Cancer patients with bone metastases are at increased risk of experiencing skeletal events associated with severe morbidity. Clinical trials of palliative therapies must perform rigorous and robust evaluation of new treatments on the basis of meaningful summaries of the course of skeletal events over time, while dealing with potentially high mortality rates during observation. The purpose of this article is to present a multistate model that can be easily used to reflect possible courses of the disease process, indicate how simple methods of analysis can be used to estimate clinically relevant features of the process, and contrast this approach with some of the alternative methods. The relation between the multistate approach and previously used methods is highlighted.

Materials and Methods

Data. Hortobagyi et al. (4) report on a multicenter randomized trial designed to investigate the effect of pamidronate versus placebo on the development of skeletal events in breast cancer patients with bone metastases. Patients were accrued between January 1991 and March 1994 from 97 study sites in the United States, Canada, Australia, and New Zealand. Patients with stage IV breast cancer who were receiving cytotoxic chemotherapy with at least one predominantly lytic bone lesion ≥1 cm in diameter were randomized within strata defined by Eastern Cooperative Oncology Group status. A total of 382 women were enrolled in the study, with 185 randomized to receive pamidronate and 197 randomized to placebo control. Two patients randomized to placebo did not have bone metastases and were therefore excluded from subsequent analyses. Patients randomized to the pamidronate arm received 90 mg of pamidronate disodium via a 2-hour infusion every 4 weeks, whereas patients randomized to the placebo received dextrose infusions. Patients following a 3-week chemotherapy regimen were permitted to receive the study drug every 3 weeks. At monthly visits, patients were assessed and the occurrence of skeletal events was recorded. The skeletal events of interest include pathologic fractures, spinal cord compression, vertebral fracture, the need for surgery to treat or prevent fractures, and the need for radiation for the treatment of bone pain. After the planned 1 year of follow-up, the observation period was extended on treatment with blinding for an additional year and the results were published in the article by Hortobagyi et al. (4).

Multistate models. Multistate models are represented by multistate diagrams that indicate the finite number of clinical states a patient can occupy during follow-up. Methods for survival analysis (5, 6) may be viewed as based on a two-state model, with the first state representing an “alive” state and the second a “dead” state, where the objectives are to characterize the distribution of the transition time to the dead state. Multistate models are particularly useful, however, for more general disease processes. Figure 1 contains a multistate diagram useful for characterizing the occurrence of skeletal events and death. Patients in state $k$ are alive and have experienced $k$ events, $k = 0, 1, \ldots$, and are in state $D$ if they have died. As time passes, patients may make transitions between these states, with a forward transition occurring with each event and a downward transition into state $D$ upon death. The rate of these transitions characterizes the instantaneous risk of a move, which may vary over time. In Fig. 1, we use $r_k(t)$ to denote the rate of onset of a new skeletal event at time $t$ for a patient who has experienced $k$ events already, and $m_k(t)$ to denote the mortality rate for a patient who has experienced $k$ skeletal events. These time-dependent transition rates are naturally estimated as the proportion of patients at risk of a transition who make the transition of interest; thus, the estimated rate of new skeletal events at time $t$ among patients with $k$ skeletal events is...
simply the proportion of patients in state $k$ at time $t$ who experienced a skeletal event at time $t$.

Multistate models can also be used to gain insight into the effect of skeletal events on the risk of future skeletal events. For example, if the transition rate from the state of 1 skeletal event to 2 skeletal events is the same as the transition rate from 0 skeletal events to 1 skeletal event [i.e., $r_1(t) = r_2(t)$], then the occurrence of the first event did not materially alter the risk of subsequent events. Likewise, if $m_k(t) = m_{k-1}(t)$, then the occurrence of the $k$-th skeletal event is not associated with an increase in the risk of death over patients with $(k-1)$ skeletal events. The Andersen and Gill (7) method of analyzing recurrent events is based on the assumptions that (i) $r_k(t) = r(t)$, $k = 0, 1, ...$ (i.e., the rate of new events does not depend on the number experienced); (ii) $m_k(t) = 0$, $k = 0, 1, ...$ (i.e., there is no mortality); and (iii) the rate functions between two treatment groups are proportional. The multistate formulation can therefore be seen as a useful generalization.

