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Scientific Article

Integrating Overall Survival and Tumor Control Probability Models to Predict Local Progression After Brain Metastasis Radiosurgery

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Purpose: Stereotactic radiosurgery (SRS) for brain metastases is frequently prescribed to the maximum tolerated dose to minimize the probability of local progression. However, many patients die from extracranial disease prior to local progression and may not require maximally aggressive treatment. Recently, improvements in models of SRS tumor control probability (TCP) and overall survival (OS) have been made. We predicted that by combining models of OS and TCP, we could better predict the true risk of local progression after SRS than by using TCP modeling alone.

Methods and Materials: Records of patients undergoing SRS at a single institution were reviewed retrospectively. Using established TCP and OS models, for each patient, the probability of 1-year survival [$p(OS)$] was calculated, as was the probability of 1-year local progression [$p(LP)$]) for each treated lesion. Joint-probability was used to combine the models [$p(LP, OS) = p(LP) * p(OS)$]. Analyses were conducted at the individual metastasis and whole-patient levels. Fine-Gray regression was used to model $p(LP)$ or $p(LP, OS)$ on the risk of local progression after SRS, with death as a competing risk.

Results: At the patient level, 1-year local progression was 0.08 (95% CI, 0.03-0.15), median $p(LP, OS)$ was 0.13 (95% CI, 0.07-0.2), and median $p(LP)$ was 0.29 (95% CI, 0.22-0.38). At the metastasis level, 1-year local progression was 0.02 (95% CI, 0.01-0.04), median $p(LP, OS)$ was 0.05 (95% CI, 0.02-0.07), and median $p(LP)$ was 0.10 (95% CI, 0.07-0.13). $p(LP, OS)$ was found to be significantly associated with the risk of local progression at the patient level ($P = .048$) and metastasis level ($P = .007$); however, $p(LP)$ was not ($P = .16$ and $P = .28$, respectively).

Conclusions: Simultaneous modeling of OS and TCP more accurately predicted local progression than TCP modeling alone. Better understanding which patients with brain metastases are at risk of local progression after SRS may help personalize treatment to minimize risk without sacrificing efficacy.

Introduction

Brain metastases are a common manifestation of advanced cancer, developing in approximately a third of patients with cancer. Brain metastases require nuanced and multi-disciplinary management strategies in comparison

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with extracranial metastatic lesions due to their potential to cause highly morbid or lethal brain injuries, including neurological deficits and obstructive hydrocephalus, as well as their privileged location behind the blood-brain barrier, which renders them inaccessible to many systemic therapeutic agents. Stereotactic radiosurgery (SRS) has become an accepted and powerful therapeutic approach to treating brain metastases for patients with a limited burden of intracranial disease.[1,2] The principles of stereotactic radiosurgery for brain metastases are similar to the principles of stereotactic ablative radiotherapy (SABR) for bone or visceral metastases in that it uses high fractional doses of highly conformal radiation with minimal setup margins with the goal of maximizing local control of the target tumor. However, the rationale for and the patient population in which it is used differs significantly from SABR.

Although SABR, with a few notable exceptions, is primarily studied and used in the setting of oligometastatic cancer with the dual goals of improving local and systemic disease control, brain SRS monotherapy replaced whole brain radiation therapy (WBRT) as the standard upfront treatment option despite high-quality data demonstrating higher rates of intracranial progression with SRS than WBRT.[3-5] Rather, the primary driver of the replacement of whole brain radiation with radiosurgery has been the finding that radiosurgery monotherapy does not measurably lower overall survival when compared with WBRT[3-5] and better preserves cognition and quality of life.[4,5] The patient population undergoing stereotactic radiosurgery for brain metastases also differs significantly from the population undergoing extracranial SABR. Median overall survival across the seminal phase 3 trials evaluating SRS ranged from ~6 to 12 months[3-5] while survival in comparably seminal SABR trials ranged from 28 to 50 months.[6,7] As such, while SRS and SABR use similar techniques and treatment principles, SRS is a treatment for which the primary goal is the preservation of quality of life, while SABR is a treatment for which the primary goal is maximizing systemic disease control and extending survival in the highly select oligometastatic patient population.

