Longitudinal survival trends of patients with cancer with surgically managed appendicular metastatic bone disease: systematic review

**Background:** Advances in systemic cancer therapies have improved survival for patients with metastatic carcinoma; however, it is unknown whether these advances have translated to improved survival for patients with appendicular metastatic bone disease (A-MBD) after orthopedic interventions. We conducted a study to evaluate the trend in overall survival for patients who underwent orthopedic surgery for A-MBD between 1968 and 2018.

**Methods:** A systematic search of Embase and Medline to identify studies published since 1968 evaluating patients treated with orthopedic surgery for A-MBD was conducted for a previously published scoping review. We used a meta-regression model to assess the longitudinal trends in 1-, 2- and 5-year overall survival between 1968 and 2018. The midpoint year of patient inclusion for each study was used for analysis. We categorized primary tumour types into a tumour severity score according to prognosis for a further meta-regression analysis.

**Results:** Of the 5747 studies identified, 103 were retained for analysis. Meta-regression analysis showed no significant effect of midpoint study year on survival across all time points. There was no effect of the weighted average of tumour severity scores for each study on 1-year survival over time.

**Conclusion:** There was no significant improvement in overall survival between 1968 and 2018 for patients with A-MBD who underwent orthopedic surgery. Orthopedic intervention remains a poor prognostic variable for patients with MBD. This finding highlights the need for improved collection of prospective data in this population to identify patients with favourable survival outcomes who may benefit from personalized oncologic surgical interventions.

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The burden of bone metastasis is considerable, with an estimated 280,000 new cases per year in the United States. The extremities, particularly the femur, humerus and tibia, are common sites of bone metastasis. The morbidity associated with appendicular metastatic bone disease (A-MBD) poses a challenge for orthopedic surgeons, as bony involvement is a sign of advanced disease and affects quality of life substantially. The role of orthopedic surgery in this palliative setting is not to improve survival but, rather, to alleviate pain and restore musculoskeletal function for the remaining lifespan of the patient while balancing the morbidity associated with surgery.

Overall survival in patients with cancer is increasing annually. Improvements in survival have also been observed in those with metastatic cancer, including difficult-to-treat metastatic cancers such as renal cell carcinoma, lung cancer and melanoma. Using Surveillance, Epidemiology, and End Results (SEER) Program data, Jemal and colleagues found significant improvements from 1975 to 2012 in 5-year survival for metastatic cancers to all distant sites, especially for lung cancer (relative increase 122%), breast cancer (relative increase 80%) and renal cell cancer (relative increase 72%), all of which commonly metastasize to bone. The improvement in survival among patients with metastatic cancer has been attributed to modern targeted systemic therapies, earlier detection of metastatic disease, more aggressive disease management, and improved screening and diagnostic imaging.

Current orthopedic management of A-MBD is based on the premise that survival for these patients remains limited. Deciding whether to operate and which reconstructive technique to use requires knowledge of the patient’s prognosis and is heavily influenced by a variety of factors, such as primary tumour type, extent of metastatic disease, functional status and, more recently, molecular cancer genotypes predictive of sensitivities to targeted therapies. Although standard protocols are lacking, patients with extensive disease and a predicted short life expectancy are often treated with less-invasive strategies, whereas those with estimated longer life expectancies are considered for invasive procedures and more durable reconstructive strategies. Furthermore, in patients with oligometastatic disease or favourable molecular profiles, more aggressive orthopedic procedures may have local control or survival benefits. However, outcomes after orthopedic surgery in this population are difficult to determine given the lack of prospective research in this field and the heterogeneity in primary tumour types, location of metastases, extent of metastatic disease and the patient’s overall health. One-year survival rates are very heterogeneous, ranging from 17% to 69.5% for all primary tumour types since 1990.

It remains unclear whether the improved outcomes seen in patients with metastatic cancer have been attained in those with A-MBD after orthopedic management. To our knowledge, there are no longitudinal studies analyzing trends in mortality rates in this population. The purpose of this study was to evaluate the trends from 1968 to 2018 in overall survival in patients who underwent orthopedic surgery for A-MBD to determine whether survival in this patient population improved over time. We chose this time frame as a 50-year period in which major advances were made in cancer care.

