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Editorial

The role of orthopaedic surgeons in the management of fractures in cancer patients

Cancer is the second leading cause of death worldwide. According to Global Burden of Disease Cancer Collaboration,[1] there were 17.5 million cancer cases worldwide and 8.7 million deaths in 2015. Between 2005 and 2015, cancer cases increased by 33%, with population ageing contributing 16%, population growth 13% and changes in age-specific rates contributing 4%. For men, prostate cancer was the most common cancer, and lung cancer was the leading cause of cancer death and disability-adjusted life years. For women, breast cancer was the most common cancer and the leading cause of death and disability-adjusted life years.

In Hong Kong, cancer is the number one killer, accounting for 30.5% of all death in 2016. From the data of the Hong Kong Cancer Register,[2] the most frequent cancers were colorectal cancer (16.6% of total new cancer cases), followed by lung (15.7%), breast (12.9%), prostate (6.0%) and liver (5.9%) cancers. These five cancers account for more than half of all new cancers in 2015. During the past decade (2005–2015), the number of new cancer cases in Hong Kong rose at an average annual rate of 2.9%. Compared to a decade earlier, new cases of lung (mainly adenocarcinoma in women), colorectal, breast and prostate cancers showed a substantial rise, largely because of an ageing population, while the increase in number of liver cancers was relatively modest. Since 2005, the number of increase in new cases was 100% for prostate cancer, 80% for invasive breast cancer and 80% for pancreas cancer. The risk of developing cancer before the age of 75 years is 1 in 4 men and 1 in 5 women based on the cancer statistics in 2015.

Bone is the third most common site of metastases after lung and liver. Almost all patients with multiple myeloma, 65–75% of patients with breast or prostate cancer, 60% of patients with thyroid cancer, 30–40% of patients with lung cancer and 20–25% of patients with renal cancer develop skeletal metastasis.[3] Of over 70% bone metastases, the primaries are from lung, breast, prostate, kidney and thyroid. With increased incidence and survivals, bone metastases are now seen in other primary sites. Of the five top cancers in Hong Kong, bone metastases from colorectal cancer and liver cancer may not be as uncommon as previously believed. The incidence of bone metastases in colorectal cancer was report as 10.4% in 1,020 patients.[4] Using dual tracer positon emission tomography/computer tomography, the incidence of bone metastasis from hepatocellular carcinoma was reported as high as 19.4% in 257 patients.[5] Survival varies among different cancer types. The median survival time from diagnosis of bone metastases is measurable in years for breast or prostate cancer and in months for lung cancer. For example, the median survival in patients with bone metastases was 25 months with surgery and 43 months without surgery for breast cancer.[6] The median survival in patients with bone metastases was 17.8 months for colorectal cancer,[7] while the median survival was only 4.9 months for lung cancer.[8] Prognostic models are useful in predicting the survival and selection of optimal surgical treatment for bone metastases. One of such model based on prognostic factors including primary cancer, preoperative haemoglobin, fracture versus impending fracture, Karnofksy score, visceral metastases, multiple bony metastases and American Society of Anaesthesiologist's score demonstrated satisfactory prediction of survival after surgery due to bone metastases in extremities.[9]

Bone metastases are the most common cause of cancer-related pain. Radiotherapy is the mainstay of treatment for painful bone metastases. Pain relief ranges from 49 to 88% after 1 month and from 60 to 74% after 3 months of radiotherapy.[10] For nonresponding or recurrent painful bone metastases, re-irradiation is recommended for its high response rate.[11] For painful spinal metastases, stereotactic body radiation therapy gives better pain relief and local control than conventional external beam radiation therapy.[12]

Nearly 50% of patients with bone metastases develop one or more complications collectively termed skeletal-related events (SREs) including pathological fracture (20.7%), metastatic spinal cord compression (0.9%), radiation to bone (8.0%), surgery to bone (1.2%) and hypercalcaemia.[13] In patients with advanced cancer, one of these SREs occurs on average every 3–6 months.[13] SRE may occur very early in aggressive cancer e.g. as early as 5–6 months after the diagnosis of bone metastasis in non–small cell carcinoma of lung.[14] In a breast cancer cohort followed up for a median of only 3.5 years, the risk of SRE of metastatic spinal cord compression or pathological fracture was each close to 10%.[15] SRE is associated with pain, functional dependence, reduced quality of life and reduced survival. The reduction of morbidities due to SRE is the primary goal of management of bone metastases.

