Use of endoprostheses for proximal femur metastases results in a rapid rehabilitation and low risk of implant failure. A prospective population-based study

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ABSTRACT

Background and objectives: Endoprosthesis is considered a durable implant for treating metastatic bone disease of the proximal femur (MBDf).

Objectives: • What is the revision risk after surgery for MBDf using endoprosthesis versus internal fixation?
• When do patients with MBDf treated with endoprosthesis restore quality of life (QoL) and how long time does it take to rehabilitate functional outcome?

Methods: A prospective, population-based, multicentre study of 110 patients. Patients were followed for a minimum of two years after surgery. No patients were lost to implant failure nor survival follow-up.

Results: Forty-four patients were treated with internal fixation and 66 patients received endoprostheses. Two-year implant failure risk for internal fixation was 7% (95CI: 0–14%) versus 2% (95CI: 0–5%) for endoprostheses (p = 0.058).

Eq-5D improved to the same level as one month prior to surgery six-weeks after surgery, and the score improved further six months after surgery (median score from 0.603 to 0.694, p = 0.007). MSTS score increased from 12 points after surgery to 23 points six-months after surgery (p < 0.001).

Conclusions: Endoprosthesis for treatment of MBDf results in low implant failure rate. Patients are satisfied with the functional outcome. QoL is restored six-weeks after surgery. Authors advocate for caution using internal fixation for MBDf due to findings of a possible high early postoperative revision risk.

1. Introduction

Treating metastatic bone disease (MBD) is in most cases a matter of preserving quality of life (QoL) for patients at their end of life [1,2]. Currently no uniform consensus upon treatment strategy for lesions involving the proximal femur exists, but several expert opinions have been published [3–10]. The choice of implant is either internal fixation, known from acute fracture settings, or an endoprosthesis that may be with or without major bone resection (the first known as a tumour prosthesis).

The evidence level for implant performance and revision risks remains low, as illustrated in a systematic review [11]. This review identified 40 studies, all retrospective, and only 28% described a clear definition of outcome measures. Furthermore 43% of the studies were evaluated as being at high risk or unknown risk of attrition bias.

A study has identified MBD to be a significantly driver of overall cost of oncology treatment in the U.S. [12], and thus the economic burden of treating pathological femur lesions could pose a major impact on health economies. The decision to perform surgery, and choosing the right implant, is ideally made between the physician and the patient. For the physician, it is widely accepted that residual life expectation is the driving factor for choosing between internal fixation or endoprosthesis, as the use of endoprosthesis is considered to be a more durable implant for long-term survivors [13]. To make an informed decision the patient needs information regarding expected functional outcome and QoL for the two treatment modalities, but the evidence for

Synopsis: Treating metastatic lesions of the proximal femur with endoprostheses can be performed without prolonged inpatient stay and seems to have a low revision risk on short-term compared to internal fixation. Endoprosthesis also result in fast recovery in quality of life and functional outcome.

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2. Material and methods

2.1. Study design and setting

A prospective cross-sectional multicentre observational study was conducted including all patients having surgery for MBD in the eastern part of Denmark [16] in six institutions (five secondary surgical centres/trauma units and one tertiary referral musculoskeletal tumour centre). The study period was from the 19th May 2014 to the 18th May 2016. Due to the social healthcare system in Denmark no patient will be treated outside these hospitals, hence, the cohort is representative of an entire population of patients undergoing surgery for MBD and no selection bias of patients was present.

2.2. Participants

Patients were included at time of surgery and informed consent was obtained for inclusion into prospective clinical follow-up. Only metastatic lesions located in the proximal and/metaphysical part of the femur (corresponding to the AO (Arbeitsgemeinschaft für Osteosynthesefragen) [17] fracture classification type 31/32, where diaphyseal lesions were excluded) were eligible for the current study (n = 118), regardless of a complete or a pending fracture. Patients treated by a Girdlestone procedure (n = 2) were excluded from the current study and in case of bilateral surgery during the study period, the second implant was excluded as well (n = 6). Thus, a total of 110 patients were included for further analysis.

