Prognostication and local management in bone metastatic disease

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Chapter 11

General discussion and future perspectives

Part I

Life expectancy is one of the most important factors when it comes to surgical decision making in patients with a spinal metastasis. If a breast cancer patient with known liver, brain, and bone metastases comes in with a pathologic spine fracture with a Spinal Instability Neoplastic Score\(^1\) in the grey area (7-12; potentially unstable), should she be operated on or not? Deciding not to operate could lead to an increase of pain and neurologic deterioration, while an operation could lead to complications and would require recovery time. If this patient has a prognosis of more than a year, she will likely benefit from the surgery. If this patient only has a few more months to live, she may be better off spending as much time as she can at home with her family and friends. Accurate survival prediction is therefor of great importance. In clinical practice, decision-making in patients with a spinal metastasis is done in a multidisciplinary setting, in which each of the team members has his/her own expertise; a radiation oncologist determines if radiation is an option, a surgeon determines if surgery is an option, taking into account the rehabilitation period and complication risks, and a medical oncologist determines if other treatment modalities are an option, judges if a patient is fit enough for surgery and estimates what his/her prognosis is. Together, taking into account the patient’s wishes, they decide which treatment is best. A previous review has shown that clinicians are unable to accurately estimate survival in patients with advanced cancer.\(^2\) The study in chapter 2 of this thesis confirms this, suggesting that surgeons that treat spine metastases are not capable of making accurate survival predictions. This justifies the development and encourages the use of multiple prognostic models that help physicians estimating survival in this group of patients.\(^3\)\(^-\)\(^8\) Of course there can be discussion about our study; the survey, that was sent to the spine surgeons, only contained 12 cases. One could question how representative these are for the whole group of patients with a spine metastasis. However, the results for each of the 12 cases was clear: there was very little agreement between surgeons and estimations were far removed from the truth. In future research, it would be interesting to prospectively compare surgeons’ survival estimates with the estimates of an (externally validated) prediction model.
In conclusion, this part of the thesis demonstrated the need for tools to help spine surgeons to estimate survival in patients with a spine metastasis, before doing any surgical decision making. Of course, the decision to operate or not is not solely up to the spine surgeon but it is a ‘shared’ process that includes the patient in addition to a multidisciplinary team.

Part II

In part II we studied the association between \( PIK3CA \) mutation status and \( TP53 \) mutation status and metastatic pattern in breast cancer. As breast cancer deaths are mostly related to metastasis, understanding the mechanisms behind the process of metastasis is of great importance. The ability to accurately predict if, when, and where a patient will develop metastases, would ensure that each patient gets the treatment and follow-up care they need. Metastases may then be detected at an earlier stage and patients that are not in need for frequent follow up will be spared of those appointments and the unnecessary stress that comes with it. However, breast cancer is a complex and heterogeneous disease and we have not been able yet to understand the exact mechanisms of metastasis. In this study we did not find any associations between \( PIK3CA \) and metastatic pattern, but we did find associations between \( TP53 \) mutation status and location of metastasis. The study has its limitations (retrospective, only patients that had developed metastases were included, the use of Sanger sequencing instead of Next-generation sequencing) and the results need to be validated. \( TP53 \) mutation status alone will not be enough to determine a patient’s treatment and follow-up plan, but it may in the future be one of the input variables for an algorithm predicting metastasis in breast cancer.

