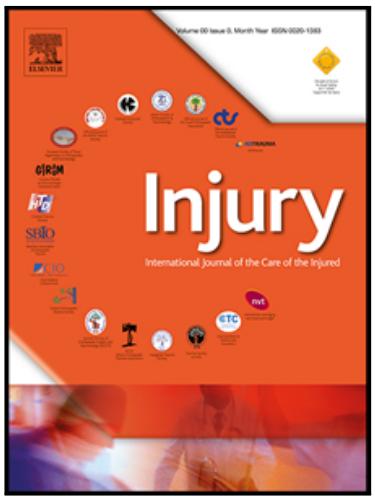

New concepts in the surgical treatment of actual and impending pathological fractures in metastatic disease

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HIGHLIGHTS

- There is an increased incidence of bone metastases due to improved of cancer patients survival.
- "Oligometastases" represents a disease with metastatic localisations in a limited number (3 - 5) in the same body district.
- Survival of oligometastatic patients is similar to patients with a single metastasis, requiring similar treatment.
- Optimal implants survival curves should stay above the curves of patients survival.
- Oligometastatic patients need to be treated with resection and reconstruction instead of using intralesional procedures such as nailing.

New concepts in the surgical treatment of actual and impending pathological fractures in metastatic disease

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Each author certifies that the research has been performed following the ethical standards in the 1964 Declaration of Helsinki. Each author certifies that all patients or their relatives gave written informed consent to be included in scientific studies at hospital admission. Since this analysis is a retrospective review of our routine clinical practice with anonymised data, Research Ethics Committee Approval was not necessary for our Institution.

Declaration of Interest statement:
Pietro Ruggieri is Consultant and Designer for Stryker and Exactech.
Each author certifies that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

ABSTRACT

Introduction: Long bone metastases are a disease of high social importance. The goals of surgical treatment are to relieve pain, maintain or restore joint function, and prevent or treat pathological fractures. "Oligometastases" is a disease with a limited number (3-5) of metastatic lesions in the same body district, where an aggressive treatment can be carried out with "curative" intent. This study aimed to evaluate patients with bone metastases surgically treated to determine how surgical treatment can influence prognosis and quality of life, comparing solitary metastasis, oligometastases, and multiple metastases.

Patients and Methods: This is a retrospective analysis of 130 patients with long bone metastases surgically treated between October 2015 and August 2019: 40 patients had solitary metastasis; 38 had less than three metastases (oligometastases), and 52 had multiple metastases. Surgery was resection and reconstruction with a cemented prosthesis (95) or nailing (35).

Results: Overall survival was significantly better in patients with solitary metastasis or oligometastases than in those with multiple metastases ($p < 0.0001$). Patients treated with resection and prosthesis had significantly better survival than those treated with nailing ($p < 0.0001$). Implant complications requiring surgical revision occurred in 20 patients treated with prostheses, while no complications occurred in patients treated with nailing.

Discussion: Survival of cancer patients has improved in the last two decades, leading to an increase of diagnosed metastases. Patients with oligometastases have a survival similar to those with a single metastasis. Optimal implants survival curves should stay above the curves of patients survival.

Conclusions: Since there are no differences in survival, patients with oligometastases should be treated as patients with a solitary lesion, with more aggressive surgery (wide resection and reconstruction with prosthesis). Intramedullary nailing is still indicated in metaphyseal or diaphyseal metastases in patients with advanced disease or poor prognosis when the life expectancy does not overcome the expected survival of the nail, avoiding the need for further surgery.

Keywords: Bone metastasis; Oligometastases; Modular prosthesis; Intramedullary nailing.

MANUSCRIPT

Introduction

The musculoskeletal system is the third site of metastases after liver and lung [1-3]. Long bone metastases are a disease of high social importance for frequency and impact on patients' prognosis and quality of life. Their incidence is continuously increasing due to early diagnosis and increased cancer patients' survival thanks to secondary prevention and improvements in cancer treatments [4-8]. Moreover, metastases in long bones can cause pain and be complicated with Skeletal Related Events (SRE), such as actual or impending pathological fractures [9-12].

Treatment of patients with bone metastases requires a multidisciplinary approach (surgery, radiation therapy, selective arterial embolisation, chemotherapy, bisphosphonates) aimed at quality of life improvement and disease control [13-18]. Goals of surgical treatment are to relieve pain, maintain or restore joint function and ambulation, and prevent or treat bones pathological fractures [19-39].

