

COMMENTARY

Skeletal-Related Events among Breast and Prostate Cancer Patients: Towards New Treatment Initiation in Malaysia's Hospital Setting

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Abstract

The human skeleton is the most common organ to be affected by metastatic cancer and bone metastases are a major cause of cancer morbidity. The five most frequent cancers in Malaysia among males includes prostate whereas breast cancer is among those in females, both being associated with skeletal lesions. Bone metastases weaken bone structure, causing a range of symptoms and complications thus developing skeletal-related events (SRE). Patients with SRE may require palliative radiotherapy or surgery to bone for pain, having hypercalcaemia, pathologic fractures, and spinal cord compression. These complications contribute to a decline in patient health-related quality of life. The multidimensional assessment of health-related quality of life for those patients is important other than considering a beneficial treatment impact on patient survival, since the side effects of treatment and disease symptoms can significantly impact health-related quality of life. Cancer treatment could contribute to significant financial implications for the healthcare system. Therefore, it is essential to assess the health-related quality of life and treatment cost, among prostate and breast cancer patients in countries like Malaysia to rationalized cost-effective way for budget allocation or utilization of health care resources, hence helping in providing more personalized treatment for cancer patients.

Keywords: Skeletal related events - bone metastases - quality of life - breast cancer - prostate cancer - cost

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Introduction

The human skeleton is the most common organ to be affected by metastatic cancer commonly termed as skeletal or bone metastases in literatures (Bagi, 2005). Estimated 169.3 million years of healthy life were lost to cancer in 2008 globally, in which female breast and prostate cancers were among the main contributors of different type of cancers for most regions of the world (International Agency for Research on Cancer and Cancer Research UK, 2012). Based on Malaysian National Cancer Registry Report 2007, the five most frequent cancers among Malaysian male include prostate with an age-standardized rate (ASR) for prostate cancer was 6.2 per 100,000 populations. Whereas, the most frequent cancers among females were breast, with ASR for breast cancer of 29.1 per 100,000 populations (Ariffin and Nor Saleha, 2011). Cancer staging were reported for 48.7% of the new cancer

cases in 2007 but among those staging at diagnosis were made, there were 57.6% of cancers already at the advance stages of cancers (Ariffin and Nor Saleha, 2011). The high prevalence of bone metastases could add more burden of disease in cancer. Bone metastases are major causes of cancer morbidity (Dhillon and Lyseng-Williamson, 2008) whereby consequently cancer treatment could cause a significant financial implication to healthcare system, such as leading to extensive health-care resource utilization. Neoplasm contributed 11.12% out of the ten principal causes of Hospital death in Ministry of Health, Malaysia in 2011 (Ministry of Health, 2012).

Bone Metastases

Bone is a common site of metastasis in patients with haematological malignancy or solid tumour (Dhillon and Lyseng-Williamson, 2008). Skeletal metastases are

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most common in breast, prostate and lung of primary solid tumour (Bagi, 2005; Castellano et al., 2011). Bone metastases become clinically importance in breast and prostate cancers partly contributed by the reason of prevalence of these diseases. The prevalence of skeletal disease is greatest in breast and prostate carcinoma (Coleman, 2006) because patients with these cancers have a relatively long median survival time after diagnosis of bone metastases (Coleman, 2004). For instance, about 65.0% to 75.0% of patients with metastatic breast cancer or prostate cancer will develop skeletal metastases (Coleman, 1997). Among patients dying of different cancers, about 70.0% of breast cancer or prostate cancer showed evidence of metastatic bone disease at post-mortem examination (Coleman, 2006). Metastatic bone disease is a more frequent cause of malignancy and morbidity in skeleton than primary bone cancer (Bagi, 2005). Bone metastasis is a lesion that weakens the bone structure, causing a range of symptoms and complications, including skeletal complications that are known as skeletal-related events (SREs) (Coleman, 2004). Metastatic bone disease indicates the cancer disease progression and appears to be more resistant to treatment than visceral metastases (Bagi, 2005).