Because of its primarily palliative intent, SRS dose selection should carefully balance the potentially competing goals of maximizing tumor control and minimizing the risk of treatment related toxicity. This principle has been reflected in the radiosurgery literature since radiation therapy oncology group (RTOG) 9005 found a significantly lower maximum tolerated dose for tumors greater than 2 cm in diameter than for smaller lesions.[8] Since then, multiple studies have demonstrated additional associations amongst tumor size, treatment dose, and brain dose-volume metrics and the risk of adverse events after radiosurgery (for review see Milano et al[9]). As a result, many radiosurgery trials have mandated lower treatment doses to larger tumors, with the goal of preventing radiation necrosis. However, beyond tumor size and, in select cases, histology, few factors are standardly considered in selecting the treatment dose for radiosurgery, with many practitioners and modern trial protocols adhering closely to the maximum tolerated dose established by RTOG 9005 (eg, NCT04114981, NCT03550391).

Recently, significant improvements have been made in our ability to predict the expected survival of patients with brain metastases.[10-12] Recent prognostic models have found that the expected survival of patients with brain metastases depends not only on their burden of intracranial disease, but also on their age, performance status, histologic and molecular tumor factors, and burden of extracranial disease. These models suggest that patients with brain metastases are at high risk of death from causes independent of their intracranial tumor control. This finding is reflected in the fact that trials frequently fail to prove a survival benefit to more aggressive brain radiation in the metastatic setting.[3,4,13,14]

Simultaneously, recent work has improved our understanding of how tumor size and treatment dose impact tumor control probability (TCP), the risk of local recurrence after SRS.[15] Although there are significant challenges in establishing precise TCP curves due to the heterogeneity of both treatment technique and study population across the published literature, efforts such as that of the hypofractionated treatment effects in the clinic (HyTEC) working group have established reasonable quantitative models of the relationships between tumor size, treatment dose, and risk of local recurrence.

Our improving understanding of the factors that impact survival and local control for patients with brain metastasis creates the opportunity to tailor the choice of radiosurgery dose more rationally to fit the needs of individual patients and to pick a dose that will result in a low risk of local recurrence within that patient's lifetime without exposing them to excess risk of treatment-related toxicity. It also allows us to better quantitatively understand the tradeoffs involved with dose-escalation and de-escalation for individual patients.

In this article, we assess the impact of patient prognosis on the risk of local recurrence after stereotactic radiosurgery for intact brain metastases. We hypothesized that a model predicting both overall survival and tumor-control probability would better predict the risk of a local recurrence after SRS than a model predicting TCP alone. To test this hypothesis, we applied a recently published prognostic model, the updated diagnosis-specific graded prognostic assessment (GPA) model[10-12] and a recently published TCP model, the HyTEC TCP model,[15] to the radiosurgery outcomes at a single institution.

Methods and Materials

Institutional Review Board approval was provided for this retrospective study. Patients who underwent single fraction or fractionated stereotactic radiosurgery for intact

brain metastases in our department between January 1, 2012, and December 31, 2022, were identified. All patients underwent treatment using a linear accelerator-based radiosurgery platform. Clinical features of each patient were extracted from the electronic medical record. Tumor size and prescription dose were extracted from the treatment planning system.

For each identified patient, the GPA at the time of brain metastasis diagnosis was calculated using an online GPA calculator (brainmetgpa.com), which is based on the GPA models described by Sperduto et al.[10-12] From the GPA and the date of radiosurgery, the eligibility quotient, the probability that the patient will survive one year from a chosen date, was calculated.[10-12] From here forward eligibility quotient will be designated by the term $p(OS)$ or the probability of overall survival (OS).

For each treated lesion, the 1-year tumor control probability was determined based on the HyTEC model,[15] which determines TCP based on lesion size and prescription dose. For fractionated SRS the physical dose is converted into a single fraction equivalent dose, assuming an alpha/beta ratio of 20.[15] Note that although the article described this model, a separate TCP model is described for melanoma metastases, in this work, melanoma metastases were analyzed using the combined model, as the melanoma-specific model was built only from studies assessing single fraction radiosurgery for small melanoma metastases. From here forward, rather than using the term TCP, we will use the term "probability of local progression" ($p(LP)$) wherein $p(LP) = 1 - TCP$ when we refer to the risk of local progression after radiosurgery.

Because the updated diagnosis-specific graded prognostic assessment model[10-12] was used to predict overall survival, only patients with primary tumors for which a GPA could be calculated were included. This limited the population to patients with primary lung, breast, renal, or gastrointestional cancer, or melanomas. Similarly, because the HyTEC model[15] was used to predict TCP, only intact brain metastases were included in the analysis.