Surgical treatment could be divided into "conservative" (nailing, plating) and "aggressive" (resection and reconstruction with prosthesis) [19-39]. Historically, "aggressive " treatment was reserved for patients with good general health status, young age, long free interval (> 3 yrs), favourable histotype (kidney - thyroid) and solitary lesion [19,23,25,27-32,35].

Nowadays, new treatments are developing around the concept of “oligometastases” [40-47], introduced by Hellman and Weichselbaum in 1995 [41]. “Oligometastases” represents a disease with metastatic localisations in a limited number (3 - 5) in the same body district, where an aggressive treatment can be carried out with curative intent [41,42]. This concept is very engaging, opening up a new scenario in more vigorous treatment of metastatic disease than in the past. Recent studies demonstrate that aggressive treatment of oligometastases significantly influences prognosis [43,44]. In literature are reported increasing studies on bone oligometastases (from lung, prostate, and breast

cancer) confirming the role of aggressive radiotherapy [45-47]; however, the role of surgical resection is still less defined.

This study aimed to evaluate patients with long bone metastases surgically treated to determine how surgical treatment can influence prognosis and quality of life, comparing solitary metastasis, oligometastases, and multiple metastases.

Patients and Methods

This is a retrospective analysis of patients with long bone metastases surgically treated between October 2015 and August 2019 in our Department. One-hundred-thirty patients were included in this study: there were 51 males (39%) and 79 females (61%) with a mean age of 69 years (range 41-91 years). Biopsy for histological confirmation was performed in all cases. It was performed with a trocar before surgery in all patients with a solitary lesion, oligometastases or without a history of cancer; in patients with multiple lesions in which diagnosis of metastases was reliable, it was obtained as a frozen section during surgery. The most frequent primary cancers were breast (42%), followed by lung (14%) and kidney (13%). The demographic and oncological data are summarised in Table 1. In 15 patients (15/130, 7.4%), the finding of the primary tumour was after the diagnosis of bone metastasis. In patients with a well-known cancer history, the mean interval between treatment of primary tumour and onset of bone metastases was 7.5 years. Sites of bone metastases included: proximal femur (75), humerus (28), femoral shaft (15), distal femur (7), tibia (3), and ulna (2). At the time of surgical treatment, 40 patients (31%) had one solitary bone metastasis, 38 patients (29%) had less than 3 bone metastases, and 52 patients (40%) had multiple bone metastases. All patients were evaluated for risk of pathologic fracture and classified according to Mirels' score at high risk [11]. There was an impending fracture in 66 cases, whereas a pathologic fracture occurred in 64 cases.

Surgical treatment was chosen after a multidisciplinary evaluation of general health status and life expectancy. In patients (35 cases) with poor general health status, multiple lesions, and poor

prognosis a “conservative” treatment with intramedullary nailing was chosen to obtain pain relief, pathologic fracture prevention and treatment, recover of patient’s activities and maintaining of limb function. On the contrary, in patients with good general health status, good prognosis, and solitary lesion (40 cases) or oligometastases (38 cases), an “aggressive” treatment with resection and reconstruction with cemented modular prosthesis was chosen. Resection and reconstruction with prosthesis (tumour prosthesis in 11 cases and conventional prosthesis in 6 cases) was also performed in patients with multiple lesions (17) with massive involvement of the metaphyseal region in which nailing could not guarantee stability. According to our surgical indications, 95 patients (95/130, 73%) were treated with prostheses (89 tumour prostheses, 6 conventional endoprostheses) and 35 patients (35/130, 27%) with nailing. We always preferred cemented prosthesis in metastatic patients due to the thermic effect of cement on tumour cells and the possibility to give early weight-bearing [27-30, 35, 39]. Moreover, these are patients with inadequate bone stock, considering their advanced age and need for postoperative radiotherapy [27-30, 35, 39]. Both nailing and reconstruction with prosthesis were followed by radiotherapy and chemotherapy, according to histotype. We obtained wide margins in all patients with solitary metastasis and oligometastatic disease. In patients with multiple lesions, marginal or intralesional margins were obtained; in those cases, the surgery always has been followed by radiotherapy to reduces the risk of recurrence and local disease progression.

