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Surgical decision-making for long bone metastases

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CHAPTER 1

General Introduction

Bone metastasis occurs when cancer cells spread from their original site via the bloodstream to bone tissue.[1] Skeletal metastases (secondary bone tumors) account for 70% of all malignant bone tumors; the remainder being primary bone tumors such as osteosarcoma and chondrosarcoma.[2] Management of skeletal metastases is almost always palliative and therefore different from management of primary bone tumors.

HISTORY

The earliest archaeological examples of metastatic carcinoma of the skeleton were found in Egypt and date from 3000 to 500BC.[3-6] Historically, bone metastases were less common as a result of shorter life expectancy –most people did not live long enough to develop cancer– and differences in life-style (smoking, dietary constituents, pollution).[4,7,8] Advances in medical care, sanitation, and nutrition in the 19th and 20th century considerably improved life expectancy and markedly changed disease patterns: cancer became more prevalent and is currently the second leading cause of death in developed countries (after cardiovascular disease).[9,10] In the United States, 1.7 million people were diagnosed with cancer in 2015 and about 600,000 died as a result of cancer (United States population in 2015: 321 million).[11] In the Netherlands, 100,000 people were diagnosed with cancer in 2015 and about 40,000 died as a result of cancer (Netherlands population in 2015: 17 million).[12] The number of people with a history of cancer continues to grow due to: (1) a growing number of cases in the aging population, and (2) longer survival secondary to early cancer detection and improved medical treatment.[13,14] In the United States on January 1, 2014, there were 14.5 million living people with a history of cancer and in ten years, this number is estimated to increase to 19 million.[14]

INCIDENCE

Breast, lung, and prostate cancer are the most common primary tumors in developed countries and are also tumors that are most likely to metastasize to bone.[11,12,15,16] After the lungs and liver, bone is the most common site of metastases and these metastases are more common in the axial skeleton than in the appendicular skeleton.[1,17-19] The femur and humerus are the most frequently affected long bones.[1,18] In autopsy studies, the incidence of bone metastases among cadavers varies substantially based on the primary tumor type: among people who died of breast or prostate carcinoma about 70% had bone metastases, while among people who died of lung, kidney, or thyroid carcinoma about 30% had bone metastases.[19,20] It is estimated that approximately 280,000 adults were living with bone metastatic disease in the United States in 2008.[21] The economic burden of patients with metastatic bone disease was estimated at $12.6 billion, which is 17% of the total direct medical costs related to cancer ($74 billion) in the United States (in 2004).[13] Bone metastases often occur in the final stages of life and can result in skeletal related events such as bone pain, nerve root compression, spinal cord compression, hypercalcemia, and pathological fracture.[22] Three population based cohort studies from Denmark present the rates of bone metastases and skeletal related events among patients with newly diagnosed breast, lung, or prostate cancer between 1999 and 2010. Jensen et al. demonstrated that among 35,912 breast cancer patients, 4.2% (n=1,494) had bone metastases either at the time of the primary cancer diagnosis (0.6%) or during followup (3.5%), and 48% (712 of 1,494) developed a skeletal related event (median followup: 3.5 years).[23] Cetin et al. demonstrated that among 29,720 lung cancer patients, 6.8% (n=2,032) had bone metastases either at the time of the primary cancer diagnosis (1.1%) or during followup (5.7%), and 56% (1,146 of 2,032) developed a skeletal related event (median followup: 7.3 months).[24] Nørgaard et al. demonstrated that among 23,087 men with prostate cancer, 14% (n=3,261) had bone metastases either at the time of the primary cancer diagnosis (3.0%) or during followup (11%), and 52% (1,691 of 3,261) developed a skeletal related event (median followup 2.2 years).[25] Hence, about half of the patients with bone metastases develop skeletal related events.[26] Pathological fracture is a common skeletal related event with rates varying from 16% to 42% among patients with bone metastases.[1,27-31] The increasing number of patients with a history of cancer has been linked to an absolute increase in the number of patients living with bone metastatic disease, which probably results in a larger number of patients developing a pathological fracture. Skeletal related events –pathological fractures in particular– cause decreased quality of life, decline in physical function, loss of independence, and decreases survival.[20,22,32]