The study was purely observational and no influence upon referral for treatment at tertiary treatment centre was present and no influence on treatment (internal fixation or endoprosthesis) from the current study was present. As such, the treatment was purely dependent on the evaluation made by the attending surgeon as currently no national guideline for treatment of MBD is present in our country. In general, it must be expected that a patient in poor performance status is not referred for treatment at a tertiary treatment centre, where the use of tumour endoprosthesis is the preferred treatment of choice for MBD.

Clinical follow-up was performed at six weeks, three months and six months postoperatively and included evaluation with Karnofsky score [18], Musculoskeletal Tumor Society Score (MSTS-score) [19], European Quality of life – 5 Dimensions (EQ-5D) [20] questionnaire and x-ray, where country specific index score and Visual Analog Scale (VAS) are reported. Clinical follow-up was offered to all participants, and if consent was obtained to participate in clinical follow-up, a telephone reminder was given twice (once a week) in case of a no show. Patients were free to withdraw consent at any point. Clinical follow-up interval was ± one week for six-week follow-up, ± two weeks for three- and six-months follow-up. Clinical follow-up was performed by two surgeons (MSS/PFH).

Reoperation is reported as all cause revision (all surgical revisions performed in relations to the surgical implant and thus include everything from superficial debridement to total removal of an implant). Closed reduction of a dislocated hip was not considered a surgical revision. Implant failure included surgeries with revision of bone anchored implant parts only. We chose not to include closed reductions as revision in the analysis as it would be side-lined with a fatigue failure of intramedullary nail and we believe that a procedure that requires few hours admittance (closed reduction) does not cause the same functional impairment for the patient as removal of an implant and thus is not relevant for comparison, and furthermore closed reductions of total hip arthroplasties (THA) are not considered a revision in arthroplasty registries.

All patients were observed for revision surgery and failure of implant until end of study (the 18th May 2018) resulting in a minimum of two-year follow-up. Due to the Danish civil registry system no patients are lost to survival nor revision surgery follow-up [21].

2.3. Aftercare

Likewise, the postoperative regime and rehabilitation (physiotherapy) solely depended on the attending surgeon and patient’s preferences. Due to the social healthcare system in Denmark, all patients have equal access to rehabilitation, and differences between patients will be expected to be influenced only by patient preferences.

2.4. Statistical analysis, study size

As data were not expected to be normally distributed, variables are reported by median and interquartile range (IQR). Upon admittance for surgery, patients were asked to evaluate their EQ-5D as they remember it was one months prior to surgery. This, and the Karnofsky score [22] one month prior to surgery, was evaluated by the surgeons (MSS/PFH) during a patient interview.

Revision risk, implant failure and risk of dislocation were assessed by competing risk analysis (Aalen–Johnson estimate) with death as a competing risk for implant survival, and death and implant removal as competing risks for revision. Gray’s test was used to identify a potential difference in risk between internal fixation and endoprostheses. Due to a relatively low sample size, we chose not to stratify for major or minor bone resection for the endoprostheses. Survival was reported as an overall all-cause mortality and estimated by the Kaplan-Meier analysis. Differences in survival between groups were assessed by log-rank test.

Chi² test was used to evaluate potential differences between categorical variables and Mann-Whitney test for continuous variables. P-values below 0.05 were considered statistically significant and confidence intervals are reported as 95% (95CI).

All statistics were performed using R-studio [23].

2.5. Demographics, description of study population

A total of 110 patients were included with a median age of 68.5 (IQR: 60–76.75), with an equal distribution between males and females (Table 1). The most common cancers causing the lesions were: breast (n = 29), lung (n = 24), prostate (n = 19) and renal cell (n = 13).

Fifteen patients were alive at the end of follow-up with a minimum time of follow-up of 768 days and a maximum of 1468 days. Two-year overall survival for the entire cohort was 22% (95CI: 14–18%) and no difference in survival was seen between the two treatment groups (p = 0.332 (Fig. 1).