Patients were followed until 1 of 3 events occurred: (1) they experienced a local recurrence after radiosurgery, (2) they died without evidence of a local recurrence, or (3) they were censored at the last available follow-up timepoint. Local recurrence was scored as such if the recurrence was pathologically confirmed, if the patient underwent re-irradiation for a presumed recurrence, or if the patient was deemed based on imaging to have recurred by the team of treating physicians but died or enrolled on hospice prior to confirmation. Lesions that enlarged at some timepoint after treatment but were not intervened upon because they were not symptomatic or were considered more consistent with radiation necrosis by the treatment team at the time were not scored as local recurrences. Patients who enrolled on hospice and were lost to follow-up thereafter were scored as deaths without recurrence if there was no evidence of recurrence at the time of hospice enrollment. Patients who were lost to follow-up and patients who were known to be alive and without recurrence were censored at the last available imaging timepoint.

Survival analyses were conducted at both the patient level and individual metastasis level. For analyses at the individual metastasis level, each lesion was analyzed independently even if multiple lesions were treated for a single patient. Lesions treated at different timepoints were analyzed with respect to their individual treatment dates. For analyses at the patient level, patients were scored as having experienced a recurrence if any treated lesion was determined to have recurred. For patients that underwent multiple courses of radiosurgery over time, only the first course of treatment was considered in the patient-level analysis. This was done because of the difficulties of determining a single time-to-event for multiple lesions treated at different timepoints. Competing risk analysis was used to calculate the cumulative incidence functions of local recurrence and competing death. Fine-Gray regression was conducted using the *cmprsk* package in R.[16,17]

For each patient and for each lesion, a $p(OS)$ and a $p(LP)$ were assigned based on their GPA and TCP, respectively. From these, the probability that the patient would be alive 1 year after treatment and would have experienced a local recurrence was calculated as $p(LP, OS) = p(OS) * p(LP)$ such that $p(LP, OS)$ was the simple joint probability of these 2 events under the assumption of their statistical independence. $P(LP)$ and $p(LP, OS)$ were used as regressors in survival analyses and to calculate expected rates of death and local recurrence at the group level. The total number of metastases for each patient was also used as a regressor as the GPA model lacks granularity with respect to brain metastasis number.

The expected rates of death and local recurrence were estimated by simulation. For the analysis the individual metastasis level each lesion was assigned 3 event probabilities, $p(OS)$, $p(LP)$, and $p(LP, OS)$. For each lesion and for each event, a random number was drawn from a uniform random distribution between 0 and 1. If the randomly drawn number was less than the event probability, then the event would be scored as having occurred (e.g. if $p(OS) = 0.6$ and 0.5 was drawn then the patient was "alive"; if $p(LP) = 0.1$ and 0.05 was drawn, then the lesion "progressed"). For a given simulation the rate of deaths and rate of recurrences were calculated. The simulation was repeated 10,000 times allowing estimation of the median expected recurrence rate as well as the 95% confidence interval of the expected recurrence rate.

For the analysis at the patient level, each patient was assigned a $p(OS)$ based their GPA. For each patient a combined probability of local progression, $p_{comb}(LP)$, was defined as $p_{comb}(LP) = 1 - \prod_{i=1}^{N} \left(1 - p_i(LP)\right)$. Where $p_i(LP)$ is the probability of recurrence of the i^{th} lesion of a patient with N total lesions. In words this is simply one minus the probability that not a

single lesion recurs. For the patient level model $p_{comb}(LP, OS) = p_{comb}(LP) * p(OS)$. Expected rates of recurrence and survival at the patient level were estimated by simulation in the same manner as they were for the metastasis level analysis.

Results

The characteristics of the study population are shown in Table 1. Most patients in the cohort had primary breast or lung cancers. Most tumors were less than 1cc in volume and a majority were treated with single fraction radiosurgery.

