Assessment of extracranial metastatic disease in patients with brain metastases: how much effort is needed in the context of evolving survival prediction models?

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Abstract

Survival prediction models may serve as decision-support tools for clinicians who have to assign the right treatment to each patient, in a manner whereby harmful over- or undertreatment is avoided as much as possible. Current models differ regarding their components, the overall number of components and the weighting of individual components. Some of the components are easy to assess, such as age or primary tumor type. Others carry the risk of inter-assessor inconsistency and time-dependent variation. The present publication focuses on issues related to assessment of extracranial metastases and potential surrogates, e.g. blood biomarkers. It identifies areas of controversy and provides recommendations for future research projects, which may contribute to prognostic models with improved accuracy.

Commensurate with changes in treatment paradigms aimed at optimizing local control and preserving cognitive function [1-3], considerable multi-institutional efforts have led to refined survival prediction models in patients with brain metastases. Such models may serve as decision-support tools for clinicians who have to assign the right treatment to each patient, in a manner whereby harmful over- or undertreatment is avoided as much as possible. Undertreatment increases the risk of neurological death and shortened life expectancy, while overtreatment causes financial and toxicity burden, and represents poor resource utilization [4, 5]. After appropriate validation, prognostic models such as the recursive partitioning analysis (RPA) classes and the graded prognostic assessment (GPA) [6, 7] have been utilized in a large number of published studies (>300 for RPA and >200 for GPA, respectively; in PubMed, accessed August 19, 2020). Other models based on scores or nomograms have also been proposed, as critically reviewed by Zindler et al. [8] and Nieder et al. [9, 10]. Recently, diagnosis-specific GPA scores have replaced the older GPA [11-14]. All these models differ regarding their components, the overall number of components and the weighting of individual components. Some of the components are easy to assess, such as age or primary tumor type. Others carry the risk of inter-assessor inconsistency, as exemplified by numerous studies on the rating of a patient's performance status [15, 16]. If tumor mutational status is included, available tissue might or might not include metastatic lesions. Importantly, heterogeneity between individual metastases may also exist. Furthermore, some model components can be considered moving targets, i.e. are prone to change over time. The latter include blood test results and stability of extracranial sites of disease. Stable disease may turn into progression within a few weeks, and blood test results may change even faster. In most retrospective studies, assessment of radiological and laboratory work-up has not been standardized [17, 18]. Despite such inconsistency, e.g.,

serum biomarkers such as lactate dehydrogenase and albumin have emerged as prognostically relevant and inexpensive baseline staging parameters, but are not universally obtained or reported [17-20].

In addition, the presence of extracranial metastases (dichotomized yes/no) is a component of the majority of nomograms and scores. Extracranial involvement is indeed very common. For example, in a German series of more than 5000 patients, extracranial metastatic sites were observed in 59% of patients (1 to 7 sites) [21]. The lungs were the most common concurrent metastatic site. The even larger multi-institutional study by Sperduto et al. confirmed that more than 50% of patients have extracranial metastases (minimum 52% in lung non-adenocarcinoma, maximum 85% in renal cell carcinoma) [14]. Some groups have suggested replacing the "yes/no" classification by a more specific tiered parameter, which includes not only the absence or presence of extracranial disease, but also an additional category of extracranial metastases affecting more than one organ [17, 22]. Rades et al. evaluated 1146 patients who received whole-brain radiotherapy (WBRT) alone for brain metastases [22]. In this retrospective study, the 6-month survival rates, based on the involvement of 0, 1, 2, 3, and ≥4 extracranial organs were 51, 30, 16, 13, and 10%, respectively ($p<0.001$). On multivariate analysis, the number of involved extracranial organs retained significance. In the subgroup analyses of patients with involvement of one and two extracranial organs, survival was not significantly different based on the extracranial organ involved. However, the complexity of extracranial spread is not reflected in any of the common scores and nomograms. McTyre et al. reported an increased hazard of non-neurologic death in a study of upfront radiosurgery (>700 patients) with increasing age ($p=0.03$), non-melanoma histology ($p<0.001$), presence of extracranial disease ($p<0.001$), and progressive systemic disease ($p=0.004$) [23]. Given that many patients with brain