3. Results

Forty-four patients were treated with internal fixation (cannulated-screws (n = 1), plates (dynamic hip screw) (n = 5) and intramedullary
Table 1

Demographics of the patient cohort.

|                      | Endoprosthesis | Internal fixation | p*   |
|----------------------|----------------|-------------------|------|
| Age (median)         | 66 (IQR:58–77) | 69 (IQR:62–75)    | 0.427|
| Sex (M/F)            | 34/32          | 21/23             | 0.846|
| ASA (n =)            |                |                   | 0.106|
| 1                    | 2              | 1                 |      |
| 2                    | 21             | 15                |      |
| 3                    | 40             | 20                |      |
| 4                    | 3              | 8                 |      |
| Diabetes (yes/no)    | 7/59           | 4/40              | 0.195|
| Ischemic heart disease (yes/no) | 7/59 | 2/42 | 0.435|
| Systemic treatment (n =) |               |                   | 0.089|
| None                | 28             | 19                |      |
| Chemotherapy        | 16             | 17                |      |
| Hormonal therapy    | 18             | 4                 |      |
| Targeted therapy    | 4              |                   |      |
| Preoperative radiation (yes/no) | 16/50 | 11/33 | <0.001|
| Visceral metastases (yes/no) | 25/41 | 23/21 | 0.195|
| Bone metastases (n =) | 4              |                   | 0.466|
| Solitary            | 10             | 9                 |      |
| Multiple appendicular | 8             | 2                 |      |
| Multiple including spinal | 48            | 33                |      |
| Primary cancer (n =) |               |                   |      |
| Breast              | 20             | 9                 |      |
| Lung                | 13             | 11                |      |
| Prostate            | 16             | 3                 |      |
| Kidney              | 4              | 9                 |      |
| Myeloma             | 11             | 5                 |      |
| Days from diagnosis to surgery (median) | 382 (IQR:125–2249) | 342 (IQR:51–2216) | 0.277|

* Mann–Whitney–Wilcox test for continuous variables and Chi² for categorical.

* Defined as diabetes treated by medication at time of admittance.

* Defined as cardiac output < 50%.

nails (n = 38)) and 66 patients received an endoprosthesis. Thirty-eight conventional hip prostheses (normal stem length/long-stemmed implants = 16/22, hemiarthroplasty/total joint replacement/total joint replacement + partial pelvis replacement = 18/18/2), 26 tumour prostheses (hemiarthroplasty/total hip replacement = 12/14) and two intercalary spacers (implants designed for reconstruction of a diaphyseal bone defect without replacing the joint) were used. For the most common implants used see Fig. 2.

Patients treated by internal fixation had shorter surgery time (p = 0.032) and less peroperative blood loss (p = 0.003) compared to the endoprosthesis-group. This did, however, not result in an increased hospital stay (p = 0.886) nor a higher percentage of patients that died during the follow-up (p = 0.395) (Table 2).

Implant failure risk for internal fixation was 7% (95CI: 0%–14%) and for endoprostheses 2% (95CI: 0%–5%) two years after surgery (p = 0.058) (Fig. 3). One endoprosthesis was removed (aseptic loosening of an uncemented intercalary spacer) and 4 internal fixations were removed (breakage of nail/plates) during follow-up (Table 3).

Risk of revision was 7% (95CI: 0%–14%) for internal fixations and 5% (95CI: 0%–10%) for endoprostheses two years after surgery (p = 0.531). All surgically treated implant-related complications are summarized in Table 3.

For the patients that received an endoprosthesis in risk of dislocation (n = 64), four experienced one dislocation, and two patients experienced two dislocations (Table 3). All dislocations occurred within 76 days after surgery, resulting in a 6% (95CI: 0%–12%) risk of experiencing a dislocation within three months after surgery.

