Prognostication and local management in bone metastatic disease

Thio, Q.C.B.S.

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Chapter 1

General introduction and outline of this thesis

“λέγειν τὰ προγενόμενα, γινώσκειν τὰ παρεόντα, προλέγειν τὰ ἐσόμενα...”

“(The physician must be able...) to tell the antecedents, know the present, and foretell the future...”. – Hippocrates, Epidemics 1.2.11

The incidence and mortality of cancer is growing rapidly worldwide, although survival rates have increased due to early detection and advanced treatment options. Lung cancer, breast cancer and prostate cancer are the most commonly diagnosed type cancers and all three have a high propensity to metastasize to bone. It is therefore expected that both the incidence and prevalence of bone metastatic disease will increase. Prognostication is important at different time-points in the course of bone metastatic disease. Before the onset of cancer, identifying risk factors is crucial for the development of adequate screening programs for early detection of cancer. Once a patient has cancer, prediction of the effectiveness of the available therapeutic options becomes essential in treatment decision-making. It is also important then to determine the risk of the cancer to metastasize for adequate follow-up. When a patient develops bone metastases, the cancer generally cannot be cured and prognostication is needed to guide in the clinical decision making for these patients in order to achieve a personalized optimal balance between quality of life and survival time. After this, when the form of treatment is chosen, it is important to know the (risk of) adverse events of that treatment.

This thesis focuses on prognostication (or: foretelling the future) in patients suffering from bone metastatic disease, addressing the last three issues: 1) the metastatic pattern of a primary tumor, 2) survival in patients with a bone metastasis, and 3) the complications of common treatment modalities.

From primary tumor to metastasis

After a patient is diagnosed with cancer, one of the biggest questions is how likely the tumor is to metastasize. Joseph Recamier (1774-1852) was the first to use the term
“metastasis” in his treatise to describe the spread of cancer, the word coming from the Greek μετάστασις: “a removing, removal, migration, change”. Since then, different theories have been proposed to understand the mechanics of metastasis. Virchow, for instance, believed that metastasis was random and determined by mechanical factors: the arrest of tumor-cell emboli in the vasculature. In 1889 Stephen Paget introduced his “Seed and Soil” hypothesis, which argued that the process of metastasis was not random. He studied autopsy results of patients with different primary tumors and found that these had specific organ metastatic patterns. For instance, women with breast cancer had a greater chance to metastasize to bone than to other organs. He explained these results by comparing tumors to plants: “When a plant goes to seed, its seeds are carried in all directions; but they can only live and grow if they fall on congenial soil.” In his comparison, the circulated tumor cells act as ‘seeds’, which have an affinity for particular organs or ‘soil’. Thus, only when a compatible seed is being planted in the right soil will distant metastases develop. In short, metastatic dissemination occurs in the following sequence of steps: tumor cells invade locally surrounding tissue, enter the microvasculature of the lymph and blood systems (intravasation), transfer through the bloodstream (in which they survive the body’s immune response) to the capillary bed of distant tissues, exit the blood stream (extravasation), survive the microenvironment and adapt to it to facilitate cell proliferation and the formation of a macroscopic metastasis.

Early prognostication in breast cancer

One of the cancers that most frequently metastasize to bone is breast cancer, and that is the primary tumor type that will be discussed in the next part.

Breast cancer - the ‘plant’

Despite improvement in early detection and advances in treatment options, breast cancer remains one of the major causes of cancer related death in women. Death is not caused by the primary tumor itself, but by the development of distant metastasis; the 5-year survival rate of patients with metastatic breast cancer is 27%. Approximately 10-15% will develop distant metastases within three years after the initial diagnosis and 20-30% of all patients will eventually develop distant metastasis. Breast cancer is a clinically heterogeneous disease and it is therefore difficult to assess factors that contribute to the development of metastasis.

Histologically, breast cancer can be categorized into in situ carcinoma and invasive carcinoma of which the majority are invasive ductal carcinomas and the rest are invasive lobular carcinomas. Invasive ductal carcinomas have a tendency to metastasize to lungs, distant lymph nodes and brain, whereas invasive lobular carcinomas are more likely to metastasize to peritoneum, gastrointestinal tract, and ovaries. Breast cancer is also categorized in molecular subtypes, as determined by immunohistochemical staining or microarray-based gene expression profiling. Several studies have shown that molecular subtype is associated with metastatic pattern. A number of studies have used microarray-based gene expression profiling to identify signatures associated with certain distant metastases. So far, different gene expression profiling signatures exist to predict metastasis to bone, lung, and brain. Still, much remains unknown about the mechanisms behind metastasis in breast cancer.
Bone - the ‘soil’

Once the metastatic cells arrive in the microenvironment of the bone, they encounter different cells that play a trivial role in maintaining homeostasis of the bone. These cells include: osteoclasts, osteoblasts, osteocytes, endothelial cells, and cells of the bone marrow. Bone is constantly remodeling, which is regulated by osteoclasts and osteoblasts. Bone resorption is done by osteoclasts, while osteoblasts are responsible for bone formation. Different systemic factors and locally secreted cytokines control osteoclast activation. RANKL (receptor activator of nuclear factor-dB ligand), a family member of tumor necrosis factors (TNF) is expressed on the surface of osteoblasts and it activated osteoclasts by signaling through its receptor RANK, resulting in the resorption of bone.