metastases ultimately die from uncontrolled extracranial disease [23-25], this highly relevant prognostic factor should be assessed in a more standardized and specific fashion. Maybe the simple scoring as present or absent is one of the main reasons why current prognostic models still feature a tail of long-term survivors in the group with poor prognosis, and early death events continue to be observed in the good prognosis group. Highlighting this is the observation that assigning the same nomogram points or score to patients with two small asymptomatic lung metastases, disseminated lung metastases with malignant pleural effusion, or impending liver or bone marrow failure due to extensive spread, introduces a modifiable source of inaccuracy. Consensus on how to stage extracranial metastases is needed, because most of today's prediction models are unable to reflect the nuanced decisions experienced clinicians and tumor board meetings will make on the basis of a patient's recent radiological studies, while also taking into account the longitudinal information from a series of follow-up scans.

It is very important to utilize the most recent TNM staging version, as exemplified by patients with primary lung cancer. For this disease stage T3 includes associated separate tumor nodule(s) in the same lobe. Stage T4 includes separate tumor nodule(s) in a different ipsilateral lobe. These nodules would be classified as lung metastases (stage M1) in patients with other primary tumors. Comparable attention and adherence is needed when it comes to lung cancer with supraclavicular lymph node metastases (N3) versus upper cervical nodal metastases (M1), Figure 1. In case of extrathoracic primary tumors with a mixture of classical nodular lung metastases, pleural metastases and thoracic lymph node metastases, should we register three different sites of extracranial metastases or should we stage this pattern of spread as "thoracic metastases" (single site), assuming that we are going to abandon the current dichotomized "metastases yes/no" approach? And for malignant melanoma, should

we lump together metastases to the skin, subcutaneous tissues and muscles? To answer these questions we need to collect detailed information in a large database and look at the survival curves for the different staging options. If no difference emerges, the simplest approach would be preferred.

Other classification systems that may be useful include “extracranial metastases no/single/oligometastatic/polymetastatic” (whatever consensus definition eventually will define the term “oligometastatic”) [26-28] or a volumetric measure of overall extracranial burden of metastases, e.g. 200 cc in total, with 150 cc in the liver and 50 cc in the adrenal glands). The latter may be cumbersome to calculate and particularly difficult in the bones as a common site of spread. In brain metastases, velocity after initial treatment has been identified as an additional prognostic factor [29]. Therefore, the number of new extracranial metastases during a given time period before treatment of brain metastases (extracranial velocity) may also be worth studying. When developing such refined assessment of extracranial metastases, it would be prudent to register the aforementioned serum biomarkers and to analyze their predictive impact together with that of the new extracranial classification in multivariate models. This research strategy would answer the question “do we need imaging and laboratory parameters because they all are independent prognostic factors or are they measuring the same thing (and are redundant)”?

Agreement is needed on how to classify patients with extracranial metastastic disease who have received radical treatment, e.g. surgical removal of liver metastases from colorectal cancer or lung metastases from soft tissue sarcoma. Given that long-term survival is possible, both after surgery or other ablative measures including stereotactic radiotherapy [30, 31], these scenarios may qualify for the “no extracranial metastases” category.