Of the THAs in the study, nine were constrained (hip joint developed to address the problem of recurrent instability by holding the femoral head captive within the cup) from index surgery. Two constrained THAs dislocated during follow-up. In two THAs a partial pelvis replacement plate was used due to involvement of the acetabulum and in this group one dislocation was observed. No dislocation of hemiarthroplasties was observed during the study period. All hemiarthroplasties (n = 30) were implanted with a bipolar head without piriformis preserving procedure. Risk of dislocation was not tested for differences between resection type or implant type due to the low number.

At six weeks, three months and six months after surgery 89 patients, 72 patients and 58 patients were alive and therefore eligible for clinical follow-up. A total of 49 patients were not included into the questionnaire part of the current study at the time of surgery: 15 patients did not want to participate in clinical follow-up, 20 patients were not able to participate in questionnaire assessment (dementia, not speaking Danish, too poor functional status to participate as evaluated by attending oncologist) and 14 patients were not informed preoperatively that a malignant lesion was suspected prior to surgery, and thus not included into this prospective study.

As the majority of patients receiving internal fixation did not wish to participate in the follow-up or was lost to follow-up (67%, 77% and 77% at six weeks, three and six months, respectively), we decided to exclude this group from subgroup analysis. The main reasons for lost to follow-up were: hospital admittance due to other health problems, or patients being too exhausted to attend the clinical follow-up.

Patients attending clinical follow-up at six weeks were more likely to have higher preoperative Karnofsky score (p < 0.001), younger age (p < 0.001), poorer overall survival (p < 0.001), and less had visceral metastases at the time of surgery (p = 0.006).

For patients treated with an endoprosthesis, we identified that the EQ-5D index improved to the same level as one month prior to surgery and the index score was further improved statistically significant six months after surgery (median score improved from 0.603 to 0.694, p = 0.007). However, the EQ-5D VAS score did not improve beyond the score one month prior to surgery at any time point postoperatively.

At six weeks of follow-up, 5% of patients that received an endoprosthesis was ambulatory without any walking aid, whereas 14% was ambulatory with the use of one crutch, 77% with two crutches or a walker, and 4% had no ambulatory function and was thus bedbound. At three months, this had changed to 26% being ambulatory without aid, 30% walking using one crutch, 35% using two crutches or a walker and 9% having no ambulatory function. At six-months of follow-up 40% of patients were ambulatory without any aid, 30% using one crutch and 30% using two crutches or a walker. No patients surviving to and attending the six-months follow-up were bedridden. These changes in walking ability were also reflected in the changes in the MSTS-score as

![Kaplan Meier for overall survival](image-url)
we observed an increased median MSTS score from 12 points six-weeks after surgery to 23 points six months after surgery ($p < 0.001$) (Fig. 4).

As for the Eq-5D analysis, we also chose to exclude internal fixation from further subgroup analysis of functional outcome. In the endoprosthesis group, we saw that Karnofsky performance score markedly decreased from one month prior to surgery to the time of surgery (median changed from 75 to 40, $p = 0.096$), but the performance of the patients did not improve statistically significant after this period (Fig. 4).

4. Discussion

Currently it is widely accepted that surgical treatment of MBDf should be performed using internal fixation in case of less than six months of expected postoperative patient survival [13], however, this is not evidence based. The use of an endoprosthesis is considered, to be preserved for long-term survivors as the reconstruction using an endoprosthesis is believed to result in a prolonged rehabilitation period, that short time survivors may not live to benefit from. In the current study, we have challenged this hypothesis. We find that the use of endoprosthesis results in low complication risk, return to QoL, and fast rehabilitation.

