RESEARCH ARTICLE

Challenges in the Management of Breast Cancer in a Low Resource Setting in South East Asia

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Abstract

Background: Breast cancer is the second most common cancer in women in Cambodia, a low income country in South-East Asia. The Sihanouk Hospital Centre of Hope (SHCH) is a charity hospital set up by an international non-governmental organisation, HOPE Worldwide. In 2008, SHCH partnered with AmeriCares, a global health organisation to set up and deliver a breast cancer programme to provide education, diagnosis and treatment for women with breast cancer. The objective of this study is to characterise the presentation, diagnosis, treatment and outcomes of women treated under this program. Materials and Methods: A total of 215 women newly diagnosed with breast cancer from 1 March 2008 until 31 March 2011 were studied. Age at diagnosis, tumour size, histological type, tumour grade, ER, lymph node involvement, treatment modalities (surgery, radiotherapy, chemotherapy, hormone therapy) were recorded. Data on mortality at 3 years were obtained whenever possible. Results: The median age was 47 years old. Some 77.8% were diagnosed with stage 3 and 4 lesions, and 78.5% underwent mastectomy, of which 28.4% the intent was palliative. Of those whose ER status were known, only 48.3% were ER positive. Only 6 patients could afford chemotherapy while only 1 patient had radiotherapy. Hormone therapy was provided free for those who were ER positive. The overall survival rate at 3 years was 39.1%. Conclusions: Breast cancer presents at a late stage, and because treatment is suboptimal, survival is poor in Cambodia. A more aggressive approach to early detection and treatment needs to be developed to improve outcome from this potentially curable disease.

Keywords: Breast cancer - stage - treatment - survival - Cambodia

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Introduction

Cambodia is a low income country (Gross National Income per capita of USD 1090.1 in 2014) in South East Asia and has a population of 15 million. 17.7% of the population live below the poverty line. (The World Bank at http://data.worldbank.org) Breast cancer is the second most common cancer in Cambodian women with an age-standardized rate of 19.3 per 100 000. With a mortality rate of 9.3 per 100 000, the mortality-incidence ratio (MIR) of breast cancer in Cambodia is 0.49, which is much higher than the world-wide MIR of 0.3. (GLOBOCAN 2012 at http://globocan.iarc.fr)

There is no universal health coverage in Cambodia and public hospitals charge a fee for services rendered. While there are some arrangements for Health Equity Funds or other special funding mechanisms, many poor people are challenged in their ability to access quality health care. Women who are unable to pay the medical fees are severely challenged in their ability to get adequate diagnosis and treatment for a variety of women's concerns, especially for cancers. Frequently, the NGO sector provides supportive medical services to the poor and vulnerable through medical missions, clinics or a handful of charity hospitals operating in the country. One such organization is the Sihanouk Hospital Center of Hope (SHCH).

SHCH was founded in 1996 with a dual mission to train and educate medical professionals and provide health care to the poor and vulnerable. Located in Phnom Penh, the hospital has comprehensive services (including a pathology laboratory) and 30 inpatient beds. In 2008, SHCH expanded an existing gift-in-kind partnership with AmeriCares, an emergency response and global health organization committed to saving lives and building healthier future for people world-wide, to include funds for training surgeons, building capacity of the pathology lab and to deliver product donations of treatment drugs for women with hormone receptor positive breast cancer. This effort was funded through AstraZeneca and now delivers a breast cancer program that includes community-based education by breast cancer survivors, diagnostic services, surgeries and hormonal therapy drugs.

As of March 2014, the program has conducted 2,458 screenings with either ultrasound or mammography, performed 782 surgical procedures (including biopsies

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and mastectomies) and diagnosed 498 women with breast cancer.

A retrospective study of breast cancer specimens collected from 2003 to 2004 in a pathology laboratory in Cambodia showed that the majority of breast cancers were infiltrating ductal carcinoma (82.3%), Grade 3 (76.6%) with nodal metastases (83.9%). No immunohistochemistry studies for estrogen receptor (ER) or progesterone receptor (PR) were carried out. (Serey et al., 2011) Other than this pathology-based study, few data exist about the presentation, management and outcomes of women with breast cancer in Cambodia.

The purpose of this observational study is to characterize the diagnosis and management of women with breast cancer in SHCH between March 2008 and March 2011. This study provides important epidemiological data, including age and stage at presentation, treatment provided and patient outcomes.

