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Extent of Surgery Does Not Influence 30-Day Mortality in Surgery for Metastatic Bone Disease

An Observational Study of a Historical Cohort

Michala Skovlund Sørensen, MD, Klaus Hindsø, MD, PhD, Thea Bechmann Hovgaard, Bach. Med., and Michael Mørk Petersen, MD, DMSc

Abstract: Estimating patient survival has hitherto been the main focus when treating metastatic bone disease (MBD) in the appendicular skeleton. This has been done in an attempt to allocate the patient to a surgical procedure that outlives them. No questions have been addressed as to whether the extent of the surgery and thus the surgical trauma reduces survival in this patient group.

We wanted to evaluate if perioperative parameters such as blood loss, extent of bone resection, and duration of surgery were risk factors for 30-day mortality in patients having surgery due to MBD in the appendicular skeleton.

We retrospectively identified 270 consecutive patients who underwent joint replacement surgery or intercalary spacing for skeletal metastases in the appendicular skeleton from January 1, 2003 to December 31, 2013. We collected intraoperative (duration of surgery, extent of bone resection, and blood loss), demographic (age, gender, American Society of Anesthesiologist score [ASA score], and Karnofsky score), and disease-specific (primary cancer) variables. An association with 30-day mortality was addressed using univariate and multivariable analyses and calculation of odds ratio (OR).

All patients were included in the analysis. ASA score 3 + 4 (OR 4.16 [95% confidence interval, CI, 1.80–10.85], $P = 0.002$) and Karnofsky performance status below 70 (OR 7.34 [95% CI 3.16–19.20], $P < 0.001$) were associated with increased 30-day mortality in univariate analysis. This did not change in multivariable analysis. No parameters describing the extent of the surgical trauma were found to be associated with 30-day mortality.

The 30-day mortality in patients undergoing surgery for MBD is highly dependent on the general health status of the patients as measured by the ASA score and the Karnofsky performance status. The extent of surgery, measured as duration of surgery, blood loss, and degree of bone resection were not associated with 30-day mortality.

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Abbreviations: 95% CI = 95% confidence interval, ASA score = American Society of Anesthesiologist score, MBD = metastatic bone disease, OR = odds ratio.

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From the Musculoskeletal Tumor Section (MSS, TBH, MMP) and Pediatric Section (KH), Department of Orthopedic Surgery, Rigshospitalet, University of Copenhagen, Denmark.
Correspondence: Michala Skovlund Sørensen, Musculoskeletal Tumor Section, Department of Orthopedic Surgery, Rigshospitalet, University Hospital of Copenhagen, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark (e-mail: michala.skovlund@gmail.com)
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MSS: contributed to idea of concept, study design, data collection, statistical analysis and interpretation, manuscript development, and revision (principal investigator of study). KH: contributed to study design, statistical supervision, interpretation of data, and manuscript revision. TBH: data collection and manuscript revision. MMP: contributed to idea of concept, study design, data collection, statistical supervision, data interpretation, and manuscript revision (supervisor of study).
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INTRODUCTION

In the acute setting, patients with metastatic bone disease (MBD) in the appendicular skeleton often pose an extraordinary perioperative challenge. This is mainly caused by the comorbidity of patients with MBD compared with other types of orthopedic patients. Recent work evaluating a large, diverse orthopedic patient population identified MBD as a strong, independent risk factor for in-hospital mortality.[1] Furthermore, a previous study showed an increased embolic shower in patients treated with intramedullary fixation or joint replacement surgery in MBD patients compared with patients suffering from nonpathological fractures.[2]

It is well known that patient survival after surgical treatment of pathologic fractures or painful bony lesions due to MBD is relatively poor.[3–7] As such, surgical procedures are almost always considered palliative in nature, and the extent of surgery and choice of implant should be adapted to expected postoperative survival for the individual patient.[8–10] For these patients, postoperative survival is considered to depend on their general health and functional status and not the surgical trauma, as described in previous studies.[11–13] However, these studies did not consider the relative impact on mortality from various pre and perioperative factors. Since the American Society of Anesthesiologists (ASA) Physical Status classification system,[14–16] duration of surgery,[16] and blood loss[17–22] have been associated with short-term survival in other settings such as surgery of the spine and joint replacement surgery, we hypothesize that these and similar perioperative variables could be important for MBD patients as well.