WORK-UP

Metastatic carcinoma of bone should be considered in patients older than 40 years with a suspect bone lesion. The diagnostic workup for a patient with a lesion suspect for metastatic carcinoma and unknown primary tumor starts with a clinical history and physical examination of the chest, abdomen, and thyroid, and the breast in female patients and prostate in male patients.[1,33-35] This is followed by laboratory analysis for multiple myeloma and prostate cancer. Chest radiographs and radiographs of every painful bone should be obtained. Bone metastasis typically appears as osteolytic permeative (i.e. moth-eaten appearance) lesions of the diaphysis or metaphysis.[35,36] However, depending on the primary tumor, lesions can also be osteoblastic (e.g. prostate) or mixed with osteolytic and osteoblastic components (e.g. breast). Bone CT and MRI are preferred methods to further characterize the bone lesion in case a primary bone tumor is suspected. A CT-scan of the chest, abdomen, and pelvis can be made if the primary tumor has not been identified yet.[33,35] A technetium 99m or FDG-PET scan can be made to assess for other skeletal lesions and search for the primary tumor. Finally, a diagnostic biopsy of the bone lesion –preferably one that is most easily accessible in case of multiple bone lesions– can be obtained for histological confirmation. A biopsy is recommended if a patient has no previous histological diagnosis of metastatic bone disease, the patient has been disease-free for a prolonged period of time, or if the lesion is not characteristic of the known primary cancer.[1,37-39] Multiple myeloma and lymphoma are considered primary bone tumors as they originate from hematopoietic and lymphoid tissue; however, they are often grouped with bone metastases as surgical management is comparable.[40]

SURGICAL MANAGEMENT

In general, the aim of surgical treatment for a patient with a metastatic lesion is to optimize quality of life and physical function for the remaining life span while minimizing the risk of complications, mortality, and secondary surgical interventions. Patients with a pathological fracture typically present to orthopaedic oncology surgeons and trauma surgeons as it often mandates surgical intervention. As a rule of thumb, surgical treatment for a pathological fracture through a bone metastasis is indicated if the estimated life expectancy of the patient at least exceeds the anticipated recovery time from surgery.[1,41,42] This translates into a minimum of six to twelve weeks of expected survival for surgical procedures such as intramedullary nailing.[37,38] However, accurately estimating life expectancy in patients with bone metastases is difficult and therefore a potential barrier to providing optimal care.[43,44] Nonoperative management (i.e. closed reduction and immobilization) of long-bone pathological fractures is ineffective as these fractures demonstrate poor fracture healing potential due to the tumor characteristics and as a result of radiation therapy.[37,38,45]
The indication for surgery is less clear for non-fractured metastatic lesions. The two most commonly cited indications for surgical management of non-fractured metastatic lesion are an impending fracture (i.e. a metastatic lesion at risk of pathological fracture) and a solitary metastasis.[1,37,38] Impending fractures are easier to treat, with less morbidity, less costs, and faster recovery as compared to complete pathological fractures.[38,46-50] However, the downside is overtreatment of patients who would not develop a pathological fracture. Therefore, many studies aimed to establish predictors of pathological fracture occurrence to better define lesions at risk of fracture. Although no single clinical or radiographic predictor or combination is sufficiently accurate at predicting occurrence of a pathological fracture, several risk factors have been identified: pain on weight bearing, defect size >30 millimeters, lytic appearance on radiographs, location of the lesion, and more than 50% circumferential cortical destruction.[51-53] Solitary metastasis –especially in

renal cell carcinoma and thyroid carcinoma– is often mentioned as an indication for enbloc surgical resection as some studies demonstrate improved survival after complete resection; however, this is refuted by others.[1,54-57]

Common methods of fixation for long bone metastatic lesions can be categorized into: open reduction internal fixation, intramedullary nailing, and endoprosthetic reconstruction. Many different implants exist within these categories and can be combined with intraoperative adjuvants such as polymethyl methacrylate or bone grafts, creating numerous treatment strategies. However, there is no consensus about which surgical strategy is most adequate for femoral and humeral metastatic bone lesions.[58] In addition, postoperative external beam radiation therapy is often used as it might reduce the risk of tumor progression and improve function, although evidence is scarce.[59,60] As bone metastases can originate from many primary tumors, occur everywhere in the skeleton, and have multiple morphological appearances, numerous factors need to be considered in surgical decision making, including primary tumor type, life expectancy, location of the bone metastasis, presence of a pathological fracture, and presence of visceral or other bone metastases.[58]

In conclusion, patients with bone metastatic lesions have –on average– a poor prognosis and surgical management predominantly aims to optimize quality of life by providing a stable construct that outlives the patient. The purpose of this PhD thesis is to: develop tools for better patient selection for surgery, improve implant selection based on patient- and tumor characteristics, identify risk factors for adverse outcomes, and evaluate outcome after treatment for patients with long bone metastases.