Skeletal-Related Event (SRE)

SRE is a type of composite end point of bone event occurring in bone metastasis, a term used for approval basis for oncology drug marketing applications by to United States Food and Drug Administration (Johnson et al., 2003). SRE is a term used in majority clinical trial, for instance it is used in investigating benefit of a conventional treatment of prevention of skeletal complications secondary to bone metastases, which is Bisphosphonate therapy (Coleman, 2004). Typically SRE includes pathologic fracture, spinal cord compression, radiation or surgery to bone, and hypercalcemia of malignancy (HCM). A pathologic fracture can result in impaired mobility or instability and spinal cord compression could cause severe pain, irreversible paraparesis, paraplegia or increased risk of death (Saad et al., 2007). These complications contribute to a decline in patients' health-related quality of life (HRQOL) (Castellano et al., 2011), including to the family of cancer patient (Bagi, 2005), costly (Schulman and Kohles, 2007; Hagiwara et al., 2011) and among men with metastatic prostate cancer, the skeletal-related events (SREs) were found to be associated with a decrease in survival (DePuy et al., 2007).

A review stated that during the course of breast cancer disease, about 75% of women with advanced breast cancer will develop bone metastases in which for each year, they can have up to an average of four SREs and without bone-targeted therapy with two years of follow-up, about 64% of patients could experience an SRE (Aapro and Coleman, 2012). An analysis of health insurance claims database between 2000 to 2005 in United States of America (USA) revealed that for SREs among prostate cancer patients, most frequently they had undergone radiation therapy (89% of the cases), followed by a pathologic fracture (23% of the cases) and bone surgery (12% of the cases).

Among patients diagnosed as having at least one SRE, about 78% experienced one type of SRE, about 17% had two types of SREs, about 5% had three or more (Lage et al., 2008).

Health-Related Quality of Life of Patients with Cancers

A quality of life assessment usage includes justifying associated increases in expenditures for health care (Testa and Simonson, 1996). HRQOL refers to a multidimensional assessment that includes at least the physical, psychological and social domains, and may also include other domains such as cognitive functioning, sexuality and spirituality (Osoba, 2011). HRQOL assessment allows a broader understanding of the impact of patient's symptom management that also includes the overall patient's quality of life (Colloca and Colloca, 2011). Cancer patient more than often will have a poor quality of life after diagnosis and treatment of cancer and as the disease progresses, their quality of life issues become more important as well. The individual's view of their quality of life may include aspects of life that are not health-related but as event related to medical conditions becomes more demanding, the aspects of life that are not health-related diminish (Bradley, 2006). For health care providers or policy makers, the decisions on what research or treatments to invest most in health care sectors are somehow closely related to their effect of a patient's quality of life.

Breast cancer is burdensome due to its subsequent event to patient, carer or health care provider. For example, management of breast cancer complications of lymphoedema (Shih et al., 2009) and recurrence (Lamerato et al., 2006) has been associated with an increase in economic burden. Women with breast cancer experienced stressful life event associated with distressing symptoms which may begin with diagnosis, continues after completion of adjuvant therapy, and this condition may decrease quality of life (Ögce and Özkan, 2008). In South East Asian countries and Malaysia, the problem with late diagnosis is well documented in advanced presentation of women with breast cancer and the source of delay could come from problem in symptom appraisal by the patient and could also be a misdiagnosis by health provider (Taib et al., 2011).

In Asia, breast cancer patients present at a younger age compared to the West (Ng et al., 2011). However between countries which do not have a population-based breast cancer screening program (Yoo, 2010) and having almost similar socio-cultural backgrounds, like in Indonesia as compared to patients in Malaysia, the presentation pattern of breast cancer was seen at later stages, are highly likely to present with metastatic breast cancer and at a younger age in Indonesia (Ng et al., 2011). Even though the findings of the study was limited by only comparing the clinical and pathological characteristics of two tertiary hospitals in Malaysia and Indonesia, it could reflect that socio-economic factors, differences in the degree of westernization of lifestyles and or level in breast health literacy could influence the presentation pattern of

