The accuracy of predicting survival in individual patients with cancer

Clinical article

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Object. Estimating survival time in cancer patients is crucial for clinicians, patients, families, and payers. To provide appropriate and cost-effective care, various data sources are used to provide rational, reliable, and reproducible estimates. The accuracy of such estimates is unknown.

Methods. The authors prospectively estimated survival in 150 consecutive cancer patients (median age 62 years) with brain metastases undergoing radiosurgery. They recorded cancer type, number of brain metastases, neurological presentation, extracranial disease status, Karnofsky Performance Scale score, Recursive Partitioning Analysis class, prior whole-brain radiotherapy, and synchronous or metachronous presentation. Finally, the authors asked 18 medical, radiation, or surgical oncologists to predict survival from the time of treatment.

Results. The actual median patient survival was 10.3 months (95% CI 6.4–14). The median physician-predicted survival was 9.7 months (neurosurgeons = 11.8 months, radiation oncologists = 11.0 months, and medical oncologist = 7.2 months). For patients who died before 10 months, both neurosurgeons and radiation oncologists generally predicted survivals that were more optimistic and medical oncologists that were less so, although no group could accurately predict survivors alive at 14 months. All physicians had individual patient survival predictions that were incorrect by as much as 12–18 months, and 14 of 18 physicians had individual predictions that were in error by more than 18 months. Of the 2700 predictions, 1226 (45%) were off by more than 6 months and 488 (18%) were off by more than 12 months.

Conclusions. Although crucial, predicting the survival of cancer patients is difficult. In this study all physicians were unable to accurately predict longer-term survivors. Despite valuable clinical data and predictive scoring techniques, brain and systemic management often led to patient survivals well beyond estimated survivals.

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Key Words • cancer • survival • prediction • brain metastasis • brain tumor • outcome • oncology

PATIENTS and their doctors both seek a reliable prediction of survival when a diagnosis of cancer is made. The most universal question is, “How long do you think the patient will live?”22 Survival expectations are a frequent topic in doctor-patient discussions and doctor-doctor interactions. Thus, the reliability and accuracy of clinical and imaging data on individual patients outcomes

Abbreviations used in this paper: KPS = Karnofsky Performance Scale; RPA = recursive partitioning analysis; WBRT = whole-brain radiation therapy.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.
For decades, clinicians have relied on survival estimates to facilitate decision making. Our hypothesis was that cancer specialists could reliably predict individual survival times in a group of patients who will undergo stereotactic radiosurgery for cancer metastatic to the brain.1–3,16–19,27

Methods

This study was approved by the Institutional Review Board of the University of Pittsburgh. The study was performed between 2009 and 2011 and included 150 patients whose median age was 62 years (range 33–84 years). As part of a standard brain metastasis database at the University of Pittsburgh’s Center for Image-Guided Neurosurgery, we prospectively collected data on cancer histology, number of metastatic brain tumors, and extracranial disease status. The number of tumors is a proxy for tumor burden and is a metric used in the design of prior randomized trials (solitary tumor, 2–4 tumors, 1–3 tumors, and < 5 tumors). Extracranial disease was graded as follows: none; minimal; symptomatic; diffuse (multiple organ systems); and cachexia. We recorded the Karnofsky Performance Scale (KPS) score, whether the patient had received prior whole-brain radiation therapy (WBRT), and whether the primary cancer and the brain tumor diagnosis were made at the same or different times (synchronous vs metachronous presentation). We recorded whether the brain tumor was asymptomatic; caused seizures only; caused headache only; or was associated with a neurological deficit. We calculated the recursive partitioning analysis (RPA) class: Class 1 included patients with an age less than 65 years, KPS score ≥ 70, controlled primary tumor, and no extracranial metastases; Class 3 included all patients with a KPS score less than 70; and Class 2 comprised those not included in Class 1 or 3. Finally, we recorded a specific prediction of expected survival from that point in time. We then entered all the data onto a spreadsheet and requested 18 cancer specialists (6 neurosurgeons, 7 radiation oncologists, 5 medical/neuro-oncologists) to provide an estimated survival in months for each patient. The study group consisted of leaders in their respective fields. We included clinicians who had led and participated in the brain metastases guideline projects, who had published on cancer management, and who had developed clinical scoring systems. Only one physician saw all of the patients and was involved in their actual care, and this initial contact prior to recording the survival prediction included the clinic visit, history and physical examination, and review of imaging studies. This contact continued during the life of the patients.