Metastatic spinal cord compression is the most severe SRE with significant morbidity and high mortality. The challenges in management of metastatic spinal cord compression were highlighted in the editorial of the previous issue of the journal,[16] particularly the difficulty in the application of Tokuhashi score in the prediction of survival.[17,18]

Pathological fracture is another SRE that is regarded as an orthopaedic oncological emergency and the most common SRE requiring surgery treatment. Although spine is the most common site of bone metastases, pathological fractures mainly occur in femur (72.5%) and humerus (18.1%) and only rarely in spine (2.7%).[19] In this issue of the journal, Maduakonam et al[20] presented a retrospective review of 135 surgically treated bone metastases of extremity in 126 patients over 10-year period in a university hospital. Proximal

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femur and hip accounted for 78.7% of the sites of pathological fractures. Fixation for pathological fractures or impending fractures contributed to 47.4% and 43.7% of surgical procedures, respectively. The results were encouraging in maximisation of the quality of remaining life. The overall postoperative complication was 8.7%, and wound infection rate was 3.9%. Most patients (98.4%) could rehabilitate to ambulation.

Pathological fracture is a significant negative prognostic factor for survival. For those patients with bone metastases of long bones following surgery, the 1-year survival rate was 41% in 1,195 patients of the Scandinavian Sarcoma Group Skeletal Metastasis Registry.[21] In the local series, the 1-year survival was 23%, and the mean postoperative survival was 6.1 ± 1.1 months.[20] The 1-year survival rate after orthopaedic treatment was 47%–84% for renal cell carcinoma, 45%–59% for breast cancer, 29% for prostate cancer and 13% for lung cancer in a systematic review.[22]

Surgical intervention is indicated for pathological or impending fracture of long bones if an expected survival is longer than 6 weeks. The metastatic bone lesion is weakened, and healing may not be reliable. The construct should allow full-weight bearing in lower limb and return to function immediately. The entire long bone should be addressed regardless of the location of the lesion or the fracture. For patients with expected survival over a year, more durable endoprosthetic reconstruction is preferred to intramedullary nailing for pathological proximal femur fractures,[23] related to the fewer treatment failures and lower reoperation rate.[24] Postoperative radiation therapy should be utilised to minimise the disease progression.

The optimal treatment of pathological fracture is preventive. Prophylactic treatment to impending fracture will help to maintain patient function and mobility. Prophylactic fixation is technically easier than reactive fixation and is likely to be associated with less morbidity, better recovery and shorter length of hospital stay. For femoral metastases, prophylactic nailing for impending fractures was associated with a lower transfusion rate, lower immediate postoperative mortality, shorter hospital stay, higher percentage of regain walking and long survival time than reactive nailing for pathological fractures.[25] Accurate prediction of which bone metastases are most likely to fracture is essential. The Mirels' system is commonly used to calculate the risk of pathological fractures occurring in long weight-bearing bones within 6 months.[26] Besides the Mirels' score, the anticipated life expectancy and the functional demands of patient should also be considered.[27] A bone metastatic lesion producing functional pain after radiation therapy should be operated. In summary, prophylactic surgical interventions to prevent fracture occurrence is an important goal in impending fractures.

In cancer patients with bone metastases, orthopaedic surgeons have important roles in (1) decompression for metastatic spinal cord compression and stabilisation of spine in spinal metastases; (2) stabilisation and reconstruction of pathological fractures (reactive surgery) and (3) fixation of metastatic deposits at risk impending fracture (prophylactic surgery).

Besides fractures from SRE, fractures can occur in nonmetastatic bones in cancer patients from cancer treatment–related bone loss. Many treatments for hormone-responsive cancers have deleterious indirect effect on bone turnover, bone mineral density (BMD) and bone quality. Examples are aromatase inhibitors (AIs) in hormone receptor–positive breast cancer and androgen-deprivation therapy (ADT) by orchiectomy or luteinising hormone-release hormone analogues for prostate cancer.