Patients were followed in outpatient clinic with lung CT-scan and X-rays of the region surgically treated to analyse complications and local recurrence/progression, every three months for the first 3 years, every four months for the next 1 year, every six months for the next 1 year, and then annually.

The analysis was based on data collected from medical records and, if not otherwise possible, by telephone consultation. Oncologic results were assessed for local recurrence, metastases, or death at the latest routine check. Patients were divided into no evidence of disease (NED), alive with disease (AWD), or dead with disease (DWD). Survival was defined as the time from surgery to the last

follow-up or death. Prosthetic failures were classified according to Henderson et al. [39] in Type I (soft tissue failure), Type II (aseptic loosening), Type III (breakage), Type IV (infection) and Type V (local recurrence). Patient's and implant's survival was analysed using the Kaplan–Meier analysis, and comparison of the curves was estimated using the log-rank test. Statistical significance was defined as a P-value of 0.05 or less.

Results

At a mean follow-up of 15 months (1 month – 5 years), 18 patients were NED, 38 were AWD, and 74 were DWD. No patients were lost during the follow-up. The mean survival time was 20 months (range, 6-87 months) in patients with solitary metastasis, 18 months (range, 4-54 months) in oligometastatic patients, and 9 months (range, 1-40 months).

Overall patients survival was 40% and 28%, respectively at 2 and 4 years (Fig. 1A), without differences between patients with single or oligo metastases ($p = 0.941$), while there was a statistically significant difference between them and those with multiple metastases ($p < 0.0001$) (Fig. 1B). Survival of patients treated with prosthesis was 48% and 38%, respectively at 2 and 4 years, whereas survival of patients treated with nailing was 14% and 0%, respectively at 2 and 4 years. Considering surgical indications, patients treated with resection due to single and oligometastases had significantly better survival than those treated with prosthesis due to mechanical concerns ($p=0.0137$) or with intramedullary nailing ($p < 0.0001$) (Fig. 2).

Implant complications requiring surgical revision occurred in 20 patients treated with resection (20/95, 21%). There were 6 wound dehiscences (Type I), 8 dislocations (Type I), 1 poly wear and prosthesis disconnection (Type III), 2 periprosthetic fractures (Type III), 2 infections (Type IV) and 1 local recurrence in soft tissue (Type V). All patients retained their prosthesis, except in cases of infection where implant removal was required. No complications were observed in patients treated with nailing. Curves of implants survival were above of those of patients survival, after treatment with both nailing and prosthesis (Fig. 3 A-B).

Discussion

Survival of cancer patients has improved in the last two decades, thanks to early diagnosis and advances in multidisciplinary treatment, leading to an increase of metastases [4-8]. The musculoskeletal system is the third site of metastases since several carcinomas (such as breast, prostate, thyroid, lung, and kidney) have a marked tropism for bone [1,3]. Consequently, bone metastases are frequent and represent a social health problem. Treatment of patients with bone metastases requires a multidisciplinary approach: prevention and treatment of pathological fractures are one of the main objectives of orthopaedic treatment to improve quality of life and restore joint functions [9-18].

Surgical orthopaedics treatment depends on biological criteria, such as tumour histotype, the extension of disease (single or multiple bone lesion, presence of visceral lesions), general patient condition, disease-free interval, sensibility for non-surgical therapies (chemotherapy, radiation therapy, and hormone therapy) [15-18]. Biomechanical criteria, such as presence or risk of pathologic fracture (site and size of the lesion, lytic or sclerotic lesion) also need to be considered [9-12].

In the last few years, a new concept of "oligometastatic disease" was introduced [40-47]. "Oligometastases" represents a disease with a limited number (3 - 5) of metastatic localisations in the same body district, which could be classified as intermediate between purely localised lesions and those widely metastatic [41-42]. Lu et al. [43], analysing patients with bone metastases from renal cell carcinoma treated with Sunitinib, reported a statistically significant difference in overall survival between oligometastatic patients (30 months) and non-oligometastatic ones (13 months).