When cancer infiltrates the bone, the metastatic lesions are usually characterized by their radiologic appearance: they can be described as osteolytic (in which bone is broken down), sclerotic (in which bone is formed), or mixed (a combination of osteolytic and sclerotic). Osteolytic lesions are more prone to causing complications such as pathological fractures and hypocalcaemia due to increased bone resorption.

Late prognostication in bone metastatic disease

Bone is the third most common site of metastasis, following the lungs and liver. Bone metastases most frequently originate from prostate or breast cancer and most commonly appear in the thoracic spine, ribs, pelvis and proximal long bones.

Clinical presentation

Patients with bone metastases often present with severe bone pain. They can experience tumor pain which is worst at night and/or mechanical pain, which results in immobility. The metastases can weaken the bone and can cause pathological fractures. In the appendicular skeleton, the most common site for such a(n) impending pathological fracture is the femur.

Patients with a spinal metastasis can also present with neurologic impairment, often preceded by back pain. Metastatic epidural spinal cord compression (MESCC) is usually the result of tumor mass that compresses the spinal dural sac and its contents, although it can also be caused by a pathological fracture. Patients can also present with symptoms of hypercalcaemia. Especially when there is extensive bone destruction, there is a risk of hypercalcaemia. This causes symptoms such as tiredness, muscle pain, abdominal pain, nausea and vomiting, depression and confusion.

Diagnosis

Bone metastases can often be seen on X-rays. Metastases from lung, thyroid, and renal cancer are usually osteolytic, while metastases from prostate are usually sclerotic/osteoblastic and metastases from breast cancer are usually a mixture of lysis and sclerosis.

It is important to verify if the lesion is indeed a metastasis and what the primary tumor is. A bone metastasis may be the first presentation of cancer, it may be the first metastasis of a known primary tumor or it may be yet another metastasis in a
patient with known metastatic disease. In the first two cases, a total body scan should be performed and (if possible) a biopsy should be obtained to confirm the diagnosis. In all three cases it is important that a complete assessment of the oncologic status is done before any decision is made in regards to treatment.

In case of a spinal metastasis, a CT and MRI can help determine the stability of the spine with a lytic lesion or even a fracture and/or the grade of MESCC.28,29

**Treatment options**

When cancer metastasizes to bone, it is usually deemed incurable. The general goal of treatment in patients with a bone metastasis is to achieve a personalized optimal balance between quality of life and survival time. This can range from improving survival, for instance in a solitary metastasis originated from renal cell cancer, to symptom relief.4,30 If a patient is expected to have a long survival, the benefits of treatment will probably outweigh the drawbacks of treatment such as chemotherapy side effects and rehabilitation after surgery. If a patient has a limited survival time, the goal is to make him/her as comfortable as possible in their last weeks or months. There are different treatment modalities possible for patients with a bone metastasis of the appendicular skeleton or the spine:

Several therapeutic agents are available for the treatment of bone metastasis.24 Bisphosphonates function as osteoclast inhibitors and thereby reduce the risk of skeletal related events and improve metastatic bone pain.31,32 Denosumab is a human monoclonal antibody to RANKL that inhibits osteoclast-mediated bone destruction and thereby also reduces the risk of fracturing.33 Hormonal therapy is possible in tumors that are hormonally driven, such as some prostate and breast cancers.24 Chemotherapy can also be considered and may be combined with the previously mentioned therapeutics.34

Another option is radiation therapy, ideally for patients with one or few metastases. External beam radiation is effective in most patients with bone metastases and is best suitable when these metastases are uncomplicated.35 Uncomplicated is defined as by not posing an imminent risk for pathological fracture or for neurological compromise.36

Surgery may be indicated in case of (impending) pathological fractures, metastatic epidural spinal cord compression, spinal instability or if a histological diagnosis needs to be obtained.37 Surgical treatment options for the spine range from minimally invasive stabilization to corpectomy/vertebrectomy. For bone metastases of the extremity, the surgical treatment options range from cemented plate-screw or nail fixation to endoprosthetic reconstruction.25 These can be done prophylactic (to prevent the bone from fracturing) or reactive (in response to a bone fracture). There are big differences between the different surgical options in terms of surgery time, risk of complications and rehabilitation period. These differences are important to keep in mind for in each individual case.