Statistical Analysis

Kaplan-Meier analyses were performed to compare actual and predicted survivals. The log-rank test was used to assess differences in survival curves. Standard statistical processing software (SPSS v20, IBM) was used. A p value < 0.05 was used for statistical significance.

Results

Clinical Data

This study included the following tumor types in these 150 patients: non–small cell lung cancer (n = 65); small cell lung cancer (n = 16); breast cancer (n = 30); melanoma (n = 21); renal cell carcinoma (n = 8); and other (n = 10). The mean number of brain metastases was 5 (range 1–40). Thirty-eight patients had solitary brain metastasis and 112 had multiple tumors. The median KPS score was 90 (range 40–100). Prior WBRT had been performed in 69 patients (46%). The distribution of RPA classes was as follows: Class 1, 23 patients; Class 2, 122 patients; and Class 3, 5 patients (Table 1). Actual survival differences according to RPA classes were significant (p = 0.000002).

For the entire series, the average survival prediction of the 18 doctors was 9.7 months (95% CI 7.98–11.4).

### Table 1: Summary of data in 150 patients with brain metastases

<table>
<thead>
<tr>
<th>Item</th>
<th>No. of Patients/Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pathology</td>
<td></td>
</tr>
<tr>
<td>non–small cell lung cancer</td>
<td>65</td>
</tr>
<tr>
<td>breast cancer</td>
<td>30</td>
</tr>
<tr>
<td>melanoma</td>
<td>21</td>
</tr>
<tr>
<td>small cell lung cancer</td>
<td>16</td>
</tr>
<tr>
<td>renal cell carcinoma</td>
<td>8</td>
</tr>
<tr>
<td>other</td>
<td>10</td>
</tr>
<tr>
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<tr>
<td>none</td>
<td>3</td>
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<td>median KPS score (range)</td>
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<tr>
<td>prior WBRT</td>
<td></td>
</tr>
<tr>
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<td>54</td>
</tr>
<tr>
<td>no</td>
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</tr>
<tr>
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<tr>
<td>1</td>
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</tr>
<tr>
<td>2</td>
<td>122</td>
</tr>
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<td>3</td>
<td>5</td>
</tr>
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</table>
The actual median survival was 10.25 months (95% CI 6.4–14.1). The median survival predictions stratified by medical specialty were 11.8 months (95% CI 10.1–13.5); 11.0 months (95% CI 9.3–12.7), and 7.2 months (95% CI 6.4–7.99) for neurosurgery, radiation oncology, and medical/neuro-oncology, respectively (Fig. 1). There was a difference in prediction accuracy between the single neurosurgeon who examined the study patients and the group of physicians who provided predictions based on data only (p = 0.002), with the group selecting more optimistic predictions that were further from actual survivals.

Survival predictions were studied according to tumor histology. For breast cancer, patients’ actual median survival was 22.5 months (95% CI 5.5–39.5) compared with an overall predicted median survival of 12.9 months (95% CI 11.5–14.3; p = 0.65). For non–small cell lung cancer, patients’ actual median survival was 10.3 months (95% CI 4.5–16.0) compared with an overall predicted median survival of 9.3 months (95% CI 7.2–11.5; p = 0.72). For melanoma, patients’ actual median survival was 9.75 months (95% CI 7.3–12.2) compared with an overall predicted median survival of 9.0 months (95% CI 8.3–9.6; p = 0.79). There was no actual survival difference among these 3 tumor types (p = 0.69). There was no survival difference for patients who had or had not received prior WBRT (p = 0.91).