Because estimated risks may fluctuate a great deal over the short term, it is customary to examine cumulative rates of transitions over time (5, 6). Plots of cumulative transition rates are created, and the slopes of the cumulative rates reveal trends over time and facilitate comparisons between rates of events among groups of patients with different disease histories. These estimated cumulative transition rates are called Nelson-Aalen estimates (8) and are obtained by adding the daily rates over time [i.e., the cumulative transition rate for the $(k + 1)$-st event after the $k$-th event is $R_k(t) = r_k(1) + ... + r_k(t)$]. The steeper the cumulative rates plots, the greater the transition rates over the corresponding interval. Multistate models can also be used to obtain estimates of so-called transition probability functions, which report the probability of being in a particular clinical state (or group of states) as a function of time, given the initial state. For example, one may estimate the probability that a patient is alive and has not experienced their $k$-th skeletal event by time $t$, the probability a patient has experienced at least $k$ skeletal events over time, or the probability a patient has experienced exactly $k$ skeletal events over time. These probabilities are estimated according to the Aalen-Johansen method (8, 9) and yield convenient graphical summaries of the data. Estimated transition probabilities may also be used to estimate the expected number of skeletal events over time. The cumulative expected number of events is estimated as

$$1 \times P(1 \text{ event at time } t) + 2 \times P(2 \text{ events at time } t) + \ldots + K \times P(K \text{ events at time } t) + \ldots$$

This can be plotted against time to reveal the cumulative expected number of events over different periods of follow-up.

The multistate model in Fig. 1 can also be used to estimate the survival distribution in a cohort of patients based on the Aalen-Johansen estimate of being in state $D$ over time. This, in general, is slightly different from the usual Kaplan-Meier estimate (10) based on a two-state (alive or dead) model and may be preferable in settings where patients are withdrawn from a study based on their response.

**Results**

Figure 2 contains plots of the cumulative rates of transition between successive skeletal event states with initial state 0, 1,
and 2 for placebo and pamidronate-treated patients. Among the placebo patients, the relative steepness of the curves for subjects with 1 and 0 events reveals that patients who have experienced 1 event (dotted line) are at higher risk of an event than subjects who have experienced 0 events (solid line). There is a slight further elevation in risk following the second event. A similar pattern is seen for pamidronate-treated patients but the cumulative transition rates for the first event and second event are somewhat lower for most of the duration of follow-up, reflecting the effect of treatment. Figure 3 shows the corresponding plots of the cumulative transition rates out of states 0, 1, and 2 into the death state. For placebo-treated patients, the cumulative transition rates for death are steepest for transitions out of the higher event states, reflecting the increased mortality rate among patients with a greater cumulative number of skeletal events. The pattern for pamidronate-treated patients is less clear. One explanation is because there are considerably fewer patients at risk of death from the states with the higher event counts due to the effect of pamidronate. A second issue is that pamidronate has an effect on skeletal events but not on survival; thus, treated patients will typically die with fewer events.

Figure 4 contains plots of the estimated proportion of patients at least 1, 2, and 3 skeletal events based on cumulative incidence functions (11). The cumulative incidence function plots give estimates of 78%, 66%, and 46% of placebo patients and 60%, 34%, and 25% of pamidronate patients having experienced at least 1, 2, or 3 events, respectively, by 24 months. The plots in Fig. 5 show the proportion of patients who are alive with none or exactly 1, 2, or 3 skeletal events over time from entry into the study. The estimated probability of occupying state 0 is the same as the estimate one uses for event-free survival, and the probability of being alive with k events is a so-called prevalence function, which increases only when more people are moving into state k than are leaving it due to a (k + 1)-st event or death. For both placebo and pamidronate patients, the probability of occupying state 1 increases rapidly to reflect the onset of skeletal events and then declines as subjects have more events or die. In the last 6 months of follow-up, there are slightly more pamidronate patients alive with exactly one event. The occupancy probabilities for state 2 increase more slowly and then stabilize before declining during the latter stages of follow-up; there are consistently fewer pamidronate-treated patients in this state at any time. Plots of estimates like Fig. 5 are useful in that, when examined in total, they give some indication of the probable status of a patient at any time since randomization. Moreover, as discussed earlier, they can be used to estimate the expected cumulative number of events over time. Estimates of these mean functions are given in Fig. 6 for both groups. This plot reveals a significant effect of pamidronate compared with placebo in reducing the expected cumulative number of skeletal events.

Discussion

Multistate modeling is an appealing approach to the analysis of diseases with complex courses. As illustrated herein, considerable insight can be gained into the nature of the disease process, the implications of event occurrence on the risk of subsequent clinical events or death, and the cumulative disease burden based on the cumulative expected number of events. The simple graphical analysis presented here reveals
clearly for placebo patients that the risk of skeletal events is greater after the occurrence of the first skeletal event and that the risk of death increases after the occurrence of a skeletal event. This pattern is less clear in the pamidronate arm due, in part, to the fact that there is an effect of pamidronate on events but not on overall survival.