**Challenges**

As said before, the goal of treatment for a bone metastasis is preserving or improving a patient’s quality of life. The benefits of treatment have to outweigh the drawbacks. Surgery is generally only considered if a patient’s life expectancy is longer than the expected rehabilitation period.38,39 Accurate survival prediction is therefor crucial.
Furthermore, both radiation therapy and surgery can lead to complications. Understanding the mechanisms that lead to complications and identifying patients that are at risk for complications is vital for the decision making process.

Outline of this thesis

The aim of this thesis is to provide insight and tools for prognostication in patients with bone metastases, both early and late in the course of the disease.

Part I: The importance of prognostication

The first part of this thesis will highlight the importance of prognostication tools in patients with a spinal metastasis. Chapter 2 proposes the question whether survival prediction models for these patients are actually needed. A survey consisting of cases of patients with a bone metastasis are send to spine surgeons to assess their ability to predict survival without using existing prognostic models.

Part II: Early prognostication

Breast cancer is one of the main cancer types that metastasize to bone. As survival mostly depends on the development of distant metastasis it is crucial to understand the mechanisms behind metastatic behavior for prediction of the course of the disease and for clinical decision-making. The two most frequently mutated genes in breast cancer are the tumor suppressor gene TP53 and the oncogene PIK3CA. Both have been extensively investigated in breast cancer, especially in regards to survival and response to treatment. There is, however, only limited knowledge about their association with metastatic behavior. Chapter 3 aims to investigate the association of mutations in TP53 and PIK3CA with metastatic behavior in a cohort of 195 breast cancer tumors that all ultimately developed distant metastasis. This will help to predict in which location (bone or lung/liver) patients with breast cancer are likely to develop metastases.

Part III: Late prognostication

As said before, survival estimation is crucial when it comes to surgical decision making for patients with bone metastasis. While multiple algorithms have been developed for this purpose, due to advances in treatment and new insights it is important to often revise and improve them. The first chapters of this part of the thesis aim to identify new prognostic factors for patients with a bone metastasis. Chapter 4 investigates the prognostic value of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in a group of 1012 patients that were surgically treated for a bone metastasis in two tertiary referral centers. The rationale behind this is the belief that inflammation plays an important role in cancer leading to an increase of production and release of neutrophils while the production of lymphocytes goes down. Chapter 5 aims to investigate serum alkaline phosphatase as prognostic marker in a cohort of 1090 patients that were treated for a bone metastasis of the extremity. Alkaline phosphatase is a well-known marker of hepatobiliary pathology and bone turnover and mineralization and therefor may prove to be an indicator of metastatic tumor
Chapter 6 explores the prognostic value of serum albumin in two different cohorts of patients that were surgically treated for a bone metastasis. Although it has been well-established as a marker for nutritional status and as a prognostic marker in patients undergoing surgery or with a critical illness it is not present as a prognostic factor in existing prediction models for these patients. Chapter 7 and 8 concentrate on the development of machine learning (ML) algorithms for the survival prediction of patients with a bone metastasis, using previously identified prognostic factors. Machine learning is a growing field of statistics and computer science that is able to recognize complex combinations of predictors with the capacity of handling huge amounts of data and is therefore perfectly suitable for the creation of different kinds of diagnostic or predictive models in the medical field. Chapter 7 aims to develop a ML algorithm to predict 90-day and 1-year mortality in patients with spinal metastasis. It uses a cohort of 732 patients for this purpose and follows the guidelines proposed by Steyerberg et al. regarding model development and assessing its performance. Chapter 8 has the same goal as the former chapter, predicting 90-day and 1-year survival, but focuses on patients with a metastasis of the extremity, using the cohort of 1090 patients that was used in chapter 4 and 5.

Part IV: Treatment outcomes

The last part of this thesis focuses on the outcomes and complications of different treatment modalities for bone metastasis. Radiation can lead to complications such as radiation-induced osteoporosis, insufficiency fractures, physeal arrest in children, and non-union of fractures. Exact mechanisms behind this are still poorly understood. Chapter 9 is a pilot study that aims to investigate the short-term effect of radiation on bone structure and remodeling in nine patients that are treated for a sacral chondrosarcoma or chordoma, using QCT scans and bone histomorphometry to give more insight on the exact mechanisms. Chapter 10 investigates factors associated with complications after surgery of a bone metastasis and the impact of complications on mortality. Although other studies exist that describe the frequency of complications in those patients, it remains unclear what kind of different complications occur and what the consequences are.

Part V: Discussion and summary

This thesis will be concluded by a general discussion including future perspectives (chapter 11) and a summary of its findings in English and Dutch (chapter 12).
References


