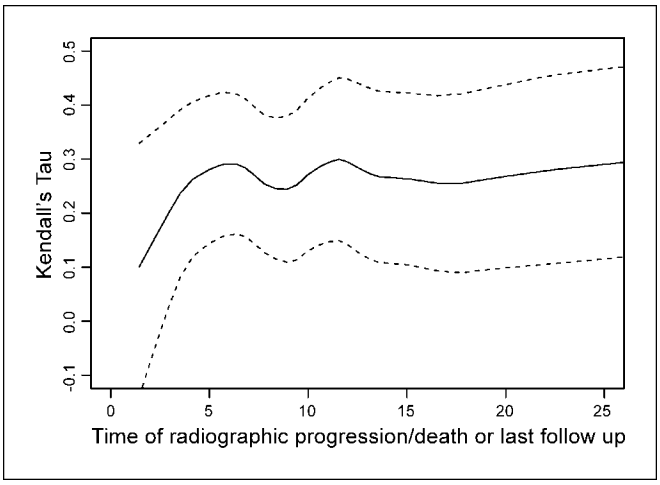

Fig. 4. Association between radiographic progression-free survival and survival as a function of the time of the progression-free survival event (radiographic progression, death, or censoring). Solid line, local Kendall's τ estimates; dotted lines, the corresponding 95% pointwise confidence intervals.

The relationship between radiographic progression-free events and survival events was weakest for the early progression-free events (Fig. 2). To explore this association as a function of the follow-up process, a smoothing procedure was applied to produce a local measure of Kendall's τ. Figure 4 illustrates the association between radiographic progression-free survival time and survival time as a function of when the progression-free survival event was recorded. The association is weakest early in the follow-up process. Twenty percent of the radiographic progression-free events were recorded at the time of the first scheduled scan within 3 months from the start of treatment. Because by design, the first scan was scheduled in this time period, one explanation for the weak association in the early follow-up period is that these progressions occurred prior to the first posttreatment scan, resulting in a significant loss of information. If, however, the radiographic progression-free events or last follow-up time were recorded later in the follow-up period, the association measure stabilized at ~ 0.30.

In contrast, the PSA progression-free survival and overall survival association was weaker in the later follow-up period (Fig. 3). Figure 5 depicts this conditional on the PSA progression-free event time. In contrast to the radiographic association plot, the association reached its maximum early in the follow-up period. We conjecture that the three consecutive PSA increases in the pretreatment period that led to trial enrollment were an indication of aggressive disease and provided a moderate mirror for the time to death ($\tau = 0.25$). Conversely, patients who experienced three consecutive PSA increases later in the follow-up period may have less aggressive disease and their survival time was likely to be affected by a multitude of other factors. The result was a reduction in the association measure in the later follow-up period.

It is interesting to note that the local association measures, at their maximum, do not achieve the global association measures of 0.40 and 0.33 for radiographic and PSA progression-free survival, respectively. This was due to interval censoring. The local association measures were based on observations in a neighborhood around each progression-free event time. Within this neighborhood, the actual progression time was unknown; instead, the progression time was assigned based on the scheduled scan time. Thus, although the concordance for a pair of subjects was maintained for subjects with very different progression-free survival event times, the ordering for a subject pair may get perturbed if their progression-free survival event times were close. The local Kendall's τ measure was based on a significant proportion of subjects in a small neighborhood of progression-free event times; thus, increasing the proportion of observations that were affected by the difference between the observed scheduled progression-free survival event time and the actual (unobserved) progression-free survival event time. This increase in the proportion of affected observations contributed to the reduction in the local association measure.

Discussion

Survival time is an event of unquestioned significance that is measured accurately on a daily basis. Combined with safety, survival time for a patient group can be used to estimate the risk/reward ratio of an intervention. The requirement that a drug be shown to prolong life before it is approved has the potential to delay its availability to patients in need of treatment and to limit the number of agents that can be brought forward in definitive trials. In addition, survival times can be influenced by the secondary or salvage therapies that a patient receives, which confounds an assessment of the effect of the initial study drug. A critical issue is whether end points that occur earlier in the follow-up process could reliably predict that a treatment or approach will prolong life. Doing so would allow needed therapies to be available sooner, and reduce the patient, investigator, and financial resources necessary to evaluate these approaches in the clinic.