We aimed to evaluate if perioperative parameters such as blood loss, extent of bone resection, and duration of surgery

TABLE 1. Patient Demographics

Number of patients	270
Female/male	110/160
Age at surgery, y; median, range	64 (21–90)
ASA group (n = 259)	
Group 1	14
Group 2	121
Group 3	115
Group 4	9
Major bone resection (n = 273)	
Yes/no	165/108
Duration of surgery, min (n = 264)	
Median (range)	156.5 (60–494)
Blood loss, mL (n = 248)	
Median (range)	937.5 (100–7000)
Karnofsky score (n = 266)	
Mean (range)	70% (30–100%)
Patients ≥70%	170
Patients <70%	96
Fracture/impending (n = 270)	
Fracture	198
Impending	72

ASA = American Society of Anesthesiologist.

were risk factors for 30-day mortality in patients having surgery due to MBD in the appendicular skeleton.

METHODS

Study Population and Design

We retrospectively identified a consecutive cohort of 270 patients who underwent joint replacement surgery (n = 270) and intercalary spacing (n = 3) for MBD at our facility, a tertiary referral center for orthopedic oncology, from 2003 to 2013 (Table 1). Three patients had 2 or 3 skeletal sites treated as a 1-stage procedure. Joints replaced were the hip (n = 210), the knee (n = 25), the shoulder (n = 29), or the elbow (n = 6), and intercalary spacers were inserted in the femur (n = 2) or the humerus (n = 1). Examples of surgical implants used are shown in Figure 1. The patients who underwent surgery in 2003 to 2008 have previously been described in Sørensen et al,[6,23] and patient demographics of the complete study cohort are shown in Table 1. All patients had adequate follow-up to establish survival at 30 days postsurgery. In case of multiple operations during the inclusion period, patients were included in the study at the time of the first operation only.

Variables

We collected intraoperative variables including duration of surgery, blood loss (counted from blood in the drains and weight of the surgical laps), and the degree of bone resection. This was chosen as parameters for describing the magnitude of the surgical trauma. The degree of bone resection was classified as major, if resection was done below the lesser trochanter at the hip, above the femoral condyles at the knee, below the surgical neck of the proximal humerus, or above the condyles of the distal humerus. In addition, age, gender, ASA score[24] from the preoperative evaluation by the anesthesiologist, and data for estimating the Karnofsky performance score[25] were collected from the patient files.

We grouped the parameters as follows: blood loss above or below the median (938 mL), duration of surgery above or below the median (157 min), ASA scores were pooled into 2 groups (1 + 2 and 3 + 4), and age as described by Bauer and Wedin[26] (below/equal to or above 65 years of age). Karnofsky performance score[25] was grouped as above/equal to or below 70%. This grouping was selected because a Karnofsky score above/equal to 70% equals patients able to care for themselves in daily activities. Primary cancers were divided into 3 different