In patients with oligometastases, treatment can be done with curative intent, such as demonstrated by recent studies [40-47]. Increasing studies on bone oligometastases (from lung, prostate, and breast cancer) confirmed the role of aggressive radiotherapy [45-47]. Tosol et al. [46] reported results after stereotactic ablative radiation therapy (SABR) in 33 patients with non-spinal bone metastases, demonstrating that local control can improve overall survival in single/oligo-metastatic setting compared to multiple metastatic diseases ($p < 0.001$). Similar results were

reported by Kennedy et al. [47] in their review on SABR: excellent local control rates ranging from 70% to 90% with long-term survival up to 20-40% are obtained in oligometastatic disease, confirming that an aggressive local treatment ameliorates prognosis in oligometastatic patients. However, the role of surgical resection is still less defined. We reported our experience after surgical treatment of patients with long bone metastases comparing solitary metastasis, oligometastases, and multiple metastases to determine how surgical treatment can influence prognosis and quality of life.

A more aggressive surgical treatment with "curative" intent has been already reported for patients with single bone metastasis [19-39]. Mavrogenis et al. [35] analysed 110 patients with proximal femur metastasis treated with intramedullary nail (53) and resection and prosthesis (57). At a mean follow-up of 18 months, the survival of patients, even if reduced, was significantly higher those treated with resection than with nailing (p=0.009). Angelini et al. [27] analysed 40 patients with impending or pathologic fractures of the proximal femur treated with intramedullary nail (7), endoprosthesis (4), and modular prosthesis (29). They found that only histotype (renal cancer and myeloma) and type of treatment (resection and prosthesis) influenced the prognosis at the multivariate analysis. Trovarelli et al. [28] reported the use of modular reverse shoulder prosthesis after resection of the proximal humerus in 10 patients with a single site of metastasis or myeloma. All resections were performed with wide margins with satisfactory patient and implant survival. In the present study, the overall survival was statistically better in patients with single or oligo metastasis compared to those with multiple metastases ($p < 0.0001$), while no differences were found between patients with single lesion or oligometastases ($p = 0.941$). Our results confirm what has already been reported in the literature. Since there is no difference in survival among patients with solitary metastasis and oligometastatic ones, also the last should be treated surgically in an aggressive way (wide resection) since this might also have a therapeutic purpose. Moreover, once excluded those treated with prosthesis due to mechanical concerns, patients treated with resection and prosthesis had longer survival/better prognosis than those treated with nailing ($p<0.0001$). In

other words, longer survival/better prognosis is observed in oligometastatic or single metastasis patients when they are treated with resection: these two conditions contribute together to a better prognosis. On the contrary, treat oligometastatic patients with intralesional procedures (nailing) would negatively impact on prognosis.

Implant durability is crucial, especially in metastatic patients, since re-interventions due to reconstruction failure would lead to a suppression of medical treatments with a deterioration of prognosis. Moreover, reoperations are usually complicated and potentially fatal, increasing morbidity and decline of patients' health status. For these reasons, we firmly believe that it is fundamental that the survival curve of the implants should always be above the survival curve of the patients, especially in metastatic disease [32]. It is widely reported that resection and prosthetic reconstruction is associated with a lower risk of complications and more extended durability compared to other systems of fixation [32-38]. Steensma et al. [32] reported complications after surgical treatment of 298 patients with proximal femur metastasis. They find a statistically significant difference in the incidence of failure (3% in endoprosthesis, 6% in nailing, and 42% in plate) with a statistically significant difference in the reoperation rate ($p<0.05$), concluding that endoprosthetic treatment is more durable for pathologic proximal femur fractures. Wedin and Bauer [37] in 146 cases of metastasis of the proximal femur reported failures in 16% of patients treated osteosynthesis, and in 8% of those treated with prosthetic reconstruction, with a significantly higher risk of 2-year reoperation after osteosynthesis ($p = 0.07$). Calabrò et al. [29] analysed patients treated with reconstruction of the proximal femur with a modular prosthesis in a cohort of 109 patients (75 bone metastasis and 34 bone sarcomas); 46 of them had pathologic fracture at diagnosis. Even if the survival of metastatic patients was poor (20% and 13%, respectively at 4 and 8 years), implant survival was satisfactory, avoiding the need for reoperation. In our study, implant complications occurred all after treatment with the prosthesis, never after nailing (probably due to the shorter patients survival). In particular, implant survival at 2 and 4 years was 76% in prosthetic reconstruction and 100% in nailing. It is proof that our surgical indications were correct: there was

no need for reoperation for the patients treated with nailing since the curve of their survival was lower than the implant survival curve. On the contrary, when local surgery is performed with "curative" intent, it is justifiable a more demolitive surgical approach to ensure an improvement of patient survival, also accepting the risk of complications.