The prediction accuracies were determined for the 3 main cancer types. Predictions were accurate within the following ranges. For breast cancer, prediction was accurate within 0–3 months in 30%; 3–6 months in 19%; 6–9 months in 18%; 9–12 months in 12%; 12–18 months in 13%; and greater than 18 months in 8%. For non–small cell lung cancer, prediction was accurate within 0–3 months in 28%; 3–6 months in 25%; 6–9 months in 18%; 9–12 months in 13%; 12–18 months in 12%, greater than 18 months in 5%. For melanoma, prediction was accurate within 0–3 months in 39%; 3–6 months in 17%; 6–9 months in 13%; 9–12 months in 1%; 12–18 months in 12%; and greater than 18 months in 8%.

There was great variability in survival predictions. All physicians had predictions that were incorrect by as much as 12–18 months, and 14 of 18 physicians had individual predictions that were wrong by greater than 18 months. Of the 2700 predictions made, 65 (2.4%) were

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**Fig. 1.** A: Actuarial survival plot of 150 treated patients with brain metastases compared with the plot of averaged survivals predicted by physicians at time of initial management. B: Actuarial survival plot of 150 treated patients with brain metastases compared with the plot of averaged survivals predicted by physicians according to their subspecialty. MO = medical or neuro-oncologist; RO = radiation oncologist; NS = neurosurgeon. C: Actuarial survival plot of 65 treated patients with non–small cell lung cancer brain metastases compared with the plot of averaged survivals in the same patients predicted by physicians at time of initial management. D: Actuarial survival plot of 30 treated patients with breast cancer brain metastases compared with the plot of averaged survivals in the same patients predicted by physicians at time of initial management.
Predicting survival in cancer patients

off by greater than 18 months. Of the 2700 predictions, 1226 (45%) were off by greater than 6 months (434 underestimated and 792 overestimated) and 488 (18%) were off by more than 12 months (103 underestimated and 385 overestimated). We conducted an interperson analysis to determine if predictions were consistent for individual patients. The median range (shortest prediction to longest prediction) for each patient was 14 months (SD 5.98). When we excluded the outliers (shortest and longest), the median range was 12 months (SD 5.0); after excluding the two shortest and two longest, the median range was still 11 months (SD 5.5).

We studied the survival of common subgroups with unfavorable clinical characteristics. There were 38 patients with non–small cell lung cancer who had multiple brain tumors, a KPS score lower than 100, and active extracranial disease. In this group, 4 patients (11%) lived longer than 12 months, and none lived beyond 18 months. For those whose status was RPA Class 2 (n = 122), 47 lived more than 12 months (39%) and 23 lived beyond 18 months (19%). Of the 5 patients whose status was RPA Class 3, none lived more than 12 months.

We evaluated how the clinician predictions compared with longer-term survival. Overall, neurosurgeons and radiation oncologists were more optimistic (median estimates of 11.8 and 11 months; 95% CI 10.1–13.5 and 9.3–12.7, respectively) and medical oncologists predicted shorter survivals (median estimate 7.2 months; 95% CI 6.4–7.99). In the group of patients who all died ≤10 months after radiosurgery, the median survival was 4.25 months. The median predictions in this group were 8.7, 8.3 and 7.0 for neurosurgeons, radiation oncologists, and medical oncologists, respectively. The medical oncologists made 21 predictions that survival would be less than 4 months; 3 of these patients lived more than 12 months and 2 more than 18 months. When the medical oncologists’ prediction was less than 6 months (n = 67), 22 patients (33%) lived more than 12 months and 9 patients lived more than 18 months. Neurosurgeons’ predictions that survival would be less than 6 months (n = 14) were followed by actual survival of more than 12 months in 4 patients and by more than 18 months in 1 patient. Radiation oncologists’ predictions that survival would be less than 6 months (n = 23) were followed by actual survival of more than 12 months in 6 patients and by more than 18 months in 1 patient.

