Surgery for skeletal metastases in lung cancer
Complications and survival in 98 patients

Rudiger J Weiss and Rikard Wedin

Background and purpose  Most lung cancer patients with skeletal metastases have a short survival and it is difficult to identify those patients who will benefit from palliative surgery. We report complication and survival rates in a consecutive series of lung cancer patients who were operated for symptomatic skeletal metastases.

Methods  This study was based on data recorded in the Karolinska Skeletal Metastasis Register. The study period was 1987–2006. We identified 98 lung cancer patients (52 females). The median age at surgery was 62 (34–88) years. 78 lesions were located in the femur or spine.

Results  The median survival time after surgery was 3 (0–127) months. The cumulative 12-month survival after surgery was 13% (95% CI: 6–20). There was a difference between the survival after spinal surgery (2 months) and after extremity surgery (4 months) (p = 0.03). Complete pathological fracture in non-spinal metastases (50 patients) was an independent negative predictor of survival (hazard ratio (HR) = 1.8, 95% CI: 1–3). 16 of 31 patients with spinal metastases experienced a considerable improvement in their neurological function after surgery. The overall complication rate was 20%, including a reoperation rate of 15%.

Interpretation  Bone metastases and their subsequent surgical treatment in lung cancer patients are associated with high morbidity and mortality. Our findings will help to set appropriate expectations for these patients, their families, and surgeons.

Patients and methods  This study was based on data recorded in the Karolinska Skeletal Metastasis Register (Wedin and Bauer 2005). The register is a quality-control database that prospectively collects individual-based information for cancer patients admitted to Karolinska University Hospital in Stockholm. All data are collected based on the national registration number (a 10-digit number), which is unique for each Swedish resident. The criterion for inclusion in the database is surgical treatment for complete or impending fractures due to skeletal metastasis.

The register gathers data on patient identity, age, sex, primary tumor, location of metastases, type of pathological fracture, and surgical treatment such as method of fixation, type of implant, and postoperative complications. It includes staging information for patients diagnosed with lung cancer.
We identified 98 individual lung cancer patients (52 females) treated surgically for skeletal metastatic lesions. The median age at surgery was 62 (34–88) years. Most patients in this cohort (n = 88) were current or former smokers at diagnosis of the disease. Adenocarcinoma was found in most cases (n = 58) followed by squamous cell carcinoma (n = 14) (Table 1). The lung cancer patients were grouped in the following stages: 11 IA + IB, 11 IA + IIB, 5 IIIA, 73 IIIB + IV, and such data were missing for 8 patients.

### Table 1. 98 lung cancer patients with skeletal metastases

| Category                                             | Total | Males | Females |
|------------------------------------------------------|-------|-------|---------|
| Number of patients                                   | 98    | 46    | 52      |
| Median age at diagnosis (years) range                | 62–88 | 60–88 | 63–88   |
| Smoking status at diagnosis                          |       |       |         |
| Former smoker                                        | 47    | 21    | 26      |
| Current smoker                                       | 41    | 20    | 21      |
| Never smoker                                         | 10    | 5     | 5       |
| Histopathology                                       |       |       |         |
| Non-small cell cancer                                | 58    | 25    | 33      |
| Adenocarcinoma                                       |       |       |         |
| Squamous cell carcinoma                              | 14    | 8     | 6       |
| Low differentiated                                   |       |       |         |
| non-small cell cancer                                | 8     | 4     | 4       |
| Large cell carcinoma                                 | 7     | 3     | 4       |
| Small cell carcinoma                                 | 6     | 3     | 3       |
| Other cancers                                        | 5     | 3     | 2       |
| Skeletal metastasis                                  |       |       |         |
| Femur                                                | 46    | 18    | 28      |
| Vertebra                                             | 31    | 12    | 19      |
| Humerus                                              | 16    | 2     | 14      |
| Other                                                | 8     | 2     | 6       |
| Type of surgical procedure                           |       |       |         |
| Internal fixation                                    | 34    | 10    | 24      |
| Endoprostheses                                       | 32    | 11    | 21      |
| Spinal decompression + instrumentation               | 17    | 12    | 5       |
| Spinal decompression                                 | 15    | 12    | 3       |
| Other                                                | 3     | 1     | 2       |
| Preoperative treatment (primary tumor)               |       |       |         |
| Chemotherapy                                         | 52    | 24    | 28      |
| Radiotherapy                                         | 27    | 10    | 17      |
| Lobectomy                                            | 12    | 5     | 7       |
| Postoperative treatment (bone metastasis)            |       |       |         |
| Radiotherapy                                         | 59    | 28    | 31      |

**Statistics**

Median values and ranges were used as descriptive statistics. Kaplan-Meier analysis was used to construct the cumulative survival with 95% confidence intervals (CIs). The time between diagnosis of lung cancer and death and time between surgical procedure and death were included in the survival analysis. The log-rank test was used to compare survival after extremity surgery with spine surgery.