However, the validity of this intuitive assumption should also be confirmed by performing the large study outlined above. In routine clinical practice, many patients with brain metastases have limited survival [32], and extensive radiological work-up may not impact treatment decisions, e.g. due to lack of further systemic therapy. In addition, cost-effectiveness must not be forgotten. However, for the sake of scientific advancement of the staging issues and prognostic models discussed in this article, radiological work-up older than 4 weeks appears outdated and potentially misleading. Given that positron emission tomography (PET) outperforms conventional contrast-enhanced computed tomography (CT) [33], stratification for imaging modality is needed when launching additional studies. In a recent analysis, fluoro-deoxyglucose (FDG)-PET-CT identified additional lesions suspicious of extracranial metastases in 27 of 64 patients (42%) [34]. The inclusion of FDG-PET-CT findings shifted the GPA score from 3 with CT alone to 2.5 for PET-CT, resulting in a predicted survival of 5.3 versus 3.8 months (significant difference). Furthermore, it appears mandatory to utilize the information available when starting treatment of brain metastases, rather than longitudinal imaging follow-up data that extends to the patients' death. Researchers should do so even in retrospective analyses in order to maintain consistency and avoid confusion, because it is the only way of acting in the setting of a prospective study, when the future development of equivocal lesions remains to be uncovered, and also in the clinic, where decisions have to be made in real time.

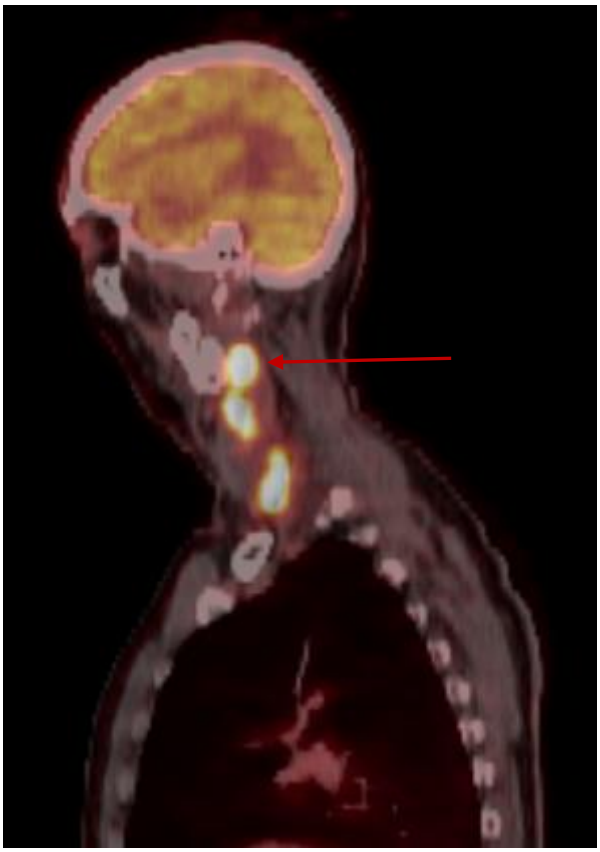
We would like to mention briefly that actionable mutations can be identified in brain metastases even when not present in the primary tumor [35] and this can modify the approach to systemic therapy, with potential survival impact. In this context, there is increasing interest in the investigation of liquid biopsies as a surrogate for tumor tissue in the management of both primary and secondary brain tumors. Literature on spinal fluid and

plasma circulating tumor cells (CTCs) and cell-free tumor (ct)DNA for diagnosis and monitoring of leptomeningeal and parenchymal brain metastases provides detailed insights into these developments [36]. Undoubtedly, the approach to brain metastases therapy has changed dramatically in many patients, e.g. with non-small cell lung cancer [1-3]. With the advent of new anti-cancer drugs, it is the response to systemic therapy (tyrosine kinase inhibitor or immune checkpoint inhibitor), which determines the local treatment of brain metastases, except in oligometastatic disease [37, 38]. In the latter, many experts still treat brain metastases with surgery or radiation before administering systemic treatment. The assessment of extracranial metastases is therefore also a function of the systemic therapeutic options that are available.

Conclusion

Refinement of current prognostic models appears feasible if our field moves away from dichotomized assessment of extracranial metastases. Both, surrogate markers such as blood test results and quantitative assessment of metastatic burden or seriousness may represent strategies towards better accuracy.

Figure 1. Sagittal positron emission tomography computed tomography (PET-CT) scan of a patient with non-small cell lung cancer who presents with fluoro-deoxyglucose (FDG) avid lymph node metastases in several neck levels, including outside of areas classified as N3 disease (red arrow).



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