Figure 1 shows the predicted and observed cumulative incidences of local recurrence and competing death at the patient level and metastasis level. At the patient level, the 1-year rate of competing death was 0.49 (0.38-0.59). This result was in good agreement with the estimated median p(OS) of 0.51 (95% CI, 0.42-0.61). The 1-year rate of local recurrence was 0.08 (95% CI, 0.03-0.15), which was in good agreement with the median estimated $p_{comb}(LP, OS)$ of 0.13 (95% CI, 0.07-0.2) but was considerably lower than the median estimated $p_{comb}(LP)$ of 0.29 (95% CI, 0.22-0.38). At the metastasis level, the 1-year rate of competing death was 0.58 (0.53-0.63). This result was also in good agreement with the estimated median $p(OS)$ of 0.53 (95% CI, 0.48-0.57). The 1-year rate of local recurrence was 0.02 (95% CI, 0.01-0.04), which was in good agreement with the median estimated $p(LP, OS)$ of 0.05 (95% CI, 0.02-0.07) but was considerably lower than the median estimated $p(LP)$ of 0.10 (95% CI, 0.07-0.13). Using multivariable Fine-Gray regression, $p_{comb}(LP, OS)$ was found to be significantly associated with the risk of local progression at the patient level ($P = .048$) while the number of metastases was not ($P = .51$). In a parallel analysis $p_{comb}(LP)$ trended toward an association with the risk of local progression at the patient level ($P = .16$) while the number of metastases did not ($P = .33$).

Table 1 Patient and treatment characteristics

Primary cancer	No. of patients	%
Breast	22	24
GI	13	14
Melanoma	15	16
Renal	8	9
Lung	34	37
	Median	**Range**
Tumor number	2	1-20
Tumor volume (cc)	0.26	0.01-26.1
Total dose (Gy)	22	12-35
Fractions	1	1-5
Age* (y)	58	28-89
KPS*	80	50-100
GPA*	2	0.5-3.5
p(LP) (metastasis level)	0.1	0.05-0.43
p(LP) (patient level)	0.24	0.05-0.95
p(OS) (metastasis level)	0.48	0.1-0.87
p(OS) (patient level)	0.53	0.1-0.87
p(LP,OS) (metastasis level)	0.039	0.005-0.31
p(LP,OS) (patient level)	0.1	0.02-0.56

Abbreviations: GI = gastrointestinal; GPA = graded prognostic assessment; KPS = Karnofsky performance status score; LP = XXX; OS = overall survival.
*At diagnosis of first brain metastasis.

At the metastasis level $p(LP, OS)$ was found to be significantly associated with the risk of local progression ($P = .007$) as was the number of metastases ($P = .045$). $p(LP)$ was not strongly associated with the risk of local progression ($P = .28$), and the number of metastases was ($P = .036$).

To better understand the predictive power of the TCP model compared with the joint TCP-OS model, we looked at the temporal pattern of local recurrence and competing death in patients deemed to be at low versus high risk of recurrence using the 2 models. To avoid overfitting this relatively small dataset we used the arbitrary but intuitive cut-point of the median $p(LP)$and median $p(LP, OS)$ to divide the cohort into low-risk and high-risk groups. Figure 2 shows the patient level analysis, and Fig. 3 shows the metastasis level analysis. At the patient level, subjects for which $p_{comb}(LP, OS)$ was high (above median) had both a significantly increased risk of local recurrence ($P = .047$) and a significantly decreased risk of competing death ($P = .019$) compared with their low-risk counterparts. Conversely, at the patient level, patients for which $p(LP)$ was high (above median) were not significantly more likely to experience local recurrence ($P = .33$) or competing death ($P = .96$). Analyzing the data at the metastasis level produced similar results. Metastases for which $p(LP, OS)$ was high had both a significantly increased risk of local recurrence ($P = .041$) and a significantly decreased risk of competing death ($P = .0064$) compared with their low-risk counterparts. Metastases for which $p(LP)$ was high were numerically but not statistically significantly more likely to experience a local recurrence ($P = .47$) but trended toward an increased risk of competing death ($P = .0511$) when compared with their low-risk counterparts. Close examination of the temporal characteristics of the metastasis level cumulative incidence curves sheds some light into the difference in the populations portioned based on $p(LP, OS)$ versus $p(LP)$. For the $p(LP)$-high cohort (Fig. 3A) most local recurrences occur in year 1, and none after year 2. Conversely in the $p(LP)$-low cohort, local recurrence events continue to occur from years 2 to 5. On the other hand, when patients were divided based on $p(LP, OS)$ (Fig. 3C) many of the