**Methods**

The study has been registered with the International prospective register of systematic reviews (PROSPERO) (registration CRD42018102980). The systematic review protocol was conducted with the use of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

**Search strategy**

A comprehensive literature search of Medline and Embase databases to identify studies published since 1968 evaluating patients treated with orthopedic surgery for A-MBD was conducted for a previously published scoping review. The search strategy is presented in Appendix 1 (available at canjsurg.ca). The search was updated in September 2018 by 3 independent reviewers (A.A., J.K.K. and M.M.), and studies identified from the scoping review were screened for inclusion. A fourth independent reviewer (C.H.) repeated the search in full. Any discrepancy between reviewers was discussed and reconciled. The search limits were English language, studies conducted in humans and full text available. The abstracts were screened independently for inclusion, then full-text screening was performed for final inclusion. In addition, reference lists of retrieved papers and review articles were screened for inclusion.

**Study selection**

Key inclusion criteria were metastatic carcinoma or hematologic malignant disease to bone, surgery to treat A-MBD, age older than 18 years and survival outcomes reported. Studies were excluded if there were fewer than 10 patients, or if they included primary bone tumours or axial bone metastases (spine or pelvis). Only complete data sets with adequate follow-up to report survival data were included; abstracts, reviews, technique papers and unpublished studies were excluded.

For each eligible study, we recorded the following information: year of publication, level of evidence, first year of patient inclusion, last year of patient inclusion, number of patients, age, median survival, mean survival, 1-year survival, 2-year survival, 5-year survival, primary tumour types included, survival by primary tumour type and method of fixation.
Assessment of methodologic quality and level of evidence

We assessed the methodologic quality of all included studies using the Methodological Index for Non-Randomized Studies (MINORS) scale, a validated scale for nonrandomized studies.26 Studies with a score of 12 or higher were considered to have “high” methodologic quality; those with a score of 9–11, “moderate” methodologic quality; and those with a score of 8 or less, “low” methodologic quality. All included studies were assessed independently by 2 authors (A.A. and C.H.); discrepancies were resolved by consensus. In addition, we assessed level of evidence using Spindler and colleagues’27 chart.

Statistical analysis

The primary outcomes of interest were overall survival and the longitudinal trend of overall survival from 1968 to 2018. We defined survival as the time from orthopedic surgery until death. We analyzed the data according to the median date of the capture period during which patients were included in each study. All data were summarized descriptively. Quality-assessment scores were reported as mean and standard deviation (SD). We used a random-effects meta-regression model to assess differences in overall survival distributions over the study period. We analyzed 1-year, 2-year and 5-year survival independently. We used the arcsine data transformation for meta-regression analysis and to obtain 95% confidence intervals (CIs). For all analyses, we report the $I^2$ statistic to estimate the variation across studies attributable to heterogeneity. We performed subgroup analysis of primary tumour type to determine mean 1-year survival in patients with breast, renal and lung cancer. Inadequate study numbers prevented further analysis of other primary tumours or any longitudinal survival analysis for any primary tumour subtypes.

We also used a meta-regression model to correlate the trend in primary tumour distribution within the data set with overall survival over time. To develop a simple prognostic scale for cancer diagnosis, we categorized each primary tumour type by prognosis based on the 5-year relative survival rates published in the 2018 SEER database. Breast, prostate and thyroid cancer and multiple myeloma were assigned a severity score of 1 (5-yr survival rate > 20%); renal cell, gastrointestinal and other cancers (apart from lung and hepatocellular cancer) and melanoma were assigned a severity score of 2 (5-yr survival rate 10%–20%); and lung and hepatocellular cancer were assigned a severity score of 3 (5-yr survival rate < 10%). We calculated a weighted average of the severity scores for each study and included it in the meta-regression to determine whether it influenced survival over time. There were insufficient data reported to use other markers of disease severity, such as presence of visceral metastasis, pathologic fracture, multiple bone metastases and Eastern Cooperative Oncology Group Scale of Performance Status, in this score.

RESULTS

The literature search identified 5747 unique titles through the database search and review of cited publications. After primary and secondary screening, 103 studies were retained for analysis (Figure 1).

A total of 6994 patients were included across all studies. The mean age was 62.1 (SD 7.1) years ($n = 6418$). The primary tumour type was reported for 5728 patients, and the method of fixation was reported for 5856 patients. The baseline characteristics by decade are summarized in Table 1.