Comparing revision risk for two different surgical methods is difficult as no consensus upon what is considered an event in such an analysis exists, and attrition bias and selection bias of patients with short expected survival treated with internal fixation, taint the readers interpretation. To perform analysis of the difference in revision risk between various surgical implants of the proximal femur, Janssen et al. [11] had to compare reoperation rate as reported by the original studies in their systematic review. They did not find any statistically significant difference in revision risk between surgical methods (internal fixation versus endoprosthesis). However, when reporting the revision risk as it is often done in the literature, and not using the cumulated risk over time, one could easily be underestimating the revision risk in a cohort with short follow-up or high early postoperative mortality, as the patients may not live to, or be observed to, the time where the implant will fail (result of a selection bias if patients with poor survival expectation are mainly treated with intern fixation). As one-year survival in the 40 cohorts included in the systematic review varies between 0% and 62% and minimum follow-up between 0 months and 36 months, this is a major bias when comparing revision risk. Also, no studies included in the review accounts for competing risks, which is known to cause overestimation of revision risk in orthopaedic procedures [24,25]. This has been shown to be of great influence in MBD patients with a high mortality [26]. As the general perception [13] is to use an endoprosthesis in long-term survivors and to treat short-term survivors with internal fixation, it is difficult to evaluate if we over or underestimate revision risk in these two patient populations. Therefore, the

![Fig. 2. Examples of the most common implant used in the study. (A) Intramedullary nail for a subtrochanteric lesion (B) plate osteosynthesis (dynamic hip screw) for a basocervical lesion (C) tumour resection prosthesis of the modular type with cemented cup (D) bipolar hemiarthroplasty.](image)

![Table 2](image)

|                        | Endoprosthesis | Internal fixation | $p$  |
|------------------------|----------------|-------------------|------|
| Surgery time (median)  | 238 (IQR:98–164) | 101 (IQR:73–163)  | 0.032|
| Blood loss (median)    | 500 (IQR:300–800) | 300 (IQR:200–500) | 0.003|
| Admission days (median)| 11 (IQR:7–15)   | 10 (IQR:6–19)     | 0.886|
| Dead at end of study   | 55 (83%)       | 40 (91%)          | 0.395|

![Cumulative Incidence of Implant Failure](image)

we observed an increased median MSTS score from 12 points six-weeks after surgery to 23 points six months after surgery ($p < 0.001$) (Fig. 4).

As for the Eq-5D analysis, we also chose to exclude internal fixation from further subgroup analysis of functional outcome. In the endoprosthesis group, we saw that Karnofsky performance score markedly decreased from one month prior to surgery to the time of surgery (median changed from 75 to 40, $p < 0.001$), whereas patients already six-weeks after surgery reported the same median score as one month prior to surgery (median from 40 to 70, $p = 0.096$), but the performance of the patients did not improve statistically significant after this period (Fig. 4).
Table 3: All surgical complications observed for the entire cohort and how they were treated.

| ID  | Time (days) | Failure             | Implant               | Treatment                                                                 |
|-----|-------------|---------------------|-----------------------|---------------------------------------------------------------------------|
| 45  | 33          | Dislocation (trauma)| Tumour resection with endoprosthesis cup | Insertion of constrained liner Implantaion of new intramedullary nail |
| 45  | 49          | Dislocation (trauma)| Tumour resection endoprosthesis with cup | Insertion of constrained linear |
| 30  | 18          | Dislocation         | Long stemmed endoprosthesis with partial pelvic replacement | Insertion of constrained linear |
| 116 | 31          | Dislocation (trauma)| Long-stemmed endoprosthesis with cup and freedom cap | Closed reduction |
| 116 | 49          | Dislocation (trauma)| Long-stemmed endoprosthesis with cup and freedom cap | Closed reduction |
| 183 | 249         | Breakage of intramedullary nail | Tumour resection prosthesis | Conversion to tumour resection prosthesis |
| 127 | 76          | Dislocation         | Tumour resection endoprosthesis with cup | Closed reduction |
| 68  | 39          | Aseptic loosening of stem | Intercalary spacer for metaphyseal lesion | Insertion of new intercalary spacer |
| 29  | 791         | Deep infection      | Tumour resection endoprosthesis with bipolar head | Debridement and removal of all bone anchored parts and lifelong antibiotic treatment without further revision |
| 157 | 96          | None union and chronic pain | Tumour resection endoprosthesis with bipolar head | Removal of implant and implantation of new endoprosthesis |

The MSTS score did increase gradually over the first six months postoperatively for the endoprosthesis group, indicating the potential for improvement over time. Most studies reporting the MSTS score in MBDF patients undergoing surgery report the score as an average at clinical follow-up at any time after surgery [29–31], and this bias the findings by Janssen et al. [11] is difficult to use in clinical settings as comparison of outcomes in the 40 different studies included, seems far from optimal taken these considerations into account.