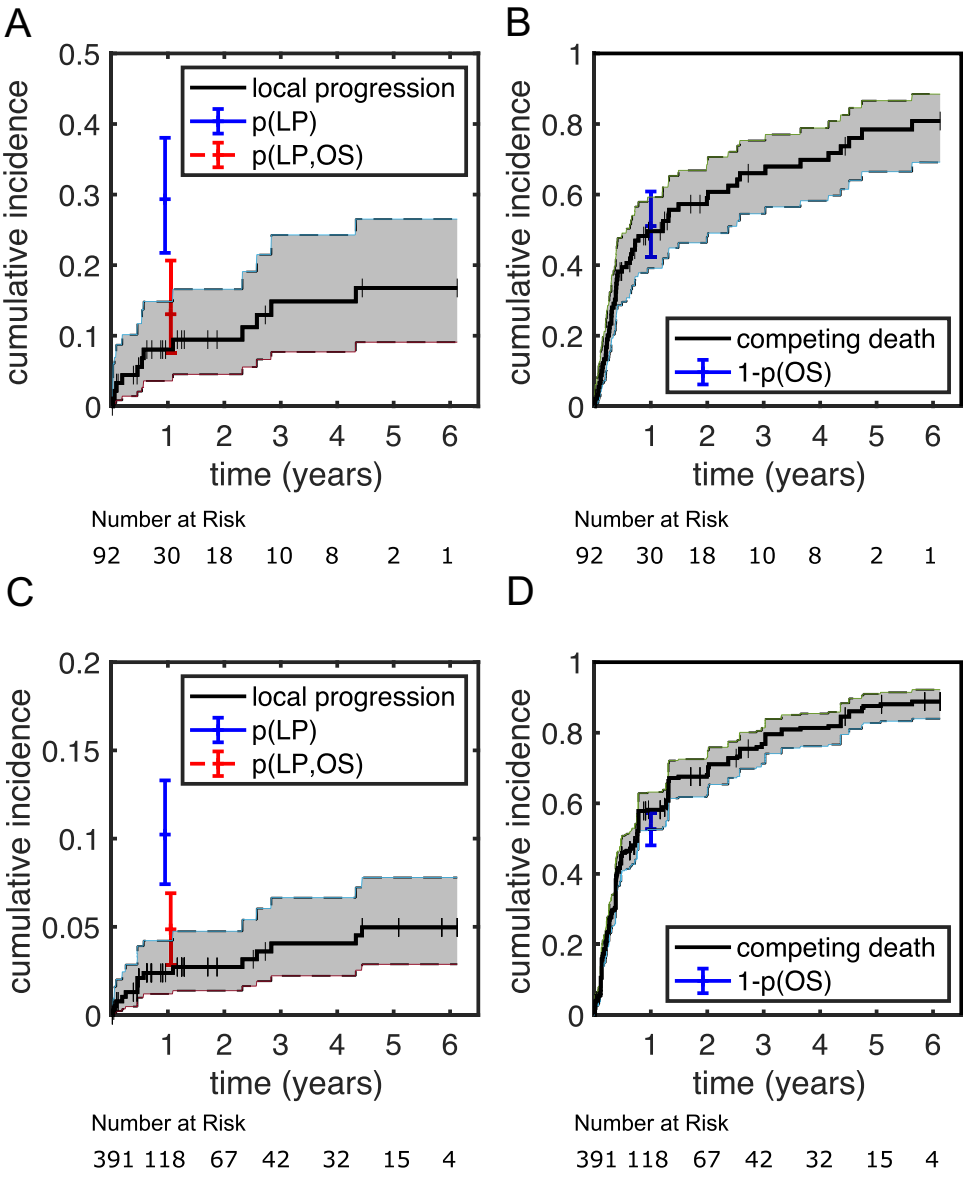

Figure 1 Predicted and observed local progression and survival after stereotactic radiosurgery. Red and blue plots represent predicted rates at 1 year using each model. Cumulative incidence curves represent observed data. Error bars are 95% confidence intervals. (A) Local progression: patient level. (B) Competing death: patient level. (C) Local progression: metastasis level. (D) Competing death: metastasis level.

subjects who experienced these late local progression events were reassigned to the high-risk cohort, likely because of a good overall survival prognosis.

Discussion

Stereotactic radiosurgery for brain metastases occupies a unique position among the growing number of stereotactic radiotherapy treatment paradigms for the management of metastatic cancer. On the one hand, it uses similar ablative or near-ablative doses to many SABR paradigms, with the shared goal of maximizing local control. On the other hand, the evidence-based rationale for using SRS over conventional techniques for brain radiation is primarily the mitigation of treatment-related toxicity, not improvement of systemic disease control nor even the prolongation of life. As such it is of particular importance that dose selection be tailored to the needs of the individual patient.