Methodologic quality and level of evidence

The mean MINORS score was 7.2 (SD 3.9), indicating low methodologic quality. Eleven studies were deemed level III evidence, and the remainder were deemed level IV evidence.
Survival trends

One-year survival was reported in 67 studies, 2-year survival in 39 and 5-year survival in 18. The average overall 1-year survival rate was 41% (95% CI 37%–45%) across all decades; the rate for the most recent period, 2010–2018, was 29% (95% CI 22%–38%) (Figure 2A). Meta-regression analysis showed no significant effect of midpoint study year on 1-year survival ($p = 0.8$), 2-year survival ($p = 0.6$) or 5-year survival ($p = 0.6$) (Figure 3). Heterogeneity among studies was high for 1-year ($I^2 = 89%$), 2-year ($I^2 = 84%$) and 5-year ($I^2 = 64%$) survival. Median survival was reported in 39 studies, and mean survival was reported in 59 studies; these trends are depicted in Figure 4. Owing to the inconsistency in follow-up duration and reporting methods, meta-regression of mean and median survival was not performed.

Primary tumours

One-, 2- or 5-year survival by primary tumour type was reported in 12 studies. There were insufficient data to perform meta-regression; however, we were able to perform subgroup analysis for 1-year survival in 10 studies including patients with breast, renal and lung cancer. This analysis showed mean 1-year survival rates of 53% (95% CI 36%–71%, $F = 66%$) from 1996 to 2016 for breast cancer, 66% (95% CI 50%–79%, $F = 85%$) from 1987 to 2001 for renal cancer, and 41% (95% CI 22%–60%, $F = 11%$) from 1996 to 2001 for lung cancer (Figure 5).

Primary tumour severity

Meta-regression showed no effect of tumour severity score on overall 1-year survival ($p = 0.9$). Meta-regression including both severity score and midpoint year of study also showed no effect on 1-year survival ($p = 0.3$ and 0.5, respectively). This indicates that there was no association between the primary tumour severity score of published studies and 1-year overall survival.

Mode of fixation

Endoprosthetic reconstruction including tumour prosthesis or arthroplasty was performed in 2493 cases (42.6%),...
and intramedullary nailing or plating procedures were performed in 3184 cases (54.4%) (Table 1). Mode of fixation by decade is presented in Figure 6.

**DISCUSSION**

The introduction of targeted molecular therapies and immune-based therapies as well as improved screening and diagnostic imaging has significantly improved survival outcomes for the general population of patients with metastatic cancer. \(^\text{11-13}\) Large population data sets have repeatedly shown improved outcomes for patients with metastatic breast, lung and renal cell cancer and melanoma. \(^\text{7-9}\) However, among the studies included in this review, 1-, 2- and 5-year survival of patients with A-MBD undergoing orthopedic management did not improve statistically significantly from 1968 to 2018.

There are several possible explanations for the lack of observed improvement in our study. Bone metastases and skeletal-related events are known negative prognostic factors for overall survival. \(^\text{91-96}\) Furthermore, inferior clinical outcomes and lower therapeutic response rates have been reported in patients with bone metastases treated with novel immunotherapies and targeted molecular therapies compared to other sites of metastatic disease. \(^\text{97-100}\) Our results suggest that survival of patients with MBD who have undergone orthopedic surgery remains poor. With improved imaging techniques, metastatic disease is diagnosed much earlier than in previous decades. \(^\text{101}\) At the time patients require orthopedic intervention, the lead time of advanced imaging techniques may be negated, especially since the indications for orthopedic intervention have not changed over time, and hence this patient population actually has more advanced disease than generalized patients with metastatic cancer reported in large population data sets. \(^\text{7-9}\) It is also possible that orthopedic intervention studies have yet to show the survival improvements trending in patients with advanced metastatic cancer. For example, Caswell-Jin and colleagues performed a systematic review to evaluate survival in patients with metastatic breast cancer and found no survival improvement from 1980 to 1990 but did find survival improvement from 1990 to 2010.