Materials and Methods

A total of 215 women newly diagnosed with breast cancer were enrolled in the breast cancer program in SHCH from 1 March 2008 until 31 March 2011. Age at diagnosis, tumour size, histological type, tumour grade (grade 1 grade 2, grade 3, unknown), ER status (positive, negative, unknown) lymph node involvement, treatment modalities (surgery, radiotherapy, chemotherapy, hormone therapy) were

Results

The patients' age ranged from 22 to 74, with a median age of 47 years. 57.5% were aged 50 years and below. (Figure 1). 117 patients (54.4%) were diagnosed clinically without a biopsy because the cancer was very obvious. Only 2% presented with a T1 tumour (2 cm or less) with the majority (41.9%) presenting with a T4 tumour (involving skin and/or chest wall). Only 22.6% were node negative. Infiltrating ductal carcinoma was the most common histological type (80.4%). Only 128 cases (59.5%) were graded, of which 87 (68%) were Grade 3. 95 patients (44.2%) did not have hormone receptor status available. Of the 120 patients with hormone receptors done, only 58 (48.3%) were ER+ and PR+/-, while 11 (9.2%) were ER-PR+. Of the 194 patients who were staged, the majority was Stage 3 (53.6%) and Stage 4

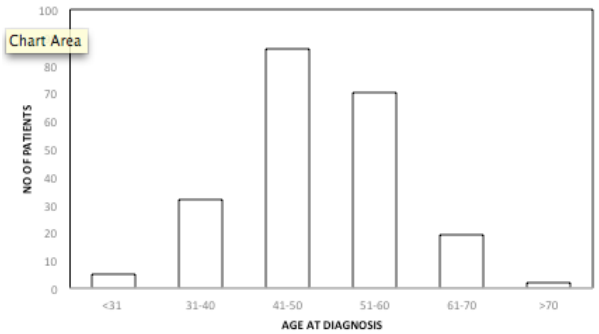

Figure 1. Age Distribution of 214 Patients. The age of one patient was not recorded

Table 1. Breast Cancer Details

		No	%
Histological type	Infiltrating ductal carcinoma	174	80.9
	Infiltrating lobular carcinoma	11	5.2
	Medullary carcinoma	1	0.4
	Others	29	13.5
Grade	1	5	3.9
	2	36	28.1
	3	87	68.0
	Total with known grade	128	59.5
Hormone receptors	ER+PR+	54	45
	ER+PR-	4	3.3
	ER-PR+	11	9.2
	ER-PR-	51	42.5
	Total with known ER/PR	120	55.8
T-stage (Size)	T1 (2 cm or less)	4	2.6
	T2 (>2cm-5 cm)	25	16.1
	T3 (>5cm)	61	39.4
	T4 (involving skin or chest wall)	65	41.9
	Total with known T stage	155	72.1
N stage (Lymph nodes)	N0	30	22.6
	N1 (1-3 lymph nodes involved)	31	23.3
	N2 (4-9 lymph nodes involved)	56	42.1
	N3 (>9 lymph nodes involved)	16	12
	Total with known N stage	133	61.9
M stage (Metastases)	M1	47	24.2
	M0	147	75.8
	Total with known M stage	194	90.2
Stage	1	3	1.6
	2	40	20.6
	3	104	53.6
	4	47	24.2
	Total with known stage	194	90.2
Surgery	No surgery	46	21.4
	Modified radical mastectomy	121	56.3
	Palliative mastectomy	48	22.3
Other therapy	Neoadjuvant chemotherapy	3	4
	Adjuvant hormone therapy	69	92
	Adjuvant radiotherapy and chemotherapy	1	1.3
	Adjuvant chemotherapy	2	2.7

(24.2%), while only 1.6% were Stage 1. (Table 1)

169 patients (78.6%) underwent surgery, all of whom had mastectomies. Mastectomy with axillary dissection was performed in 121; simple mastectomy for palliation was performed in 48 patients. 21.4% were too advanced for surgery. Chemotherapy and radiotherapy was not available in SHCH. Most patients did not have financial resources to pay for neo-adjuvant treatment in other hospitals, hence, only 7 patients were able to receive chemotherapy (6 patients) and radiotherapy (1 patient). Hormone therapy was provided free of charge to 69 women (32.1%) who were hormone receptor positive through the medicines donated by the AmeriCares-AstraZeneca Breast Cancer Programme. (Table 1)

At 3 years' follow-up, 103 out of the 169 (60.9%) patients who underwent surgery had died of their disease, giving an overall survival rate of 39.1%. For the hormone receptor positive patients who were given hormone therapy, the overall survival was 44.8% compared to 35.3% in the hormone receptor negative women.