In this article, we explored the association between progression-free survival, defined on the basis of changes in PSA, and radiographic progression in bone and/or soft tissue, and survival. These are the most common manifestations of metastatic prostate cancers that are progressing after hormone treatment. All patients received microtubule-targeted cytotoxic treatment, which has been associated with a prolongation of life in prospective randomized comparisons. We focused on a measure of when a treatment is no longer working, time to progression or

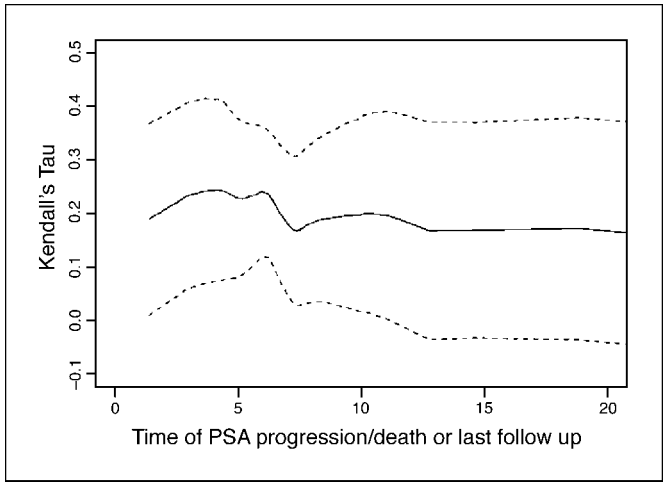

Fig. 5. Association between PSA progression-free survival and survival as a function of the time of the progression-free survival event. Solid line, local Kendall's τ estimates; dotted lines, the corresponding 95% pointwise confidence intervals.

death, in an attempt to mirror what is done routinely in clinical practice: continuing treatment as long as the patient seems to be benefitting. This acknowledges that a therapy can be effective without causing tumor shrinkage, and that cytotoxic therapies are generally continued as long as the level of PSA is not increasing even if a so-called 50% decline from baseline, the defined biochemical partial response definition (8), has not been achieved. The overall results failed to show a strong association between time to PSA progression-free survival, and separately, radiographic scan progression-free survival and overall survival. For each of these outcome measures, the associations were 0.33 or 0.40, respectively. The measure of association between PSA and the radiographic progression-free survival end point was 0.39.

To understand the low level of association for progression by imaging, we observed that 20% of the treated patients were taken off the study by 3 months at the time of the first scheduled scan. It is recognized that elevations in PSA antedate the appearance of new lesions and other factors that reflect a worsening of a bone scan. As a result, an apparent worsening of disease on a bone scan done shortly after a treatment is started may simply reflect the progression of disease that led to the enrollment on the trial, and not a failure of the treatment. It follows that associations between progression-free survival and overall survival would be underestimated if patients are withdrawn on the basis of protocol-specified definitions of progression that do not reflect a true failure of the treatment. Such was the case in the trials of the endothelin receptor-A antagonist atrasentan, in which a protocol-specified definition of progression resulted in the removal from the study in >50% of patients enrolled, even though many had declining PSA values and stable or improving symptoms (10). The higher levels of associations found $\geq$4 months after the start of therapy relative to <4 months is consistent with this interpretation. It also argues for not performing a bone scan to determine whether a treatment is working for a minimum of 3 months. Furthermore, as bone scans assess changes in the bone itself and not the tumor directly, it is possible that an apparent worsening may reflect healing and not true progression of disease. To address both of these issues and to insure that the changes seen are a true reflection of disease status, we recommend that a second scan should be done to confirm that the disease has continued to worsen, at which point, the treatment can and should be discontinued. Under this paradigm, patients with a stable follow-up scan who have no new symptoms of disease or growth in a soft tissue site would not be considered as having progressed on the treatment.

The analysis of the relationship between PSA progression-free survival and overall survival provides further support for an initial 12-week drug exposure independent of the PSA levels obtained, because the association increased during this time interval. Additional support for this approach comes from reports that a favorable effect on PSA kinetics may not occur for >8 to 10 weeks, even for a cytotoxic drug, and is consistent with this. This is especially problematic because patients often mandate a change in their therapy if immediate declines in PSA do not occur. Going further, we examined the rate of increase in PSA in patients who progressed and found that for 75% of those treated, PSA doubling times at the time of progression were $\leq$3 months. For the remaining 25%, the range was 3 to 60 months, raising the question of whether those with very slow doubling times should in fact be considered as having failed treatment.

Even with the delay in assessment to 3 months or beyond, the level of association for PSA progression and survival was low, 0.33, and was similar to what we observed previously (11). That only a proportion of cells within a tumor express PSA may, in part, explain why changes in PSA alone are not associated more strongly. In one autopsy study, that percentage of PSA-positive cells within individual tumor masses ranged from 0.3% to 99%, with a median of 39%. It is therefore possible that a drug may only affect the non–PSA-secreting cells within a tumor, whereas the PSA-producing cells continue to grow unabated (12).

The use of a progression-free survival end point for a castrate-resistant prostate cancer clinical trial is based on the assumption that progression-free survival time is highly associated with survival time. The most common forms of progression in this patient population are radiographic progression and PSA progression. Our finding that these associations are not strong suggests that the progression-free end point—at least as it is currently construed—may be problematic, particularly if used as the primary end point in a phase 3 metastatic prostate cancer clinical trial. The relatively low association suggests that other physiologic processes involving pathways that are not measured by changes in a bone scan or PSA are involved (13). Reliance on an end point that is moderately associated with survival time may lead to the failure to recognize potentially useful therapies, or conversely, the investment of significant resources into a therapy that does not have a substantive effect on survival time. At present, alternative measures of progression are needed to design efficient clinical trials in this patient population.

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