The burden of cancer treatment–related bone loss and associated fracture is tremendous.[28] AI therapy is associated with a 2–4 fold increase bone loss compared to physiological postmenopausal bone loss. After 5 years of AI therapy, about one in five women with breast cancer will sustain an AI-related fracture. A further increase of 2–3% per annum fracture risk is observed when AI treatment is extended up to 10 years. Risk of fractures is 2–4 times higher in women treated with adjuvant AI than with tamoxifen or placebo. In a prospective study, 28% of patients with invasive breast cancer sustained a fracture a 4 years after cancer diagnosis.[29] The incidence was 40 per 1,000 person-years. The mean age of patients who had fracture was 61 years. Ninety-one percent had BMD T score larger than −2.5, and 55% had a normal BMD. Thus, BMD or Fracture Risk Assessment Tool (FRAX) was not predictive of the fracture risk in breast cancer patients. Similarly, ADT is associated with a loss of 1–5% of lumbar BMD within the first year.[30] A matched cohort study of 19,079 men found the risk of fragility fracture at all sites was 17.2% for those on ADT (mean duration 6.5 years) compared with 12.7% among men not on ADT (hazard ratio (HR) 16.5).[31]

Bisphosphonates are associated with a reduced risk of bone metastases in early breast cancer [RR 0.86, 95% confidence interval (CI) 1.75 to 0.99, $p = 0.03$, 11 studies of 15,005 women in a meta-analysis].[32] Randomised controlled studies demonstrate that intravenous zoledronic acid and, to a less robust, oral bisphosphonates at initiation of AI therapy can effectively prevent AI associated bone loss.[28] Additional benefits from adjuvant bisphosphonate treatment in postmenopausal women with breast cancer include 34% relative reduction in bone metastases and 17% relative risk reduction in cancer mortality.[33] The only study to have a significant risk reduction of any clinical fracture (HR 0.5, 95% CI 0.39–0.65, $p < 0.0001$) regardless of BMD T score and age is study on denosumab.[34] In patients with advanced prostate cancer, bisphosphonates probably decrease the number of SREs (Risk Ratio (RR) 0.87, 95% CI 0.81–0.94, $p = 0.27$; 9 trials of 3,151 participants) and decrease the number of participants with disease progression (RR 0.94, 95% CI 0.90–0.98, $p = 0.006$, 7 trials of 2,115 participants).[35]

Several evidence-based guidelines exist for the use of bone-targeted agents in breast cancer, prostate cancer and multiple myeloma. A joint position statement of various professional bodies was recently published on the management of AI-associated bone loss in breast cancer.[28] Bone targeted therapy should be given to all patients with a BMD T score < -2.0 or with a T score of < -1.5 with one additional risk factor or with 2 or more risk factors (age > 65, body mass index < 20, smoking, family history of hip fracture, personal history of fragility fracture and use of steroid > 6 months) for the duration of AI treatment. Furthermore, adjuvant bisphosphonates are recommended for all postmenopausal women at significant risk of disease recurrence (node positive disease, a T2 or above, grade II/III breast tumour found to be oestrogen receptor negative or human epidermal growth factor 2 positive). The Cancer Care Ontario Clinical Practical Guideline[36] recommends bone-targeted therapy at osteoporosis-directed dosage to reduce facture risk for men with nonmetastatic prostate cancer at high risk of fracture receiving ADT. Bone-targeted therapy is also recommended for management of bone metastases in breast cancer and castration-resistant prostate cancer to reduce SRE.[36,37] Multiple myeloma patients with adequate renal function and bone disease at diagnosis should be treated with zoledronic acid to reduce SRE.[38]

Thus, bone targeted agents (denosumab and bisphosphonates) can mitigate the adverse events of cancer-related treatment bone loss and fragility fracture. In meta-analysis of randomised controlled trials, denosumab is more effective than zoledronic acid in reducing or delaying the first SRE and subsequent SRE in of patients with bone metastases.[39,40] Despite the availability of effective SRE-limiting therapies, they are typically underutilised.

The presence of bone metastases is a sign of disseminated disease with significant impact on patient's quality of life. There are advances in imaging such as positron emission tomography (PET)

for the early detection of bone metastases; stereotactic body radiotherapy and targeted therapy for the control of bone metastases and targeted bone therapy for the prevention of SREs. Collaboration among radiologists, medical oncologists, orthopaedic surgeons and palliative care physicians is important to provide the possible optimal management to patients with advanced cancer and bone metastases.

Conflict of interest

The author has no conflict of interest to declare.

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