An important observation in our cohort is that the failure of internal fixations occurs early, most of them within one year, which is contrary to the findings by Errani et al. [5]. This discrepancy can be explained by the fact that patients experiencing an early implant failure in this review are lost to follow-up due to attrition bias of analysed studies. Most importantly, we find a markedly increased risk of revision in the internal fixation group compared to the endoprosthesis group, but not statistically significant, which is explained by lack power due to small sample size. We feel that this risk is actual and advocate for precaution in treating MBDF with internal fixation. We advocate for pooling data internationally to obtain the needed power in future studies.

Due to a high number of patients were lost to follow-up, or not willing to participate in the questionnaire in our internal fixation group, we were not able to perform statistical analysis comparing post-operative function between the two groups. We know this is a limitation to our study, however, we chose to report lost to follow-up in exact number in contrast to all other published papers on functional outcome after surgical treatment for MBD in order to enlighten the reader and acknowledge that this is a difficult patient population to perform functional evaluation on, as they are terminally ill of their cancer disease and have other priorities.

The MSTS score did increase gradually over the first six months postoperatively for the endoprosthesis group, indicating the potential for improvement over time. Most studies reporting the MSTS score in MBDF patients undergoing surgery report the score as an average at clinical follow-up at any time after surgery [29–31], and this bias the outcome, as we do not know how many patients were scored 2 years after surgery or 2 weeks after surgery. Harvey et al. [29] found no statistically significantly different in MSTS score comparing treatment with internal fixation to endoprosthesis, but they also report that patients having internal fixation was followed on average of 20 months postoperatively compared to 14 months for the endoprosthesis group, allowing for further rehabilitation time for the internal fixation group,
which potentially bias their reporting. For the endoprosthesis group, Harvey et al. [29] found an average MSTS score of 24 points at an average of 14 months follow-up compared to 23 at our six months follow-up. These scores are very comparable and it may be that no benefit from further rehabilitation is gained over time or, more likely, the ceiling effect of the MSTS score is achieved already 6 months postoperatively, and therefore other questionnaires should be used instead in future studies to address gain in functional outcome over time. Peterson et al. [31] have a similar way of presenting their data, regarding patients undergoing long-stemmed hemiarthroplasty for MBDf, and report above or below one year follow-up, but again not with exact follow-up period in these two categories. They observe a gain in MSTS score over time with an average MSTS score of 27 for patients followed for more than one year after surgery. As our group of patients receiving an endoprosthesis comprise of long-stemmed hemiarthroplasty, as well as total hip replacement with (tumour prostheses) or without wide bone resection, we conclude that the MSTS score found in our population is very good.

Although the strengths of the current study are that it is prospective and populations-based design with no loss to survival or re-operation/complication follow-up, it also has some limitations. Firstly, it is not randomized and therefore selection bias of patients to a certain treatment will influence outcome in measurement of QoL and functional outcome, which is a limitation to all the literature on surgical treatment of MBD. We have chosen to limit this problem by not comparing between the two treatment arms (internal fixation and endoprosthesis). Secondly, in the internal fixation group no patients were treated with cemented implants which has been described to reduce the risk of implant failure. As the current study is purely observational it reflects the reality of how these patients are treated in our region with the current implant failure risk, and this may differ in case implants were cemented.

5. Conclusions

The use of endoprostheses for treatment of MBDf results in low implant failure risk and can be performed without longer hospital stay. Patients are satisfied with the functional outcome using endoprostheses, as measured by the MSTS score, and their QoL is restored already six weeks after surgery. Authors advocate for caution when treating MBDf with internal fixation due to findings of a possible early high post-operative revision risk using these implants.

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Supplementary materials

Supplementary material associated with this article can be found in the online version, at doi:10.1016/j.jbo.2019.100264.

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