Finally, we compared predicted survivals to actual survivals for specific and common patient subgroups. Of the 65 patients with non–small cell lung cancer, 11 (17%) outlived their prediction by more than 18 months. Of the 93 patients with a KPS score less than 100, 29 (31%) outlived their prediction by more than 18 months. Of the 122 patients whose status was RPA Class 2, 46 (38%) outlived their predicted survival by more than 12 months and 24 (20%) by more than 18 months. The median actual survival for RPA Class 1 was 22.5 months (predicted survival 16.7 months; p = 0.36). The median actual survival for RPA Class 2 was 10 months (predicted survival 11.2 months; p = 0.88). The median actual survival for RPA Class 3 was 2 months (predicted survival 6.2 months; p = 0.02) (Fig. 2).

Fig. 2. Actuarial survival plots of patients in RPA Classes 1 (A), 2 (B), and 3 (C) showing actual versus predicted survivals.

Discussion

An understanding of survival is one of the most important concepts in the care of patients with diseases that can lead to death. Whether stated, implied, or just
thought, the concept of survival time is crucial to decision making by clinicians, patients, families, and payers. In this light, treatment considerations can be hopeful, aggressive, nihilistic, unreasonable, palliative, expensive, evidence based, or part of research. As the sources of such information for an individual patient’s care, clinicians are expected to come to rational, reliable, and reproducible conclusions on survival. This competency would be learned from the peer-reviewed literature on patient outcomes and from personal experience.12,23

There are several factors that commonly are associated with a limited survival expectation. An important one is older age, which could limit access to or tolerance of treatment. Increasing disease burden, typically measured by numbers of tumors in the brain, or the number of involved organ sites, is another. Unfortunately, the number of lesions is a poor surrogate for actual tumor burden, which should be based on overall tumor volume.4 Specific histological types like melanoma, for which there are fewer proven therapeutic options, are associated with reduced survival.19 Conversely, breast cancer, with more options and treatments directed at subtypes based on histological or molecular classification, can be thought of more positively.16 Various combinations of predictive factors have been incorporated into RPAs.10,26 However, important questions remain. How do the many clinical pieces of information result in a prediction, and how accurate is that prediction? Does the survival expectation differ among medical specialties? How often is our expectation very wrong? Are clinicians overly optimistic, fairly accurate, or nihilistic?

A report by Hølmebakk et al. showed that surgeons’ accuracy in determining prognosis for incurable abdominal malignancies was poor.15 Prognoses were accurate in 27%, too optimistic in 42%, and too pessimistic in 31% of the cases. In 2001, Chow et al. reviewed 9 reports and found that clinicians were inaccurate in an optimistic direction.7 They found no difference in predictions among general practitioners, hospital doctors, or hospice physicians. One report found that non–oncology specialists were 3 times more likely to be overoptimistic.9 Several studies showed that treating physicians tend to overestimate the duration of life.9,23 Patients themselves tend to overestimate survival, and this can affect decision making.20 In a study of patients with lung or colon cancer, those who thought they were going to live at least 6 months were more likely (OR 2.6) to choose life-extending therapy over comfort care compared with those who thought there was at least a 10% chance that they would not live 6 months. In that 5-institution series, physicians’ estimates were better than patients’ estimates. In patients for whom a 90% chance of 6-month survival was predicted, 57% lived 6 months (when predicted by the patients) and 71% of patients lived 6 months (when predicted by the doctors). From these data they concluded that improving cancer patients’ understanding can assist in decision making, with the potential cost of causing loss of hope with associated deleterious effects on quality of life.29

Recently, there has been great interest in the development of evidence-based guidelines for the management of brain metastases.20 These guidelines have been of value to clinicians. At the same time, payers have begun to use clinical checklists to facilitate third-party reimbursement decision making prior to treatment approvals (for example, CareCore). These documents attempt to use the available literature and have significant implications for patient care. The paradox is that such reports use what is known from populations and identify median survivals with different degrees of variability. At present, we are also in an era of increasingly “personalized” medicine. Specific tumor biology is evaluated, receptors can be tested, and therapy can be targeted.5,13,31 How population-based and validated predictive factors relate to individuals is poorly understood.5,24,30