cancer patients to healthcare between the countries (Ng et al., 2011). A qualitative study in Malaysia showing that poor breast literacy was seen across all age groups among advanced breast cancer patients as revealed by Taib et al. (2011). The incidence and mortality rates of prostate cancer in Asian countries are on the rising side as compared to Western Countries as the percentage of advanced-stage prostate cancers remains high in Asian countries (Namiki et al., 2010). In Malaysia, prostate age-specific cancer incidence was documented to increase after age of 45 years in 2007 where 59.4% of cases with reported staging were diagnosed at stage III and IV (Ariffin and Nor Saleha, 2011). There were 42.8% of female breast cancer cases with reported staging done were diagnosed at stage III and IV already in 2007. The age-specific cancer incidence showed peak at 50-59 of age (Ariffin and Nor Saleha, 2011).

A review found that a number of disease and treatment-related symptoms that had a negative impact on patient's HRQOL is significantly affecting the majority of patients with castration-resistant prostate cancer, in which these findings highlighted the need to include the treatment based on an assessment of quality of life (Payne and Percy, 2012). Current treatment options for prostate cancer patients with bone metastases include external beam radiotherapy, surgery, systemic therapy (Bisphosphonates, hormonal therapy, or chemotherapy), and pain medications. The treatment goals are to reduce incidence of SREs; reduce bone pain and morbidity; improves patient's mobility; and overall quality of life (Goh et al., 2007). Patients diagnosed with distant prostate cancer metastases are treated with an androgen deprivation as a standard first line treatment. In general, either surgical orchiectomy or medically castration, these initial treatment of metastatic prostate cancer often provides initial temporary disease control and symptomatic relief and many patients will progress later despite androgen deprivation (Fong et al., 2012). Majority of men with castration-resistant prostate cancer have radiological evidence of bone metastases (Osanto and Van Poppel, 2012). Metastatic castration-resistant prostate cancer represents late state of prostate cancer and patient can have a detrimental impact on cancer-specific symptoms such as pain, nausea and vomiting, dyspnoea, appetite loss (Colloca and Colloca, 2011).

Management of Patients with Metastatic Breast and Prostate Cancer

As cancer can be considered as a systemic disease, with disease patterns undergoing an epidemiological transition of becoming a chronic disease and occurring among older age group worldwide, a multidisciplinary approach together with having more medical oncologists as a cancer specialist should always be made available for managing issues surrounding cancer patients (Tamura, 2012). Severe bone pain may require strong narcotics or palliative radiation therapy (Coleman, 2004). Conventional approaches for treating patients with bone metastases include standard anti-neoplastic (chemotherapy or

biologic therapies), therapies, which may be administered in conjunction with additional supportive or palliative therapies.

Treatment of Metastatic Breast and Prostate Cancer in Malaysia

Antiresorptive therapies are the standard of care for maintaining bone health in patients with advanced cancers involving bone. In the absence of antiresorptive therapies, many patients with bone metastases from solid tumours will experience potentially debilitating skeletal-related events (Hadji et al., 2012). Bisphosphonates as an antiresorptive therapy, becomes part of a recommended standard of care when treating malignant bone disease in certain clinical settings (Aapro et al., 2007; Jilani et al., 2012). Bisphosphonates as antiresorptive therapy has been established as the standard of care for the prevention of SREs in metastatic bone disease (Coleman, 2001).

The Malaysian clinical practice guideline of cancer pain management includes bisphosphonates as an adjuvant drugs used in cancer pain treatment. However, with the consideration that the cost will escalate with a prolonged usage of bisphosphonates, use of bisphosphonates is not routinely prescribed in public hospital setting but the usage follows a standard set of guideline. Bisphosphonates may be considered where analgesics and/or radiotherapy are inadequate for the management of painful bone metastases (Ministry of Health Malaysia, 2010).

Radiotherapy is used to stabilize bone lesions and may prevent impending fractures. Orthopaedics surgery is used to treat existing fractures or to prevent impending fractures or spinal cord compression (Coleman, 2004). Generally, radiation therapy is effective but might be limited in certain cases because of diffuse nature of bone metastases and chemotherapy in patients might affect bone marrow. In Malaysia, single fraction radiotherapy is the preferred schedule for uncomplicated painful bone metastases (Ministry of Health Malaysia, 2010).