The methods discussed here are all motivated by Markov models that have received considerable attention in the medical

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Fig. 4. The proportion of patients with at least 1, 2, and 3 skeletal events over time estimated based on cumulative incidence functions [data are from Hortobagyi et al. (4)].

Fig. 5. Aalen-Johansen estimates of the probability of control patients having exactly 0, 1, 2, or 3 skeletal events over time [data are from Hortobagyi et al. (4)].
literature in recent years (12, 13). However, it has recently been pointed out that these estimates of the cumulative transition rates and state occupancy probabilities are robust (14, 15) and can therefore be useful for the analysis of more general processes. This robustness makes these approaches appealing for use in clinical trials.

Other simple summary measures have been proposed in the setting of palliative trials of patients with bone metastases. Scott et al. (16) have proposed segmenting the follow-up period into different intervals within which a binary response (yes/no) is defined, indicating whether at least 1 skeletal event occurred in that interval. These rates were then smoothed in a somewhat ad hoc manner to give summary measures that can be used in regression analyses. Rigorous justification for the smoothing of the rates before analysis is not provided, and this subjective component means that different analysts studying the same data could draw different conclusions based on the extent of smoothing.

There are several obvious areas that require further development. We have not discussed the use of covariates to understand how risk factors may alter transition rates. Proportional rate regression models analogous to the Cox regression model can be fit under the Markov assumption, but interest lies in robust inferences in clinical trials (i.e., it is desirable to perform tests of treatment effects based on minimal assumptions). Formal comparisons of mean functions are also of interest based on multistate models similar in spirit to the approaches used by Ghosh and Lin (17). Moreover, robust methods for fitting regression models that give relative rates for the incidence of new skeletal events are also of interest in the spirit of Andersen and Gill (7). Such methods are currently under investigation.

Open Discussion

Dr. Berenson: There’s a recent report from the Mayo Clinic suggesting that fracture risk is largest the first year after diagnosis [Melton et al. (18)]. Would that apply to myeloma?

Dr. Cook: Are you saying that once you’ve gone past this first year, the risk of skeletal-related events drops?

Dr. Berenson: The risk of fracture decreases.

Dr. Roodman: It goes from 40% to 60%. However, there’s no analysis in that report that takes into account response to treatment, which affects the fracture rate.

Dr. Berenson: I’m not sure it’s true in myeloma that if you have an event, you’re going to die sooner. There were a lot of caveats in the group of patients who were put on those trials. They were very different from a newly diagnosed patient.

Dr. Roodman: You also have to remember that the data are cumulative over a long period for the Mayo Clinic group, and treatment patterns change.

Dr. Cook: Also, when you’re looking at, for example, the rate of events in year 2, you’re only looking at the subset of patients who made it that far.

Dr. Berenson: Myeloma patients are going to live a lot longer these days.

Dr. Suva: Can you track changes with treatment for the ability to progress from one skeletal-related event to another?

Fig. 6. Estimated cumulative expected number of skeletal events over time for control and pamidronate-treated patients [data are from Hortobagyi et al. (4)].

Dr. Cook: Yes, we can do that. We’re no longer protected by randomization to the same degree when we’re looking at covariant effects acting on rates like these. The only individuals who give you information about treatment benefit from one point to another are the subset of individuals who had a first event. It’s an interesting phenomenon, because if you have an extremely effective treatment, then the only individuals in the treatment arm who are going to have this first event are going to be worse off than the patients in the placebo or control arm who had an event.

Dr. Suva: Can you dissect out those people?

Dr. Cook: You can, but you’re not going to be protected by randomization, so it’s not as strong as the inference you make here. You can try to adjust for differences, such as the patient mix changes, and then you’re in a much firmer position to make a statement about treatment benefit. This would mean fitting a regression model to characterize differences between the groups. If you wanted to do that in an extremely rigorous way, you would rerandomize each event. I don’t know how practical that is, but in situations with these recurrent events you can do that.

Dr. Cook: There are two issues: one is the aim of making causal inferences and getting a good estimate of treatment benefit and the other is determining the population of interest. How do you define the population?

Dr. Suva: You need a pharmacogenomic theme.

Dr. Cook: So it could be based on genomics or something else, too.

Dr. Body: Have you been able to examine a group of patients who have an event immediately or quite early in the first 3 months after starting bisphosphonates? Do these patients have a worse prognosis than do patients who get an event only after 1 year of treatment?

Dr. Cook: We haven’t done that yet, but it would be possible.

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References

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