The Cox multiple-regression model was used to study risk factors for death related to the patient and to the surgical procedure. The results were expressed as hazard ratios (HRs) with corresponding 95% CI. If a HR was > 1, the patients at risk were dying at a faster rate than the patients in the reference group. The assumption of proportional hazards was investigated by hazard function plots and log-log plots for all covariates. No signs of insufficient proportionality were detected in the hazard functions and the log-log plots ran parallel for all covariates. The factors studied in the univariate Cox model were as follows: age, sex, smoking status, type of lung cancer, staging, location of skeletal metastasis, type of pathological fracture, preoperative hemoglobin levels, time period of surgery (1987–1996 vs. 1997–2006) and perioperative chemotherapy and radiotherapy (Table 1). Any variable whose univariate test had a p-value of < 0.25 was considered as a candidate for the multivariate model along with all variables of known biological importance. Wilcoxon’s signed ranks test was used to compare preoperative and postoperative neurological function in patients with spine metastases. The level of significance was set at p ≤ 0.05. All statistical analyses were performed using the PASW statistics package version 18 (SPSS Inc., Chicago, IL).

**Results**

Most metastatic bone lesions were located in the femur and vertebra. Of the 31 vertebral lesions, 22 were located in the thoracic spine and 9 in the lumbar spine. 53 of 70 non-spinal lesions had caused complete pathological fractures. Regarding treatment of the primary tumor, more than half of the patients (n = 52) had chemotherapy and 27 had radiotherapy. Postoperative radiotherapy for the operated lesions was registered in 59 patients (Table 1). None of the patients were lost to follow-up, and none were still alive at the time of this analysis.

The neurological function in patients with spine metastases improved after surgery (p = 0.001). 16 of the 31 patients gained at least 1 Frankel grade, 14 maintained their neurological function, and 1 patient deteriorated (Table 2). The main indication for surgery in these patients was spinal cord compression (n = 29) or painful instability (n = 2).

**Survival analysis**

The median survival time after surgery of skeletal metastatic lesions was 3 (0–127) months. Males had a median survival...
The cumulative 6-, 12-, and 18-month survival after surgery was 24% (CI: 15–33), 13% (CI: 6–20), and 6% (1–11) respectively (Figure).

There was a difference between the median survival time after spinal surgery (2 (0–15) months) and after extremity surgery (4 (0–127) months) (p = 0.03) (Table 3).

The univariate Cox regression analysis revealed an increased risk of death after surgery for patients with complete pathological fracture, metastatic lesions in the vertebra, preoperative hemoglobin levels less than 10 g/dL, small cell cancer, and the absence of postoperative radiotherapy. The multivariate Cox analysis with the above 5 variables and age and sex showed that complete pathological fracture was a significant predictor of survival (Table 4). All the other factors studied—such as age, sex, smoking status, staging, time period of surgery, and chemotherapy—were not associated with an increased risk of death.

Reoperations and complications
The overall complication rate including reoperations was 20/98. 15 failed reconstructions in 14 patients led to a new operation. The reasons for these reoperations were poor initial fixation, local tumor progression, periprosthetic fracture, deep infection, paraplegia, material failure, nonunion, and technical error. The median time to failure was 1 (0–13) months (Table 5).

Complications that were treated non-surgically were seen in 5 of the patients, including wound infection, gastric bleeding, poor initial fixation, and technical error (Table 6).
Discussion

Our main finding was the short survival of lung cancer patients after surgery for skeletal metastases. Complete pathological fracture was identified as an independent risk factor for death. Moreover, a high complication rate poses a considerable burden to the patients.