Part III

After confirming the importance and necessity of prediction models for patients with bone metastases in part I, this part focused on identifying new prognostic factors and the development of prediction models. Numerous studies have looked at factors to predict survival in these patients and many survival prediction models have been developed, for both extremity metastasis\(^9\)–\(^{14}\) and spine metastasis.\(^3\)–\(^8\) Interestingly, while these models use a lot of the same variables (for instance primary tumor) only few laboratory factors are used, even though these are cheap and easy to obtain in a non-invasive manner. The value of laboratory factors is shown in chapters 4, 5 and 5. In chapter 4 neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio were shown to be of value as prognostic factors in patients with bone metastases. These were chosen as indicators of inflammation. Although the prognostic value of these factors have been established in various cancer types\(^{15,16}\) they are nonspecific parameters and have, for instance, also been identified as a marker for cardiovascular disease and rheumatic disease.\(^{17,18}\) As this was a retrospective study, we were unable to assess whether the patient had any signs of infection etc when the blood draws were done. But we assume that patients with an active infection were not operated on. In any case, those ratios reflect the state of inflammation in a patient, in which non-malignant causes may also play a part. Chapter 5 demonstrated the importance of alkaline phosphatase, identifying it as a marker for metastatic burden and survival. This is not a specific marker either, as it is also high in case of liver disease. But again, it provides information on the current status of a patient with advanced cancer. Finally, in
chapter 6 the prognostic value of serum albumin was examined. Hypoalbuminemia is a well-established indicator for malnutrition and predictor of poor postoperative outcome, but it has not been included in previous survival prediction models for patients with bone metastases. This study clearly demonstrated its importance in two separate cohorts. In conclusion, all the laboratory factors studied in these three chapters are valuable as prognostic markers, they are easy to obtain and are inexpensive. They should therefore be included in the standard work up of patients with a bone metastasis. In chapter 7 a machine-learning algorithm was developed predicting survival in patients with a spine metastasis. It was the first study to use machine learning for this purpose. The model showed good performance and “black box” skepticism towards machine learning was addressed by providing both global and individual explanations for the outcomes. A similar study was done in chapter 8 this time looking at patients with a metastasis of the extremity. While both models showed good performance on the testing set, external validation with different cohort is a crucial step towards clinical use. The machine learning algorithm for spine metastasis has already been externally validated several times. First, it has been externally validated in a cohort of 176 patients. Again the performance was good but it seemed to perform less in patients treated in the last decade. It was then externally validated in a more contemporary cohort of 200 patients in which it performed well. In a cohort of 427 Taiwanese patients, the algorithm showed good performance, although 90-day mortality was underestimated. External validation of the machine learning algorithm for extremity metastasis has been done twice. In a Taiwanese cohort of 356 patients, the algorithms for 90-day and 1-year mortality showed good discrimination but survival -again- was underestimated. Another external validation in a cohort of 264 patients, in the United States, showed overall good performance. Both algorithms have thus been developed on a retrospective cohort in the United States and have been externally validated in the United States and in an Asian cohort. More studies are needed to prove/refute their validity in different cohorts, for instance in Europe. Furthermore, as treatment regimens constantly improve, it would be interesting to validate the algorithms prospectively and possibly improve them in the process.

Part IV

This last part focused on outcomes of treatment. In chapter 9 has given some insight into the effect of radiation on bone. Bone metastases are frequently treated with radiation therapy, although it can lead to complications such as osteoporosis, insufficiency fractures, non-union, and secondary tumors, even at low doses. In the study, a decrease in bone mineral density was observed in the irradiated bone while it remained stable in the non-irradiated bone. Furthermore, a decrease in bone formation rate was seen in the irradiated bone. Although the study was performed on patients with a chordoma or chondrosarcoma of the sacrum, receiving higher doses of radiation than patients with a metastasis, the study is also relevant for this last group of patients. It is important to be aware of their increased risk for an insufficiency fracture, especially when the irradiated bone is under a lot of stress or physiologic load. In patients with a long estimated survival time, theoretically, secondary malignancies may also occur. Chapter 10 was focused on postoperative complications in patients that were surgically treated for a bone metastasis of the extremity. If a patient’s estimated survival is long enough to consider surgery, another thing to consider is his/her risk of complications. In this study a number of factors were identified that increased
the risk of complications in these patients. Many of these factors overlap with the factors included in the machine learning algorithm for survival prediction. These are clearly sicker, more fragile patients and a surgeon must therefore sometimes dare to decide not to operate on them. Furthermore, complications, both major and minor, were shown to be associated with increased mortality. Surgeons should use the results of this study to counsel their patients and help in the decision-making process. Of course, this study also has its limitations, being a retrospective study, and should be (prospectively validated), especially to ensure that complications are documented well.

**Future perspectives**

After validating the prognostic factors described in this thesis and externally validating the prediction models, the next question is how to use the models in daily practice. For a physician to access and use the models described in this thesis –provided they have been extensively externally validated– he or she can access them on their PC or smartphone. This means that they would have to open another program next to their Electronic Health Records (EHR) and then enter the input variables in the algorithm which can be found in the EHR. It would make a lot more sense to integrate these applications into the HER. Platforms that enable medical applications to run across different EHRs already exist, and they will likely integrate validated models in the EHRs in the near future. It would then also be possible to automatically improve the algorithms with new data and possibly to do this globally.

Although these advances are exciting and promising, we have to be cautious and aware of the challenges they bring. Machine learning algorithms completely depend on the input variables they are fed and if these variables are incorrect, they can result in machine learning bias. If an algorithm is trained on data that reflects prejudices, stereotypes, and/or faulty societal assumptions, these biases will also be incorporated in the algorithm. A recent example of this is the Dutch childcare benefits scandal, or the “toeslagenaffaire”, in which thousands of parents were wrongly labeled as frauds and had to return years of childcare benefits. The Dutch tax authority had used algorithms trained with old data in which dual nationality for example was labeled a risk factor, which is in violation of the constitution. If a machine learning algorithm is biased, it will continue to reinforce that bias.

Other challenges such as an increase in work-load for physicians and legal issues are also important to be aware of: Who faces liability when the algorithm is biased and thereby gives incorrect outcomes?

In any case, keeping the challenges in mind, the use of Artificial Intelligence will undoubtedly continue to grow in the medical field in the years to come and it will greatly contribute to the promise of precision medicine.
References