As a field of understanding the pathogenesis of metastasis on the systemic, cellular and molecular levels are expanding, there is also expansion of advances for more effective therapeutic approaches. In which, the evolution of research in cellular origin of cancer metastases and their interaction with organ microenvironment has started in history as early as 1889 by the English surgeon Stephen Paget, providing an idea about the seminal 'seed and soil' hypothesis (Mundy, 1997; Fidler, 2003). Although antiresorptive therapies are generally well tolerated, there have been reports of associated serious adverse events such as hypocalcemia, osteonecrosis of the jaw, renal events, and acute-phase reactions (Hadji et al., 2012). The clinically approved antiresorptive therapies are generally well tolerated, especially with strict adherence to administration guidelines and with established adverse event management practices. It is important for clinicians to recognize adverse events so that they can properly manage and considering the risk-benefit profiles of those agents on a per-patient basis (Hadji et al., 2012). Although current antiresorptive therapies are generally well tolerated

in their approved regimens, clinical indications are being expanded for example anticancer effects with nitrogen-containing bisphosphonates. Furthermore, new therapies are emerging such as anti-RANKL antibody 'denosumab', which recently gained regulatory approval in the United States of America for reducing the risk of SREs in patients with metastatic bone disease from solid tumours (Hadji, 2011). Targeted therapy such as 'trastuzumab' is considered as a new group of cancer drugs and the usages in public hospital settings in Malaysia is still guided by approval by Ministry of Health Malaysia and limited to oncologists (Ministry of Health Malaysia and Ministry of Higher Education Malaysia, 2011). Selecting the most suitable antiresorptive agent is influenced many factors such as the efficacy, practicality of administration, safety, cost, patient compliance, and understanding the pharmacokinetic and pharmacodynamic properties of different antiresorptives play a role in clinical decision making for the treatment of malignant bone disease (Hadji, 2011). For example, for both in older age female and male patients of breast and prostate cancer, that is already associated with decreased bone integrity and increased risk for malignancies, they will have a high risk of metastasis to bone. The safety profile of bisphosphonates is well characterized (Mundy, 1997), given their long history of use but 'denosumab' is an example of an important new therapy (Hadji et al., 2012).

Economic Burden of Bone Metastases

Patients with advanced cancer have a diminished quality of life. The primary goal of palliative care for advanced stages of cancer is to improve or maintain patients' HRQOL and relieve symptoms to greatest possible extent (Kim et al., 2005). In Malaysia, the most problem areas of quality of life among the terminally ill cancer patients in selected hospices centres include the domain of functional well-being, followed by psycho physiological and social/spiritual domain (Shahmoradi et al., 2012). Although there were only two states in Peninsular Malaysia were sampled for the study, the study had included breast and prostate cancer patients, thus, suggesting the need to improve quality of life in terminally ill cancer patients in Malaysia.

There is a need of better understands what constitute the economic burden of cancer and how it affects the lives of cancer patients and services by health care provider. It is crucial to understand the management of cancer patients because that would affect the adjustment to cancer treatment (Meneses et al., 2012) for example the ability to pay or finance for treatment, care or health services relates to type of health care financing system in any country. An economic evaluation on management of cancer patients helps to understand the economic burden of cancer. An economic evaluation includes a comparative analysis of different courses of action in terms of both costs and health consequences, to allocate limited budgets to intervention that offer most health gain per unit of money (Cohen et al., 2008). Generally, a cancer diagnosis leads to higher economic burden. Study in USA showed that the cancer survivors also have a higher risk for high economic

burden compared with patients with other chronic illnesses (Bernard et al., 2011). Cancer survivors, have higher out-of-pocket costs for medical care as compare to persons who do not experience cancer. Patients with metastatic disease are treated with palliative intent where each of available treatments depends on many factors such as patient's underlying health, their performance status, location of metastases, treating physician, and facilities available in local settings (Konski, 2004). Metastatic bone disease is associated with significantly higher cost of treatment due to complications and prolonged hospitalization (Bagi, 2005).