The overall median survival time after surgery was only 3 months, and just 13% of the patients were still alive 1 year postoperatively. 3 of 4 patients were already classified as having an advanced stage of lung cancer at the diagnosis of the primary tumor. The 1-year survival rate of patients operated for skeletal metastases from various primary tumor sites is limited, and ranges between 30 and 54% (Bono et al. 1991, Bauer and Wedin 1995, Durr and Refior 1998, Bohm and Huber 2002, Hansen et al. 2004, Lin et al. 2007). Differences in patient selection, type of primary tumor, and indications for surgery may explain the spread in survival time. We have previously reported on the surgical outcome of 107 patients with skeletal breast cancer metastases. The postoperative median survival in these patients was 8 months (Wedin et al. 2001). Sugiura et al. (2008) reported a median survival time of 7 months in 118 patients with bone metastasis from lung cancer; however, only one third of these patients underwent surgery. Nathan et al. (2005) found that in patients with various types of cancer metastases, lung cancer patients fared the worst with a median survival time of 4 months. The short survival time has also been reported by other authors (Bauer and Wedin 1995, Durr and Refior 1998, Katagiri et al. 2005).

We found a shorter survival after operations for skeletal metastases of the spine (2 months) as compared to the extremities (4 months). Bauer and Wedin (1995) described a median 1-year survival of 25% after spinal surgery and 31% after extremity surgery, based on all types of cancer metastases. However, this difference was not statistically significant.

The decision between a surgical and non-surgical treatment of a patient with bone metastasis is influenced by the anatomical location, the tumor type, the extent of the tumor, the gen-

Table 5. Reoperations after surgery for skeletal metastases in lung cancer patients

| Sex, age, histology | Localization       | Primary operation                        | Time (months) to and reason for failure | Treatment       |
|---------------------|--------------------|------------------------------------------|----------------------------------------|-----------------|
| F, 57, b            | Humerus, proximal  | Intramedullary nail                      | 5, local tumor progression             | Hemiarthroplasty|
| F, 63, c            | Humerus, distal    | Plate                                    | 3, material failure                    | Plate           |
| F, 62, a            | Acetabulum         | Acetabular reinforcement ring + total joint arthroplasty | 1, deep infection | Debridement     |
| F, 62, a            | Femur, proximal    | Total joint arthroplasty                 | 9, periprosthetic fracture             | Modular tumor prosthesis |
| F, 74, a            | Femur, proximal    | Hemiarthroplasty                         | 3, periprosthetic fracture             | Modular tumor prosthesis |
| M, 45, a            | Femur, trochanteric| Sliding hip screw                        | 1, poor initial fixation               | Total joint arthroplasty |
| M, 73, b            | Femur, trochanteric| Sliding hip screw                        | 1, poor initial fixation               | Exchange of screw |
| F, 62, a            | Femur, subtrochanteric | Hemiarthroplasty                        | 4, poor bone stock                     | Total joint arthroplasty |
| M, 53, a            | Acetabulum         | Acetabular reinforcement ring + total joint arthroplasty | 13, non-union + local tumor progression | Hemiarthroplasty |
| M, 56, a            | Vertebra, thoracic | Decompression                            | 0, paraplegia (hematoma)               | Plate           |
| M, 55, d            | Vertebra, thoracic | Decompression + instrumentation          | 8, local tumor progression             | Removal of hematoma |
| F, 48, a            | Vertebra, thoracic | Decompression + instrumentation          | 0, poor initial fixation               | Reinstrumentation|
| M, 72, b            | Vertebra, thoracic | Decompression                            | 1, deep infection                      | Debridement     |

Table 6. Complications after surgery for skeletal metastasis in lung cancer patients

| Sex, age, histology | Localization       | Primary operation                        | Time (months) to and reason for failure | Treatment       |
|---------------------|--------------------|------------------------------------------|----------------------------------------|-----------------|
| F, 75, a            | Femur, distal      | Intramedullary nail                      | 0, fatal gastric bleeding               | Non-surgical    |
| M, 48, c            | Vertebra, thoracic | Decompression + instrumentation          | 0, wound infection                      | Non-surgical    |
| F, 48, a            | Vertebra, thoracic | Decompression + instrumentation          | 0, gastric bleeding                     | Non-surgical    |
| M, 62, b            | Vertebra, thoracic | Decompression + instrumentation          | 0, technical error                     | Non-surgical    |
| M, 55, d            | Vertebra, thoracic | Decompression                            | 1, wound infection                      | Non-surgical    |

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| F, 48, a            | Vertebra, thoracic | Decompression + instrumentation          | 0, gastric bleeding                     | Non-surgical    |
| M, 62, b            | Vertebra, thoracic | Decompression + instrumentation          | 0, technical error                     | Non-surgical    |
| M, 55, d            | Vertebra, thoracic | Decompression                            | 1, wound infection                      | Non-surgical    |

a adenocarcinoma. b squamous cell carcinoma. c large cell carcinoma. d other.
eral medical condition of the patient, and expected survival time. Surgery may be chosen if the patient is healthy enough and life expectancy is sufficiently long to benefit from pain relief, improved mobility, and care. If there is no expectation that the survival may be long enough for the patient to recover and truly benefit from surgical procedures, other palliative therapies may be chosen instead. However, this may restrict the patients involved to bed or chair.