Discussion

The age standardized incidence rate (ASR) of breast cancer is highest in high income countries, while it remains low in poor countries like Cambodia. The ASR in Cambodia (19.3 per 100 000) is only a fifth of the incidence in USA (92.9 per 100 000). (GLOBOCAN 2012 at http://globocan.iarc.fr) However, parts of Asia, especially Singapore, have seen very steep rises in the incidence of breast cancer due to rapid economic development. (Seow et al., 1996) This phenomenon is likely due to the adoption of Western lifestyles, which tend to promote changes that increase breast cancer risk, such as decreased parity, delayed childbirth, less breast feeding, a more sedentary lifestyle, and dietary changes, that have occurred in Asian countries as they modernize. (Porter, 2008) It is expected that the incidence of breast cancer in Cambodia will increase.

Breast cancer presents at a younger age group in Cambodia compared to western countries, and this trend is seen in all the Asian countries. The median age of 47 years old in Cambodia is compared with the median of 50 years seen in Malaysia and Singapore (Saxena et al., 2012), and a median of 60 years in Europe and USA. (Leong et al., 2010) Rather than a lower age-specific incidence rate in Asia compared to the West, the younger age is due to the population pyramid in Asia where the median age is younger, and hence there are more younger women compared to the elderly. The median age in Cambodia is only 24.5 years compared to 40 years in United Kingdom. The younger age is also a result of the cohort effect, where breast cancer risk increases with subsequent cohorts, hence younger women are at higher risk of breast cancer compared to older women. (Fan et al., 2009)

Stage is a function of size of tumour and extent of lymph node involvement. This is a time dependent variable, i.e., the longer the woman waits to seek treatment, the higher the stage at presentation. In low and middle income countries, women present with later stages than in high income countries. (Yip and Taib, 2012) Delayed presentation has been attributed to poverty, lack of awareness, geographical isolation and cultural beliefs. A qualitative study on why women present late in an Asian country identified fatalism, belief in traditional treatment, lack of autonomous and individualistic decision making on the part of women as barriers to early presentation and treatment.(Taib et al., 2014) In this study 77.6% of women present with Stage 3 and 4 breast cancer, compared to only 22.3% in Singapore a high income country in South East Asia. (Saxena et al., 2012)

As seen in other Asian studies, infiltrating ductal carcinoma makes up the majority of breast cancers in Cambodia. Pathological features such as grade, and molecular markers, i.e., estrogen receptor (ER) progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) are important as prognostic markers, and in high resource settings, are considered essential for decision making on treatment. Quality assurance is important to ensure accurate and reliable results. (Yip and Rhodes, 2014) However these markers are expensive to carry out and in low resource settings, they may not be done at all. In this study, 40% of the tumours were not graded, while 44.2% did not have ER or PR done. None of the tumours were tested for HER2, which is reasonable, since targeted therapy with trastuzumab cannot be given due to the high cost. In those who were graded, Grade 3 formed the majority of the cases (68%) which is higher than the 40% Grade 3 seen in another Asian population.(Saxena et al., 2012) This is similar to the 76.6% Grade 3 tumours seen in the previous pathology study in Cambodia.(Serey et al., 2011) It is difficult to determine if Cambodian women truly present with high grade tumours because grading is subjective, with inter-observer variability. The ER positive rate of 48.3% is also lower than reported in other studies. Added to the 9.2% of women with ER-PR+ tumours, the total percentage of hormone receptor cancers are 57.5%. This is important because women through the breast cancer program can access donated hormone therapy, but no chemotherapy or radiotherapy is available. The 9.2% of ER-PR+ cancers are interesting, because this is a small group comprising usually 4-5% of cases, and actually may not be a biological entity, but rather a technical artifact. (Ng et al., 2012) Survival in the ER-PR+ patients are similar to the ER+PR+ patients, which may indicate that this is the same group.(Ng et al., 2014) Variable quality control of tissue handling and processing may lead to erroneous reporting of hormone receptor status. The hormone receptor positive rate in Cambodia is similar to that seen in other Asian women, but lower than in Caucasians. (Yip et al., 2011)

The Breast Health Global Initiative (BHGI) is an international consensus group of breast cancer experts that develop practice guidelines for management of breast cancer in low and middle income countries. The BHGI recognizes that resource constraints are a barrier to the optimal treatment that is available in high income countries, however, believe that women should have the right to at least a basic level of care should they be unfortunate enough to develop breast cancer. (El Saghir et al., 2011)

In March 2004, a committee of medical professionals with expertise in breast cancer developed evidence-based national breast cancer guidelines for diagnostic and treatment of breast cancer. In spite of these national guidelines, major hurdles exist that prevent provision of a basic level of care to cancer patients today. In low income countries like Cambodia, there is a shortage of health professionals required in the management of breast cancer. In 1975, when the Khmer Rouge came into power, the health care system was devastated. With the return of peace in the 1990s, the priorities of the Ministry of Health was to control communicable diseases. (Eav et al., 2012) Although there is a move to develop a National Cancer Control Plan, the lack of surgical oncologists, medical and radiation oncologists, anaesthetists and pathologists are major barriers to providing even early detection and stage adapted comprehensive treatment to cancer patients. In 2013, there were only 7 pathologists and 10 oncologists in Cambodia, and all concentrated in Phnom Penh, leaving large areas of the population without pathology or oncology services.