The national cost burden for metastatic bone disease's patient estimated in USA was 17.0% of the US\$74 billion in total direct medical cost, suggesting that metastatic bone disease is a significant driver of overall oncology cost. Generally, for 2004, the cancer prevalence in USA was estimated at 4,861,987 cases annually, where about 5.3 % had metastatic bone disease (Schulman and Kohles, 2007). This study illustrated the impact of metastatic bone disease on a national expenditure. Bone metastases in the absence of SREs were associated with a 55% increase in total monthly healthcare costs (\$12,780 per person-year), based on the health insurance claims of prostate cancer patients between year 2002 to 2008 in USA (Hagiwara et al., 2011). For bone metastases, most of the increase in costs with or without SRE was identified to occur in the outpatient setting, predominantly during the months immediately after the diagnosis (Hagiwara et al., 2011).

The late diagnosis of bone metastases may lead to more severe or frequent SREs, which can result in increasing resource utilization and costs. For example, in the modelling analysis of Portuguese patients with metastatic breast cancers and prostate cancers study, showed that diagnosis of bone metastasis at or after SRE onset was associated with a 19% to 106% increase in treatment costs (Félix et al. 2011). Irrespective of baseline stage, grade and treatment, prostate cancer cases metastatic with PSA progression would pose a significant economic burden (Penson et al., 2004).

However, despite of all the finding in the literatures, there would be variation in SRE costs between different study population because for instance, different factors influence the cost differently such as that cost may be contributed by different classification of SREs variables, differences in unit costs of health care procedures, cost calculated largely based on experts opinion or assumption of study, different type of healthcare financing system in different countries, whether private health care providers involved in treatment or services or whether other than hospital resource utilization, or costs incurred by their patient's families are taken into account in any the design of study. A greater medical expenditure could be assumed by having an increase in the economic burden for diagnosis and treatment of cancer.

Benefits of the Economic Evaluation on Bone Metastases

The global burden of cancer can be controlled by managing patients with cancer themselves other than

implementing other evidence-based strategies which are preventing and early detection of cancer (World Health Organisation, 2011). There are issues among patients with delayed or advanced cancer presentation particularly among Asian people. The consequences of SRE may persist throughout the life span of the patient. Therefore apart from planning to implement a comprehensive strategy to detect cancer and treat accordingly, other initiatives of treatment for delaying the occurrence of bone metastases or delay the onset of SRE could possibly help preserve patients' functional independence or their HRQOL. Even though treatment resources might differ from country to country, some form of tertiary prevention initiative aiming for improvement in patient's quality of life would be the right direction for these patients. This is in line with the effort of having more targeted pharmacological alternatives in the treatment of bone metastases.

The multidimensional assessments of HRQOL for those patients is importance because treatments have beneficial impact on survival, but side effects of treatment and disease symptoms can significantly impact HRQOL. Therefore, it is essential to assess the HRQOL among prostate and breast cancer patients in particular among Asian ethnicity. Patients with risk of lower HRQOL can be identified for better risk assessment during cancer managements. Subsequently, invites policy maker to further rationalize introducing a new personalized drug to these types of cancer patients in hospital.

An informed decision requires a good evidence based information such as cost-effectiveness on cancer therapy from health economic point of view. Data gathered from the hospital settings would generate information on a burden of treatment cost of breast cancers and prostate cancers and later this information could be used for strategic planning. A hospital manager would be able to initiate any specific intervention related to the burden that would help to reduce certain healthcare utilization costs efficiently, or inviting more efficient financial management effort particularly in public hospital settings, which is currently based on previous year budget allocation.

Conclusion

There is a need to determine the health care cost and HRQOL of breast and prostate cancer with SRE status patients in Malaysia. All patients have a right to receive at least a standard therapy for their diseases in any countries. An evaluation on cost and health-related quality of life in selected hospital represent country effort in improving care to cancer patient through sufficient resources for supplying standard care to the patients. Economic evaluation research of these cancers in Malaysian public hospitals has a potential to further improve patient quality of life, hence providing better health care services delivery.

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