New therapies have been introduced to improve the survival of patients with lung cancer (Giaccone et al. 2006, Sandler et al. 2006). The median survival of patients with advanced lung cancer has increased from 6 months to 12 months with the introduction of new treatment regimens such as chemotherapy in combination with a monoclonal antibody, which acts as an angiogenesis inhibitor (Rosen et al. 2003, Sandler et al. 2006). However, the efficacy of promising new agents in lung cancer patients concerning treatment of metastases in bone, which is one of the most common metastatic sites, is unknown (Langer and Hirsh 2010).

Some authors have stated that a life expectancy of at least 2 months is usually required for meaningful surgery of limb metastases (Harrington et al. 1976), and of 3 to 6 months for spinal lesions (Cybulski et al. 1987, Atanasiu et al. 1993, Tomita et al. 1994). We think that stabilization of long-bone fractures is almost always justified unless the patient has reached a terminal stage. However, we must raise the question of whether spinal surgery would be justified in our cohort with a median survival time of barely 2 months.

Decision making regarding the management of pathological fractures is complex, balancing tumor biology, biomechanics, and functional outcome goals. We believe that surgery for vertebral metastases may be the best alternative in patients who are expected to live for at least another 2–3 months if surgery leads to a substantial difference, i.e. if the patient can avoid being bedridden or can retain the ability to ambulate independently.

More than half of our patients with spine disease improved considerably, i.e. at least 1 Frankel grade. Still, a 2-month survival will be necessary in most cases to gain real benefit from the procedure, considering postoperative pain, surgical complications, and sometimes slow neurological recovery. Today, we are more cautious with patient selection for surgery because of the short survival rate in combination with a high complication rate in this cohort.

We identified low preoperative hemoglobin levels as a negative predictor of survival. Hemoglobin has been used as a prognostic factor in metastatic prostate cancer (Matzkin et al. 1993) and in heterogeneous groups of cancer patients (Hansen et al. 2004, Nathan et al. 2005). In the multivariate analysis, we could show that complete pathological fractures had an unfavorable prognosis for survival, as described by other authors (Sugiura et al. 2008).

Almost all of the patients (14/16) with humeral metastases had complete fractures. This is probably because impending fractures in non-weight bearing bones frequently escape diagnosis due to the relative absence of load-related pain.

We found a complication rate of 20%. The total failure rate leading to reoperation of previously operated metastatic sites was 15%. We have previously reported a reoperation rate of 12% in skeletal breast cancer metastases (Wedin et al. 2001) and a failure rate of 11% in patients treated for metastatic lesions of the long bones (Wedin et al. 1999). Nathan et al. (2005) described a similar reoperation rate (11%) after surgery in patients with different types of cancer. Failures are often due to local tumor progression, stress fracture, implant failure due to nonunion, or poor fixation of osteosynthetic devices in insufficient bone stock. They appear equally often in the extremities and in the spine (Yazawa et al. 1990, Bono et al. 1991), as in our series. The high reoperation rate in our study may also be partly explained by the fact that during the 20-year time frame, many orthopedic surgeons—not all sub-specialized in orthopedic oncology—performed the operations.

Our study was limited by confounding factors. Changes in diagnostics, in selection of patients, in perioperative treatment, in indications for surgery, and in methods of fixation during the 20-year study period may have influenced the results. To address the question of whether or not to operate on lung cancer patients with bone metastases, one would want to know the survival prognosis for all patients—not only the ones who (historically) have undergone surgery—as they represent a selected group of patients. This could not be investigated, however, as our register covers only surgically-treated cancer patients.

Despite its shortcomings, the present work represents the largest follow-up study of lung cancer patients after surgery for skeletal metastases. Most studies have analyzed heterogeneous populations of patients with bone metastasis. Most analyses on indications for surgery have been based on the treatment of breast and prostate cancer, which is not necessarily applicable to lung cancer patients.

In conclusion, our findings highlight the fact that surgical treatment of bone metastases in lung cancer patients is associated with high morbidity and mortality. Thus, the selection process for the (probably) few lung cancer patients who will benefit from surgical treatment is important, especially those with spinal cord compression.

Both authors contributed to the planning of the study, interpretation of the results, and editing of the manuscript. RJW performed the data analysis and wrote the manuscript. RW collected the data.

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No competing interests declared.