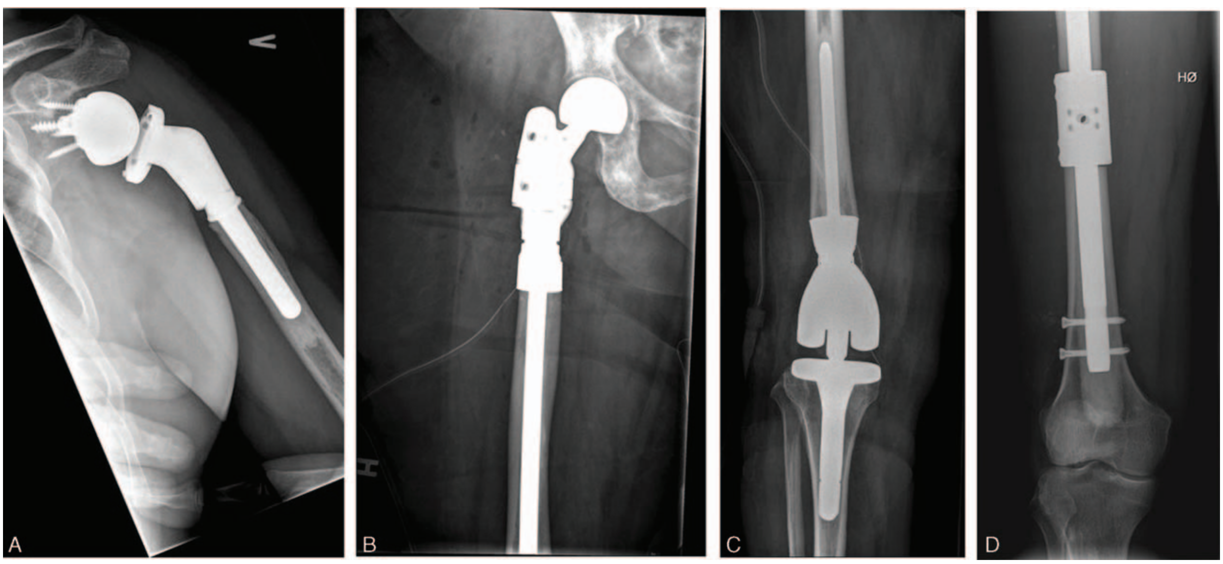

FIGURE 1. Examples of surgical implant used. (A) Proximal humerus resection and reconstruction with a tumor prosthesis (Mutars, Implantcast GmbH, Buxtehude, Germany) with a reverse shoulder joint. (B) Proximal femur resection and reconstruction with a tumor prosthesis (Segmental System, Zimmer, Warsaw, IN, USA). (C) Distal femur resection and reconstruction with a tumor prosthesis (Segmental System, Zimmer, Warsaw, IN, USA). (D) Resection of the femoral shaft and reconstruction with an intercalary spacer (Osteobridge, Merete Medical GmbH, Berlin, Germany).

TABLE 2. Type of Primary Cancer Type

	n
Slow growth	
Breast	78
Lymphoma	13
Myeloma	25
Moderate growth	
Kidney	34
Uterus	3
Prostate	27
Sarcoma	2
Fast growth	
Malignant melanoma	5
Cervix	1
Lung	39
Head and neck	4
Hepatocellular	2
Gastro intestinal	2
Pheochromocytoma	2
Colorectal	3
Bladder	7
Mediastinal	2
Angiosarcoma	2
Cancer of unknown primary site	19

Categorized into groups depending on growth rate of primary cancer. A modification of grouping proposed by Sørensen et al.[23]

prognostic groups as described by Sørensen et al[23] (Table 2). Two patients had surgery due an osteosarcoma metastasis (a primary cancer that was not described by Sørensen et al[23]) and they were grouped into the moderate growth group as proposed by Forsberg et al.[12]

Follow-Up

The follow-up on survival was until death or a minimum of 30 days postoperatively; no patients were excluded or lost to follow-up. Survival time data were collected from the Danish Civil Register on August 1, 2015 giving a complete follow-up.[27]

Statistics

Kaplan–Meier survival analysis was used for calculation of the 30-day overall survival presented with the 95% confidence interval (95% CI). Logistic regression with dichotomized variables was used, and a stepwise backward elimination multivariable logistic regression was used to identify independent risk factors for mortality, expressed as odds ratio (OR) with the 95% CI. P values < 0.05 were considered statistically significant. We used R[28] for the statistical calculations.

Ethics

The study was approved by the Danish Data Protection Agency and the Danish Health and Medicines Authority.

RESULTS

We found a 30-day overall survival of 88% (95% CI 84–92) (Figure 2). Unadjusted univariate logistic regression analyses showed a significant increased 30-day mortality with ASA score 3 + 4 (OR 4.16 [95% CI 1.80–10.85], $P = 0.002$) and Karnofsky performance status below 70 (OR 7.34 [95% CI

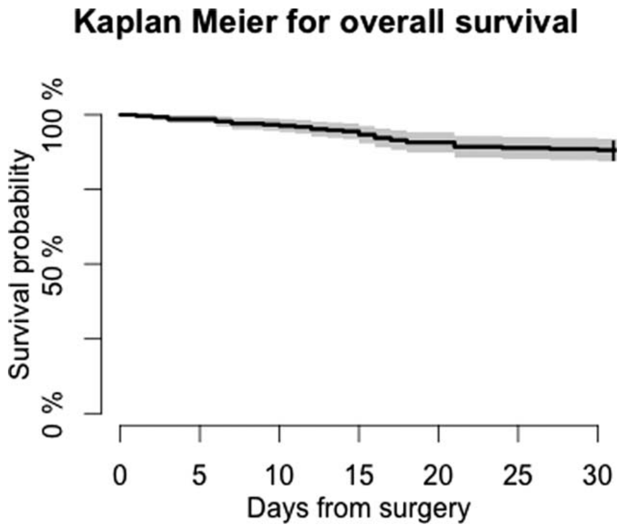

FIGURE 2. Kaplan–Meier survival curves. Thirty-day overall survival with 95% confidence interval.