In this study, we examined the local control and survival outcomes of patients undergoing SRS for brain metastases at a single institution, using recently published TCP and prognostic models to predict local progression of disease after treatment. We found that the risk of local progression was significantly over-estimated when a TCP

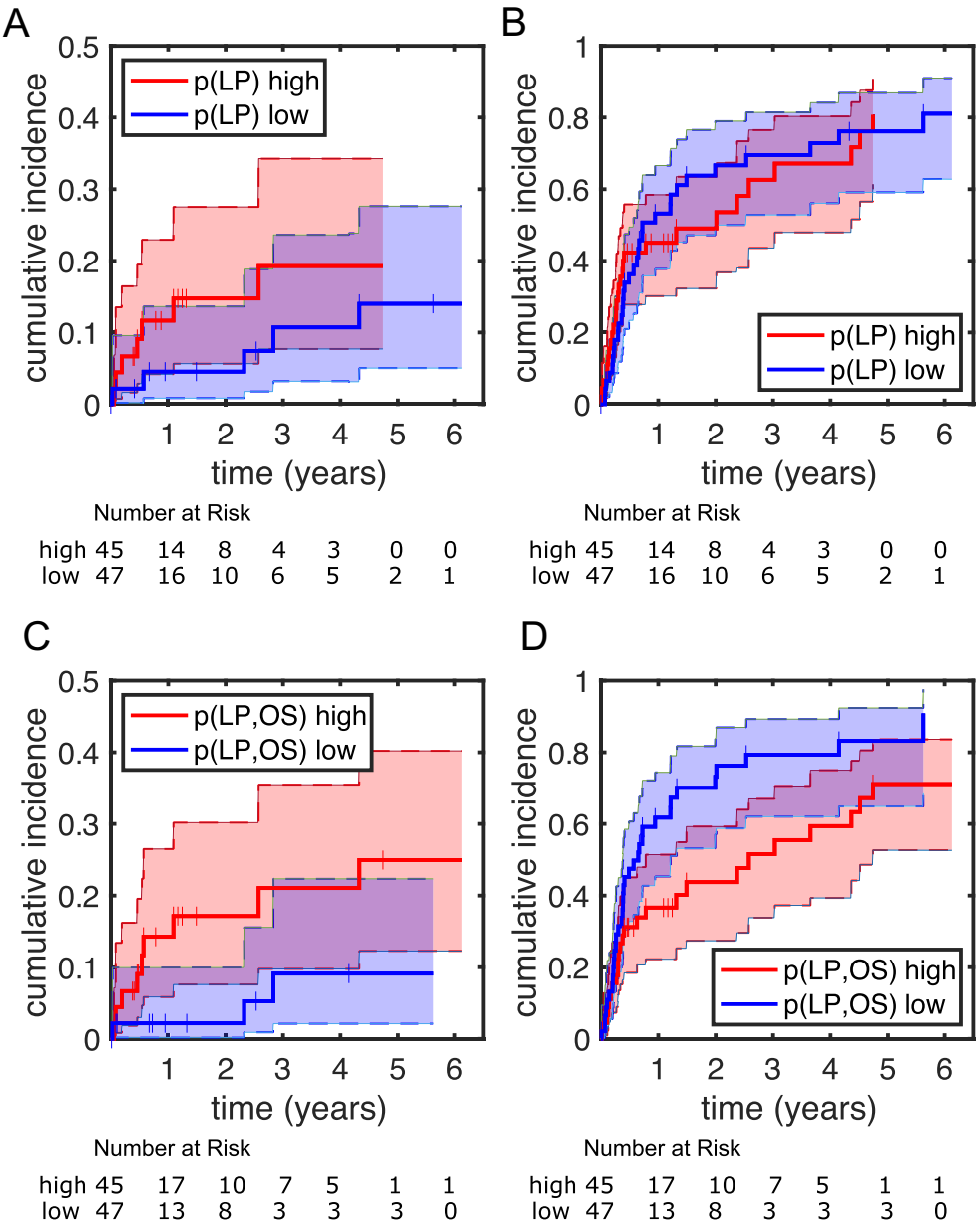

Figure 2 Local progression and survival in high-risk versus low-risk cohort (patient level). (A) Local progression: tumor control probability (TCP) model. (B) Competing death: TCP model. (C) Local progression: TCP overall survival model. (D) Competing death: TCP overall survival model.

model was used on its own. However, we also found that the integration of a TCP and a prognostic model through a simple and intuitive joint probability model both increased our ability to predict recurrence and produced remarkably numerically accurate risk-predictions at both the individual metastasis and patient levels. The implication of this finding is that overall prognosis is a primary factor in determining whether a patient will experience a local recurrence after stereotactic radiosurgery, and that a patient with a shorter predicted overall survival is likely to benefit less from aggressive SRS dose escalation than one with a longer expected survival.