OUTLINE OF CHAPTERS

Part I: Metastatic Femoral Lesions

There is debate about which implant is most appropriate for treatment of metastatic proximal femoral lesions and only a few studies compare surgical strategies. **Chapter 2** compares surgical outcomes after commonly used implants for proximal femoral metastases in a large multi-institutional retrospective cohort study. **Chapter 3** puts these findings into perspective by pooling surgical outcomes over a large number of studies using a systematic review of the literature. This review also demonstrates that –although considered important– functional outcome is only scarcely and inconsistently reported. **Chapter 4** therefore compares different questionnaires that measure physical function in patients with lower extremity bone metastases in a cross-sectional survey study. Measuring functional outcome is an important step towards establishing which implant is optimal. **Chapter 5** describes and tests an algorithm that can be used to predict occurrence of a pathological fracture through a non-fractured femoral metastatic lesion using a CT scan.

This helps to better assess which lesion is at risk of fracture and potentially benefits from prophylactic fixation.

Part II: Metastatic Humeral Lesions

Chapter 6 is a systematic review of the literature and provides an overview of outcomes after commonly used surgical techniques for metastatic humeral lesions. There is substantial variation in reported outcomes and surgical strategies used; it is unclear which implant is most appropriate for a specific situation. In **Chapter 7**, we established complication and reoperation rates in a multi-institutional retrospective cohort study with a large number of patients that underwent surgery for metastatic humeral lesions. In addition, this study determined risk factors for these outcomes to anticipate postoperative problems. These findings could help inform our patients and risk stratify them. **Chapter 8** is a case-vignette study assessing how orthopaedic oncologists and trauma surgeons approach metastatic humeral lesions. We determined which factors influence the decision for surgical treatment and the choice for a specific implant. This study also sheds light on areas with relative consensus among surgeons regarding treatment options, and areas where surgeons disagree and more evidence is needed.

Part III: Survival

Chapter 9 specifically addresses bone metastases from renal cell carcinoma and how different methods of resection influence tumor recurrence, reoperation, and survival. **Chapter 10** describes the development of different algorithms for survival prognostication in patients with long bone metastases and compares their accuracy. These algorithms help estimate life expectancy which is an important factor in surgical decision making. **Chapter 11** assesses if perioperative allogeneic blood transfusions influence survival in patients who undergo surgery for long bone metastastases.

Finally, a summary followed by a general discussion including conclusions and future perspectives are provided in **Chapter 12 & 13**.

PRIMARY STUDY QUESTIONS

Part I: Metastatic Femoral Lesions

Is there a difference in outcome –physical function, reoperations, and complications– between endoprosthetic reconstruction, intramedullary nailing, and open reduction internal fixation for proximal femoral metastasis?

What questionnaire is most useful for measurement of physical function in patients with lower extremity bone metastasis?

Can a CT-scan based algorithm predict occurrence of a pathological fracture through a metastatic femoral lesion?

Part II: Metastatic Humeral Lesions

What outcome –physical function, reoperations, and complications– can be expected after surgical treatment of humeral metastasis?

What factors are associated with reoperations and systemic complications after surgical treatment of humeral metastasis?

Is there a difference in surgical decision making for humeral metastasis based on physician, patient, or tumor characteristics?

Part III: Survival

Is there a difference in local tumor recurrence, reoperation, and survival between metastasectomy, intralesional resection, and stabilization only for renal cell metastasis?

What factors are associated with worse survival among patients who underwent surgery for long bone metastases?

What type of algorithm is most accurate for predicting survival probability after surgery for long bone metastases?

Are allogeneic blood transfusions associated with worse survival after surgery for long bone metastases?

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