3.16–19.20], $P < 0.001$; Table 3). We found no significant association between age, gender, blood loss, duration of surgery, primary cancer type, or major bony resection and the 30-day mortality in the univariate analysis (Table 3). Duration of surgery seemed to influence mortality in the univariate analysis with an OR for prolonged duration of surgery (over 157 min) of 0.46 (95% CI 0.20–1.00); however, this was not statistically significant ($P = 0.057$).

The multivariable regression analysis showed that only high ASA score and low Karnofsky score was independent risk factors for 30-day mortality with an OR for ASA score of 2.83 (95% CI 1.69–7.61), $P = 0.027$ and for Karnofsky score 5.70 (95% CI 2.39–15.18), $P < 0.001$, respectively (Table 3).

Further evaluation of the distribution of the duration of surgery in relation to ASA score revealed that confounding of low ASA score patients to prolonged surgery was present in this study (Figure 3).

DISCUSSION

We know from the literature that in general some perioperative factors such as blood loss, duration of surgery, and comorbidity poses a risk for increased mortality when performing spinal surgery or joint replacement surgery.[14–22] However, whether the extent of surgery in patients treated for MBD in the appendicular skeleton poses a risk for early mortality remains unknown. We identified a statistically significant association between 30-day mortality and the general health status of the patients expressed as the ASA score and the Karnofsky score, but we failed to demonstrate an association with intraoperative variables such as blood loss, major bone resection, and duration of surgery. We therefore conclude that the extent of surgery does not influence a patient's risk of dying within the first 30 days after surgical treatment of MBD.

The present study has limitations. Although we aimed to include patients exposed to both small and extended surgery by including patients who had regular arthroplasties as well as larger tumor-prostheses and intercalary spacers inserted, we did not have any data from patients having their MBD treated with less invasive methods such as intramedullary nailing or plating. It is also possible that other intraoperative metrics not captured by this study could add prognostic information in this patient

TABLE 3. Regression Analysis

Logistic Regression Analysis (n = 248)	Univariate Analysis Odds Ratio (95% CI)	Univariate Analysis P Value	Multivariable Analysis Odds Ratio (95% CI)	Multivariable Analysis P Value	Reference
Demographics					
Age at operation	1.87 (0.89–4.00)	0.100	n/s	n/s	<66 y
Gender	0.87 (0.41–1.86)	0.712	n/s	n/s	Male
Karnofsky group	7.34 (3.16–19.20)	<0.001*	5.7 (2.39–15.18)	<0.001*	≥70
ASA group	4.16 (1.80–10.85)	0.002*	2.83 (1.69–7.61)	0.027*	ASA group 1 + 2
Surgery characteristics					
Bone resection	0.72 (0.35–1.54)	0.399	n/s	n/s	No major bone resection
Duration of surgery	0.46 (0.20–1.00)	0.057	n/s	n/s	<157 min (median)
Blood loss	1.09 (0.49–2.44)	0.838	n/s	n/s	>938 mL (median)
Clinical					
Primary cancer					
Moderate growth cancer	0.53 (0.14–1.58)	0.282	n/s	n/s	Slow growth
Fast growth cancer	2.04 (0.91–4.67)	0.084	n/s	n/s	Slow growth

ASA = American Society of Anesthesiologist, CI = confidence interval, n/s = not significant.
*Statistically significant.

population. However, the authors find this unlikely since we attempted to capture the most objective and widely used variables, by including, for example, ASA score, primary tumor location, extent of bone resection, duration of surgery, and blood loss; each of which has been shown to be prognostic factors in other areas of orthopedic surgery.[1,9,11,15,17–22,24,29–38]

Of all variables collected, only ASA score and Karnofsky score were independently associated with 30-day mortality in the present study. Several studies have been published describing parameters that relates to peri or postoperative mortality in patients having surgery due to other pathologies than MBD. Only 1 study[32] has investigated if any perioperative variables were associated with early mortality after surgery due to MBD in the proximal femur and acetabulum. Quinn and Drenga[32] were not able to identify any association between early mortality and blood loss, duration of surgery, ASA score, type of implant, or extent of resection. However, they found a marginally significant association between the presence of a pathological fracture and early mortality with an OR 8.37 (95% CI 0.96–73.30). ASA score has been verified as a predictor for early mortality in the literature, when performing orthopedic procedures in the spine or joint replacement surgery[15,19,20,29,30,34,35] so it is plausible that the ASA score