Figure 4 illustrates this concept. Patient A is a 58-year-old woman with ER+/PR+/Her2- breast cancer, a Karnofsky performance status of 90, a solitary small brain metastasis, and no extracranial disease. Her GPA is 3, and her $p(OS)$ is 72%. Patient B is a 58-year-old woman with triple negative breast cancer, a Karnofsky performance status score of 80, and 2 small brain metastases as well as additional extracranial metastases. Her GPA is 1 and her $p(OS)$ is 26%. For patient A, dose escalation from 18 to 24 Gy in one fraction decreases $p_{comb}(LP)$ from 14% to 5% and decreases $p_{comb}(LP, OS)$ from 10% to 3.6%. Conversely, for patient B, while similar dose escalation

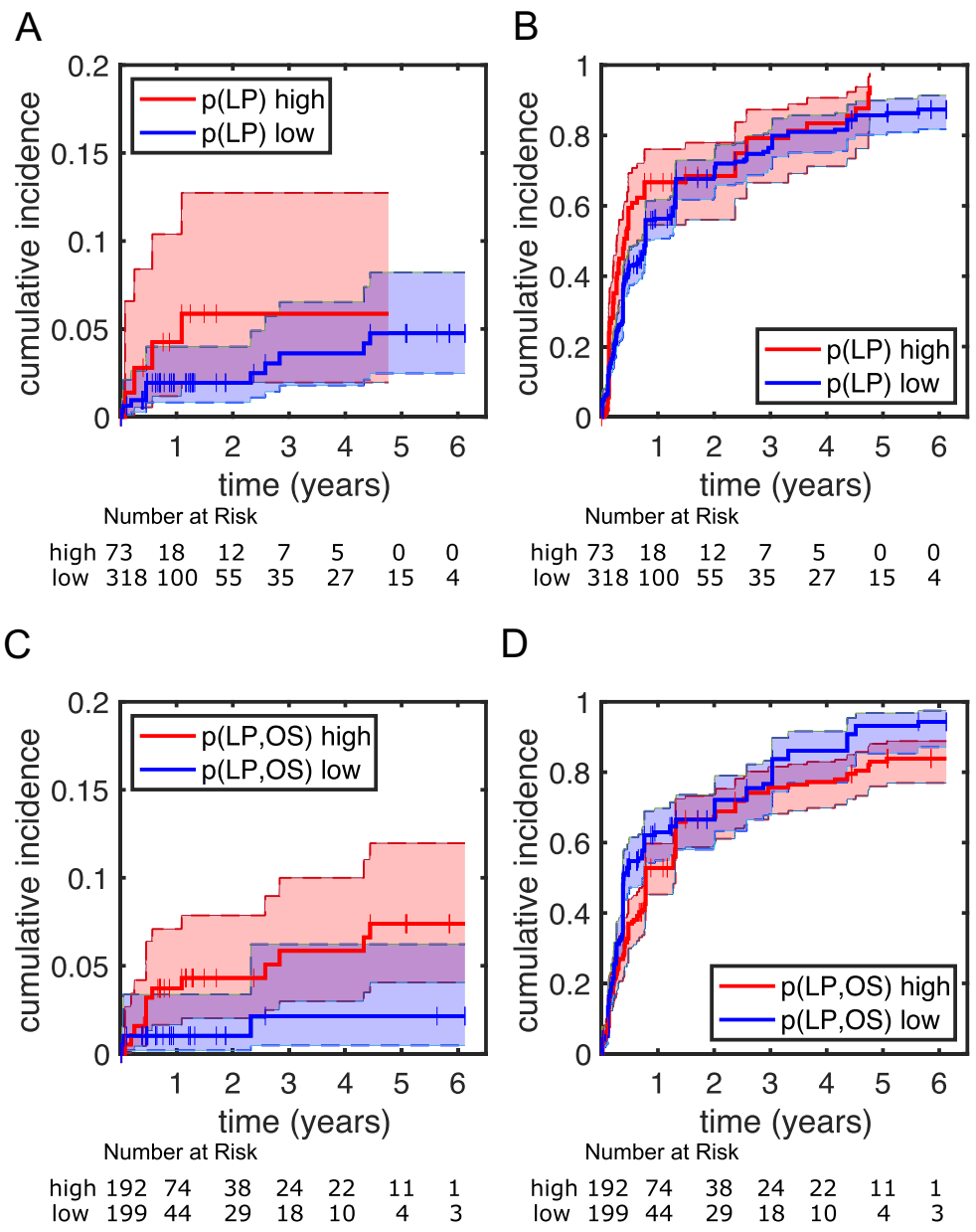

Figure 3 Local progression and survival in high-risk versus low-risk cohort (metastasis level). (A) Local progression: tumor control probability (TCP) model. (B) Competing death: TCP model. (C) Local progression: TCP overall survival model. (D) Competing death: TCP overall survival model.

decreases patient-level $p_{comb}(LP)$ from 29% to 9.8%, it only decreases $p_{comb}(LP, OS)$ from 7.6% to 2.5%. Although use of a TCP model alone would suggest that patient B would benefit more than patient A from dose escalation, a joint TCP-OS model would suggest the opposite.

Strengths of this study include the use of published TCP and prognostic models and the mathematically intuitive nature of the joint model, which reduce the likelihood of overfitting given the small size of the institutional dataset. Use of these established models as components of the joint model also likely increases its external validity, as the individual predictions generated by each component model are based on data collected from multiple institutions and thus reflect many different radiosurgical practices, medical oncological practices, and patient populations. Finally, because the model relies only on published look-up tables and simple calculations to generate predictions, it is readily accessible to clinical practitioners worldwide.

A clear weakness of the study is the small size of the supporting dataset, which is an order of magnitude smaller than many published brain metastases radiosurgical series. This limited our ability to assess the accuracy of