Thus, to test the real-world utility of predictions, we developed a study group consisting of leaders in neurological and medical oncology, neurosurgery, and radiation oncology. We included clinicians who had led and participated in the brain metastasis guidelines projects, who had published on cancer management, and who had developed clinical scoring systems. The prediction accuracy of being within 3 months of actual survival was 31%, 34%, and 57% for breast cancer, lung cancer, and melanoma, respectively. Accuracy within 6 months was 53%, 65%, and 76% for those same cancer types, respectively. A prediction that was incorrect by more than 12 months was found in 18% (breast cancer), 8.4% (lung cancer), and 5% (melanoma). Interestingly, RPA Class 2 patients, who had an actual median survival of 10 months, showed great variability, with 38% outliving their prediction by more than 12 months and 20% by more than 18 months. This large group of patients (RPA Class 2) should be approached cautiously, which is why subscores have been tested in this population.26

The survival predictions showed that medical oncologists and neuro-oncologists as a group were more accurate at predicting the survival of patients who would die within 1 year. Radiation oncologists and neurosurgeons had a more optimistic outlook. However, no group could accurately predict survivors alive at 14 months, and all physicians failed to predict patients who actually had extended survivals. All physicians had survival predictions that were incorrect by as much as 12–18 months, and 14 of 18 had individual predictions that were in error by more than 18 months. Our interperson analysis showed great variability in predictions with a median range of 14 months. Thus, predicting the survival of cancer patients is difficult. Interestingly, the 1 clinician (a neurosurgeon) who evaluated each patient in person provided predictions that were different from the other neurosurgeons (p = 0.002). This raises the issue of providing management advice (that is, a phone consultation) or management decisions (that is, a remote insurance review) without actually seeing the patient. Such remote decisions are increasingly being made. Given our findings, we believe that this process must be carefully implemented and evaluated on an ongoing basis as therapies evolve.

The limitations of this study include our evaluation of brain metastasis patients only and not other cancer scenarios, and limited analysis of cancers types that infrequently spread to the brain. We also did not include data on molecular markers, a field that is evolving rapidly for differ-
ent cancers. Another limitation is that we focused on one consistent form of therapy. On the other hand, we think that the narrow patient population is one strength of this study because it maximized our likelihood of making accurate predictions based on available evidence. There are also algorithms to estimate survival for patients with brain metastases. However, our purpose was to test physician knowledge and use of the literature with actual patient data and not to evaluate how the literature could be used for the creation of a calculation methodology. Many of the investigators had been involved in the creation of the literature in this area or had subspecialty interests in brain metastasis care. We tested how the literature is recalled and used for individual patient scenarios that often include many combinations of clinical factors beyond those that are found to be statistically significant in published reports.

Conclusions

Despite validated clinical outcome measures and predictive scoring techniques, advanced brain and systemic management often led to patient survivals well beyond estimated survivals. We conclude that even experienced physicians are relatively poor at predicting individual longer-term survivors with problems like brain metastasis. Because of that, it could be harmful to use survival predictions for health care decision making both by physicians or policymakers. Without an understanding of the patient-specific initial response to treatment that may provide a longer survival, our evidence indicates that the physician's ability to judge survival based on population data is limited.

Disclosure

Dr. Lunsford is a consultant for Elekta AB and is a stockholder. Dr. Kondziolka was a consultant to Elekta at the time of this study but is no longer. Dr. Ahluwalia is a consultant for Elekta AB and has received a travel grant from Elekta. Dr. Sperduto is a partner at Minneapolis Radiation Oncology P.A.

Author contributions to the study and manuscript preparation include the following. Conception and design: Kondziolka, Lunsford. Acquisition of data: Kondziolka, Parry, Lunsford, Flickinger, Rakfal, Arai, Loeffler, Rush, Knisely, Sheehan, Friedman, Tarhini, Francis, Lieberman, Ahluwalia, Linskey, Sperduto, Stupp. Analysis and interpretation of data: Kondziolka, Kano. Drafting the article: Kondziolka, Lunsford, Flickinger. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kondziolka. Statistical analysis: Kano. Study supervision: Kondziolka, Lunsford.

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