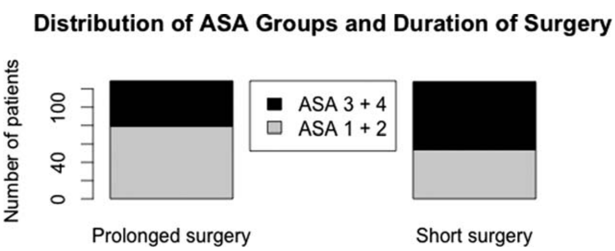

FIGURE 3. Histogram showing the distribution of ASA groups in patients with short and long surgery duration. This shows a selection of low ASA score patients to long surgical time. ASA = American Society of Anesthesiologist.

is of great importance, also when performing surgery due to MBD in the appendicular skeleton as shown in our study.

A study from the Institutional Joint Registry, Mayo Clinic, included a historical cohort of 12,727 patients undergoing surgery with total hip arthroplasty and 12,484 patients with total knee replacement.[31] They identified high ASA score (groups 3–4) and high Deyo-Charlson comorbidity index to be associated with increased 90-day mortality. Although this study only included patients suffering from a nonmalignant disease, we feel that similarities of the surgical procedures allow this study to be compared with our study to support the evidence that the general health status of the patient is the main risk factor for postoperative mortality. Wolters et al[29] found an association between increasing ASA score and increased risk of perioperative blood loss and duration of surgery, though these variables were not found to be independent predictors for postoperative mortality in our study.

Other studies have investigated if blood loss and duration of surgery pose a risk for postoperative mortality[15,33,38] and there seems to be lacking evidence as to whether or not these parameters are true predictors or just strongly related to the ASA score as indicated in 2 previously published studies.[17,18] The literature is contradictory when it comes to the relation between blood transfusions and postoperative mortality.[19,20,22] In our institution, the amount of blood loss is well documented with weighing of surgical laps and measurement of drains. Evidence of blood transfusions relation to postoperative mortality seems very weak. This might be due to the fact that using units of blood transfusion as exposure, 1 does not know whether 1 measures the effect a low preoperative hemoglobin level has on mortality, perioperative blood loss, or the true systemic reactions to transfusion and the relations to peri and postoperative morbidity as indicated by Glance et al.[21] In theory, tumors with known high blood supply (e.g., kidney tumors) might pose a risk of peri and postoperative mortality due to the risk of major bleeding. However, our study was not powered to detect such a relation with only 16 patients having kidney tumor as primary cancer (average bleeding 1712 mL;

range 250–7000 mL). With this in mind, the authors feel confident that perioperative blood loss within nonextreme bleeding situations does not pose a risk for increased postoperative mortality in patients having surgery due to MBD in the appendicular skeleton.

Prolonged surgery seemed, in the univariate analysis, to be a protective factor against high 30-day mortality rate. However, this is most likely to be the result of the bias introduced into the study by the institutional treatment philosophy: to reserve an extended surgical approach for those patients who are estimated to have a long postoperative survival. By extension, this indicates a propensity toward less invasive or palliative surgery in patients with high ASA scores, further emphasizing the importance of patient selection and survival estimates. We have shown an inverse relationship between ASA groups and duration of surgery, as shown in Figure 3, which supports this theory.

We did not find that the type of primary tumor poses a risk for 30-day mortality. Still, the authors expect that type of primary cancer poses a risk for mortality on a longer timeline. Our choice of 30-day mortality to measure early postoperative mortality was based upon the literature[15,19–21,38,39] but can be debated. Lie et al[36] propose the use of a 21-day postoperative period for measuring early postoperative mortality and argue that 60 to 90 days might be a wrong timeline. Timeline of 21- or 30-day did not make a difference in our study.

In conclusion, our findings showed that the surgical trauma does not pose an increased risk for death within the first 30 days postoperatively. Early mortality in patients undergoing joint replacement and intercalary replacement surgery for MBD is dependent on the general health status of the patients, as measured by the ASA score and Karnofsky performance score. The extent of surgery, measured as duration of surgery, blood loss, and extent of bone resection are not associated with 30-day mortality. We therefore advise that surgeons decide a surgical approach upon residual life expectancy and choose an implant that will outlive the patient, as opposed to fear that the extent of surgery and the surgical trauma poses a risk of increased mortality in this patient group. Nevertheless, further research is necessary to determine whether intraoperative or other variables are associated with very short postoperative survival in patients with MBD.

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