A recent study was conducted in eight low and middle income countries in South East Asia, including Cambodia,

which revealed that 48% of cancer patients incurred financial catastrophe (defined as spending 30% of the household income on medical expenses) in these countries. Cancer care needs to be delivered and financed better to protect patients and their families. (Action Study Group etal, 2015) Until the Cambodian Ministry of Health can increase capacity to provide a basic level of care for patient with breast cancer, there is still a strong dependence on international NGOs to support patients with breast cancer.

The two main determinants of mortality from breast cancer are early detection and treatment. For various reasons, women are fearful of coming to the hospital with breast symptoms. As part of the Breast Cancer Program in SHCH, peer educators, who are themselves survivors of breast cancer, are trained to work in the community with women, encouraging those with breast symptoms to attend the breast clinic in SHCH for diagnostic workup.

SHCH has developed surgical and pathological services, and hormone therapy is provided for those with hormone receptor positive tumours. Patients that require radiation and chemotherapy are referred to 2 public hospitals in Phnom Penh. Unfortunately, often economic constraints prevent patients from receiving necessary treatment(s). There is only one hospital in Phnom Penh with radiation facilities, while there are two hospitals with chemotherapy facilities. A study on radiotherapy facilities in LMICs carried out by the International Atomic Energy Agency-Directory of Radiotherapy Centre (IAEA-DIRAC) found that only 4.7% of the population in Cambodia had access to radiation therapy. (Datta et al., 2014) Unfortunately patients have to pay for these services, and if they cannot afford it, then the treatment is not provided.

In SHCH, because of late presentation, not all patients were operable, and of the 78.5% who were operable, more than a quarter were for palliation. No breast conservation surgery was done, not only because they were large, but also because there was no radiotherapy available. It is interesting to note that over 50% of breast cancers were diagnosed clinically without a biopsy. Although mastectomy should never be used as a method of diagnosis(Shyyan et al., 2008), in situations where the woman presents with an ulcerating breast lesion, a clinical diagnosis and expeditious surgery would be a practical solution to the problem.

Modified radical mastectomy alone in large tumours or node positive tumours will cure very few patients without adjuvant radiotherapy or chemotherapy. Only 5 patients with Stage 1 would not have required chemotherapy, and over 90% of the others would have required adjuvant or primary chemotherapy as well as adjuvant radiotherapy based on international guidelines. However, since both of these were not available in SHCH, almost all patients did not receive the necessary treatment because they could not afford the treatment in public hospitals in Cambodia. Besides surgery, the only other treatment available was hormone therapy, provided free of charge to 69 women who were hormone receptor positive through the medicines donated by the Ameri Cares-Astra Zeneca Breast Cancer Program. (Table 1) However, hormone therapy alone is unlikely to make much difference to the overall survival of these women with late staged disease, where less than 60% of women are hormone receptor positive and eligible for hormone therapy. It is also noted that almost half the patients had unknown hormone receptor status.

Follow-up data for this cohort of women is difficult to obtain. There is no effective registration of deaths available in Cambodia. Only 169 patients who were operable were followed up for 3 years. It is assumed that the rest of the cohort, the 46 women who did not have surgery, would have succumbed to their illness. The overall 3-year survival rate of 39.1% is far below the average 5-year survival of 50% seen in low and middle income countries.(Yip et al., 2015) (Anderson et al., 2011) As expected, the 3-year overall survival in those who are hormone receptor positive is 44.8%, which is better than 35.3% in the hormone receptor negative women.

Limitations, This study was conducted in a charity hospital in Cambodia which provides services to the poor and vulnerable population of Cambodia, and does not reflect the situation in the rest of Cambodia. However it is the first study that looks at presentation and outcomes of a cohort of women with breast cancer in a low resource setting.

In conclusion, breast cancer in Cambodia presents at a younger age and with more advanced stages compared to the more developed countries in South East Asia, as well as in high income countries. While the pathology of breast cancer suggests a more aggressive disease with higher grade and ER negativity, advanced stage and limited treatment options lead to a high mortality from the disease. A more aggressive approach to early detection and treatment needs to be developed to improve outcome from this potentially curable disease.

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