Another potential confounder is the higher proportion of primary cancers with the poorest prognosis (lung, liver,
Fig. 3. Estimates of A) 1-year, B) 2-year, and C) 5-year survival by midpoint year of patient inclusion. Error bars represent standard deviations.
Fig. 4. A) mean survival by midpoint year of patient inclusion. B) median survival by midpoint year of patient inclusion.

Fig. 5. Subgroup analysis of 1-year survival for A) breast cancer, B) renal cell cancer, and C) lung cancer by midpoint year of patient inclusion. Error bars represent standard deviations.
gastrointestinal, renal) represented in more recent publications. To address this, we performed a meta-regression examining tumour severity score, as defined by recent SEER data on 5-year prognosis by primary tumour type, which did not show a significant effect on 1-year survival. Meta-regression including both severity score and midpoint year of study also showed no effect on 1-year survival. This supports the hypothesis that patients with A-MBD requiring orthopedic surgery represent a population with a very poor prognosis, regardless of primary tumour type. However, these results were likely influenced by the substantial heterogeneity between studies, and our analysis may not adequately model the effect of primary tumour type on survival after orthopedic surgery.

We were unable to analyze other important prognostic factors, such as the presence of visceral metastasis, multiple bony lesions, Eastern Cooperative Oncology Group Scale of Performance Status and pathologic fracture, that help surgeons predict survival in this population. Predictive clinical decision-support tools such as PATHFx (https://www.pathfx.org) that account for these variables may be used to provide objective data on life expectancy to surgeons and patients, and assist surgical decision-making.

We performed subgroup analysis only for breast, renal and lung cancer, as there were insufficient data to perform subgroup analysis for all tumour types. Breast cancer is commonly reported as a positive predictor of survival, with 1-year survival rates in the literature ranging from 45% to 59%. The mean 1-year survival rate in our study was 53% (95% CI 36%–71%). Variable survival rates have been reported for renal cell carcinoma. We found a mean 1-year survival rate of 66% (95% CI 50%–79%). Lung cancer is commonly a negative prognostic indicator, with a reported 1-year survival rate of 30%. The mean 1-year survival rate in our study was 41% (95% CI 22%–60%). Consistent with previous studies, the femur was the most common location of metastatic disease. There were insufficient data on outcomes by location of bone lesion to perform subgroup analysis.

**Limitations**

The low MINORS scores of the included studies is perhaps the largest limitation of our study. The majority of the included studies were of level IV evidence. This is consistent with previous systematic reviews on this topic, which also identified largely level IV evidence and substantial heterogeneity in study methodology. As a result, we expected that heterogeneity would be present in our review owing to the large range of years included, variable intervention types, broad patient demographic characteristics and retrospective nature of the literature in this area. Despite this heterogeneity, we feel that meta-regression was justified for analyzing the survival trends over time given the number of studies reporting 1-, 2- and 5-year survival. Owing to small numbers, we were not able to evaluate survival in specific subsets of patients with a more favourable prognosis, such as those with solitary or oligometastatic disease.

Other limitations include lack of reporting of information on primary tumour type, fixation method and survival specific to primary tumour. We were able to perform subgroup analysis of 1-year survival only for breast, renal and lung cancer owing to small numbers.

Adjuvant treatments, including radiotherapy, chemotherapy and newer immunotherapies, can influence survival. These were poorly reported in the included studies and were therefore not extracted. Varying definitions of outcome, including the type of survival statistic reported,
as well as varying duration of follow-up limited analysis substantially. We were unable to analyze mean and median survival with meta-regression owing to the heterogeneity in reporting, which limited the number of studies that could be included in the meta-regression model. In addition, the majority of patients who underwent orthopedic surgery for A-MBD between 1968 and 2018 would not be reported on in the published series, which introduced a publication bias.

Many of these identified limitations could be best addressed with a Canadian prospective registry, such as the Scandinavian Sarcoma Group registry.105

CONCLUSION

We found no improvement in overall survival between 1968 and 2018 for patients with surgically treated A-MBD. This finding is discordant with recent findings of improvements in survival over time in the general population of patients with metastatic cancer. The survival improvements observed in large population-based data sets may not reflect the poor outcomes associated with the subset of patients with A-MBD requiring orthopedic surgery. There remains a critical need to improve prospective data collection in this population to facilitate personalized surgical decision-making for this complex and diverse patient population.

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