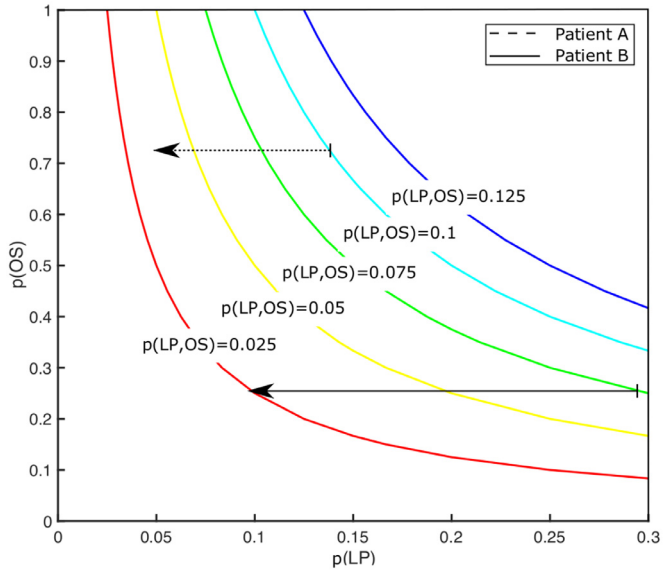

Figure 4 Effects of dose escalation on p(local progression) and p(LP, overall survival) for different levels of p(overall survival).

the model for individual tumor types or to perform other sub-analyses. The small size of the dataset also precluded investigation of optimal cut-points to define high-risk and low-risk patient populations as well as investigation of alternative prognostic or TCP models. An additional weakness of this study is that it does not specifically assess toxicity outcomes, meaning that no conclusions can be drawn from this study about the relationship between treatment dose and the probability of adverse radiation effects. Replication of this work with larger and multi-institutional datasets, exploration of different TCP and prognostic models, and assessment of treatment-related toxicity will be important avenues of future work; however, this work does establish a proof of the principle that risk of local recurrence is strongly influenced by overall prognosis after brain metastasis radiosurgery and provides a quantitative approach to estimating that risk for an individual patient.

Conclusion

In this study we found that overall prognosis plays an important role in determining the likelihood of a local recurrence after stereotactic radiosurgery for brain metastases. We found that consideration of TCP alone overestimates the likelihood of recurrence and that consideration of the joint probability of TCP and overall survival considerably improves the estimate. Furthermore, we have described a simple, accurate, and easily accessible tool that radiosurgery practitioners can use to quantitatively estimate the risk of local progression for individual patients. In addition, these findings could be used to inform a prospective trial of patient-specific radiosurgery dosing, with dual primary endpoints of non-inferior local control and reduction in treatment-related toxicity.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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