Our study has some limitations. First, this is a retrospective study. However, all patients have been treated in a limited period by the same surgical team and with consistent procedures and perioperative protocols. Second, there were different histotypes. Third, the power of our analysis is possibly limited by a relatively short follow-up. This is due to the short life expectancy overall.

Conclusions

Treatment and surgical indications should be discussed in a multidisciplinary team. The choice of surgical resection is related to prognosis/life expectancy.

Since there are no differences in survival, patients with oligometastases should be treated as patients with a solitary lesion, with more aggressive surgery (wide resection and reconstruction with prosthesis). Intramedullary nailing has still its indications in diaphyseal metastases in patients with advanced or diffused disease or poor prognosis when life expectancy is limited.

Conflict/Declaration of Interest Statement

Pietro Ruggieri is Consultant and Designer for Stryker and Exactech.

Each author certifies that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

Supplement Statement

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Figure Legends

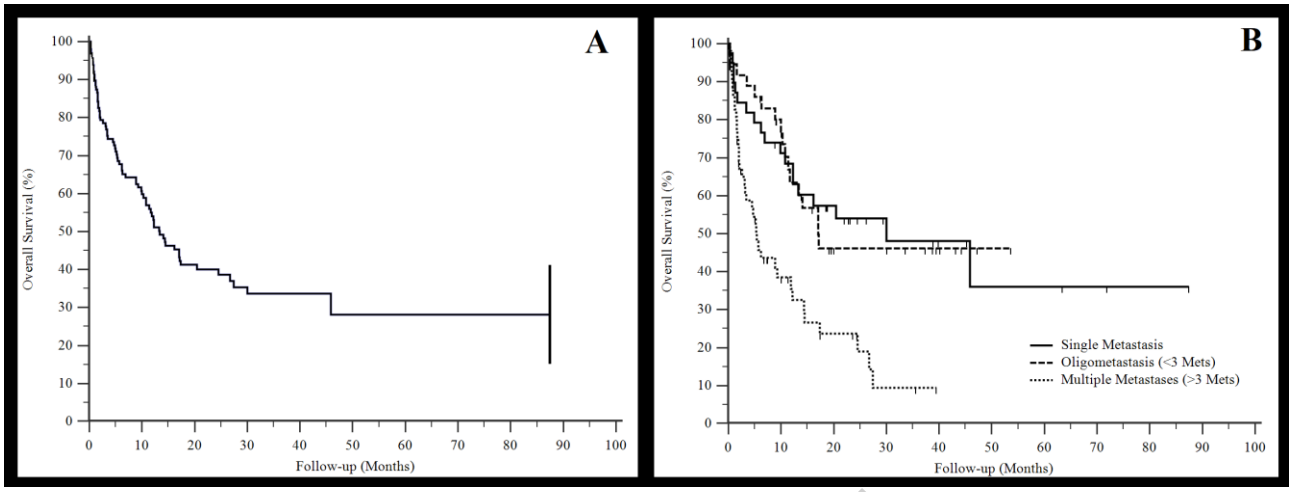

Figure 1. A) Overall patients survival was 40% and 28%, respectively at 2 and 4 years. **B)** There was no difference in survival between patients with oligometastases or solitary lesion (p = 0.941), while a significantly better survival was found comparing them to those with multiple metastases (p <0.0001).

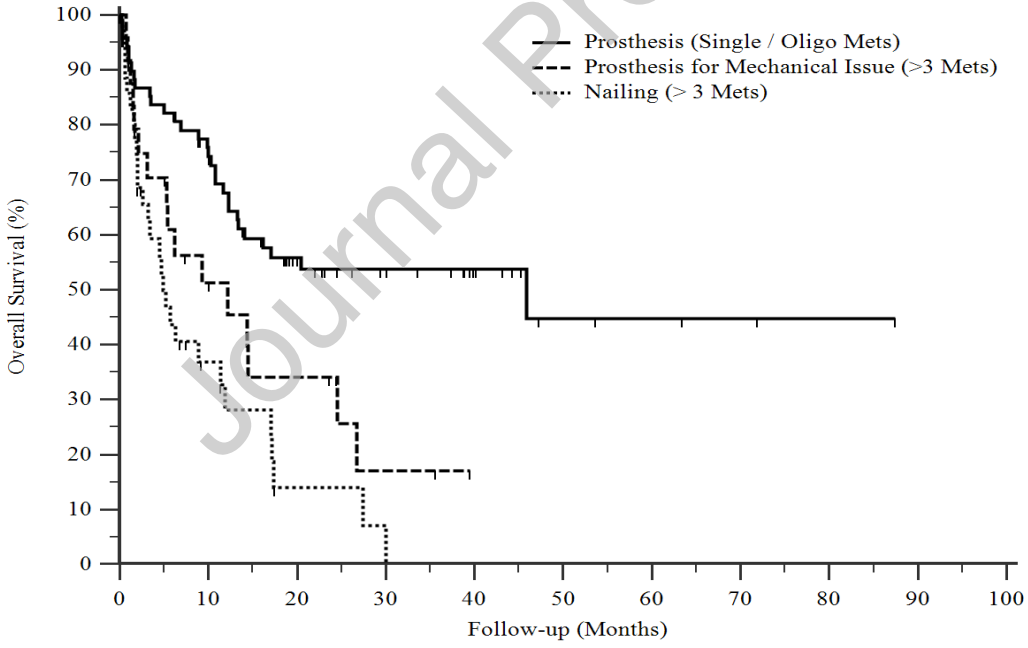

Figure 2. Survival of patients related with surgical indications: patients treated with resection due to single and oligometastases had significantly better survival than those treated with prosthesis due to mechanical concerns (p=0.0137) or with nailing (p <0.0001).

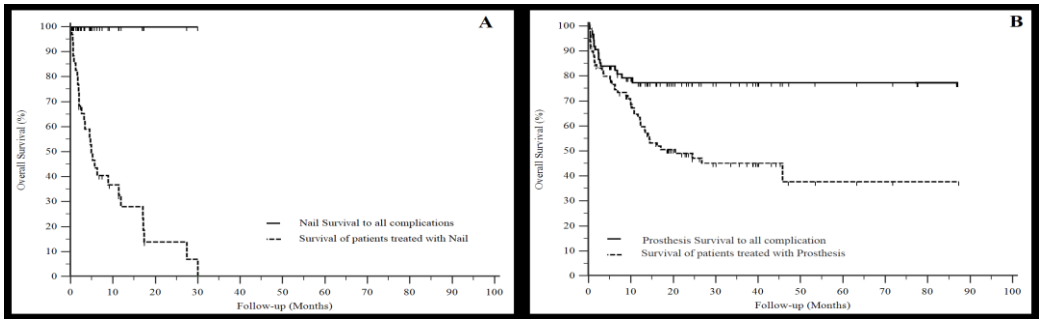

Figure 3. Curves of implants survival were above those of patients survival, after treatment with both nailing (**A**) and prosthesis (**B**).

Table 1. Demographic and oncological data of patients treated for long bone metastases (n= 130)

Data	Patients	%
Age and gender		
Age (mean years)	69 (range, 41-91)	
Gender (male/female)	51/79	
Histotype of the primary tumour		
Breast Carcinoma	42	32 %
Lymphoma/Myeloma	24	18 %
Lung Carcinoma	18	14 %
Kidney Carcinoma	17	13 %
Gastrointestinal Carcinoma	6	5 %
Undifferentiated Carcinoma	6	5 %
Prostate Carcinoma	4	3 %
Thyroid Carcinoma	3	2%
Endometrial Carcinoma	3	2%
Urothelial Carcinoma	3	2%
Hepato Cellular Carcinoma	2	1%
Seminoma	1	1%
Epithelioid Angiosarcoma	1	1%
Site		
Proximal femur	75	58%
Humerus	28	21%
Femoral shaft	15	12%
Distal femur	7	5%
Tibia	3	2%
Ulna	2	1%
Number of metastasis		
Single	40	31%
Less than 3	38	29%
More than 3	52	40%
Type of surgery		
Prosthesis in patients with less than 3 metastases (all tumour prosthesis)	78	60%
Prosthesis in patients with more than 3 metastases due to mechanical concerns (11 tumour prostheses, 6 conventional prostheses)	17	13%
Nail	35	27%