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1 Cristofanilli M, et al. *Cancer Res.* 2012;72(24 Suppl):Abstract nr P3-05-01.
2 Whitworth P, et al. *Ann Surg Oncol.* 2014 Aug 7.
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The Cover Shot

Machu Picchu,"Lost City of the Incas", high in the Andes of Peru, an UNESCO World Heritage site much worth visiting.

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Editorial

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Editor

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Although still the most common female cancer worldwide, including Hong Kong, the outlook for patients diagnosed with breast cancer has been changing for the better over time, with several significant advances coming through in the past 10 years.

New technology in breast imaging has allowed an earlier and more accurate diagnosis of breast cancer not only to improve outcome but also for better treatment planning. In the era of genomics and with the study of epidemiology of breast cancer, there is increasing understanding of the risks of breast cancer. This has allowed a different approach to individuals who are at risk particularly due to hereditary germline mutations to opt for primary and secondary prevention interventions.

Earlier diagnosis has allowed less invasive surgery, moving from mastectomy to breast conservation surgery and with the evolvement of the use of oncoplastic surgery and breast reconstruction technique, the cosmetic outcome of women who have to undergo breast cancer surgery are much more satisfactory. The increased indications of use of sentinel lymph node biopsy and lesser indications of axillary dissection will result in less complications associated with the procedure such as lymphoedema.

With the past 10 years of progress in breast cancer treatment and research, women facing the disease today have many promising options as therapies become more tailored to particular disease types and are designed to minimise side effects. HER2-directed therapies have revolutionised the treatment of HER2-positive breast cancer and have reduced recurrence risks in early-stage disease and also increased response at neoadjuvant settings. Gene expression testing helps determine a patient's risk of recurrence or metastasis based on the types of genes that the cancer expresses (*gene subtyping*) and to plan treatment to most effectively reduce this risk. Specifically, these tests help determine which patients are more likely to benefit from treatment with chemotherapy in addition to hormonal therapy and hence also select those patients who may not actually need chemotherapy. We also have better drugs and better combinations of drugs to reduce toxicities and yet not compromising the outcomes. State-of-the-art radiation treatment using sophisticated machines and techniques allows the sparing of the heart, lung and skin from being damaged while targeting the breast cancer. A multidisciplinary approach of managing breast cancer patients including not only medical care but also holistic care has given women with breast cancer a much brighter future.

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Breast cancers in Hong Kong – an overview from the Hong Kong Cancer Registry

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Director, Hong Kong Cancer Registry

With an ageing population, the number of new cancers diagnosed per year has been increasing over the 10 year period from 2002 to 2012. According to the latest cancer statistics published in last November for the year 2012 from the Hong Kong Cancer Registry, there has been a 27% increase in the number of new cancers over the 10 year period, from 21,861 in year 2002 to 27,848 in year 2012.[1] Although the 3rd place ranking in new cancer numbers for breast cancer has remained unchanged (behind lung and colorectal cancers in both 2002 and 2012), its magnitude of increase at 70% over the same period was the highest among the top 3 cancers. Fortunately, the number of cancer deaths has risen less sharply by 41%, from 427 deaths in year 2002 to 604 deaths in 2012.[1] (Table 1)

Table 1 New cancer cases and deaths in Hong Kong (2012) (Source: Hong Kong Cancer Registry)

Leading cancer types *(both genders combined)*

Rank	Site	No. in 2012	No. in 2002 *(rank)*
	All sites	27,848	21,861
1	Lung	4,610	3,941 *(1)*
2	Colorectum	4,563	3,519 *(2)*
3	Breast	3,522	2,076 *(3)*
4	Liver	1,790	1,576 *(4)*
5	Prostate	1,631	912 *(7)*

Leading cancer deaths *(both genders combined)*

Rank	Site	No. in 2012	No. in 2002 *(rank)*
	All sites	13,336	11,658
1	Lung	3,893	3,383 *(1)*
2	Colorectum	1,903	1,551 *(2)*
3	Liver	1,505	1,381 *(3)*
4	Stomach	657	620 *(4)*
5	Breast	604	427 *(5)*

Indeed, considering the rate of growth and actual numbers together, breast and colorectal cancers have been identified as the 2 most rapidly growing cancers over the past 2 decades (1993 – 2012), both of which are resource-draining for treatment. (Figure 1) According to the cancer statistics of the Hong Kong Cancer Registry, they are paralleled to a lesser extent by lung cancer. The rise in new breast cancer numbers could be accounted for by the growing and ageing Hong Kong female population on one hand, and also a genuine increase in the risk of breast cancer on the other, as exemplified by an annual percentage increase of 2.4% per year over the same 20 year period for the age-standardised incidence (ASI). The ASI has already taken into account the age-specific incidences of a cancer for different age groups in the population of a particular region having specific age distribution, by applying these age-specific incidences to a standard world population, and therefore its change over time for a particular region is indicative of a genuine change of risk of developing the cancer irrespective of ageing or growth of the population in that region.

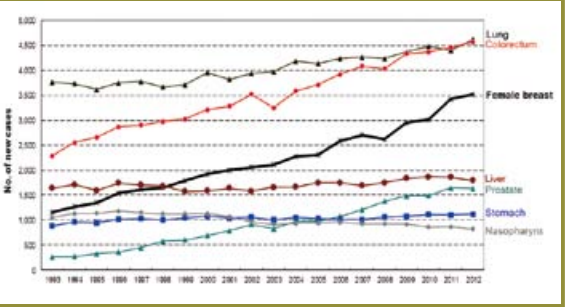

Figure 1 Trends of newly diagnosed numbers of cancers in Hong Kong since 1993 (Source: Hong Kong Cancer Registry)

The rise in ASI of breast cancer in Hong Kong might be attributed to a multitude of factors, namely westernised diet, life style changes, lack of exercise, reduced parity and breast feeding, etc, among others.[2] Despite the noticeable growth in cancer burden and ASI, the ASI of breast cancer of Hong Kong, at 56.7 per 100,000 in 2012, is still way below that of the West represented by the US (92.9 per 100,000) and UK (95 per 100,000).[3] Our ASI is even lower than that of Singapore (65.7), and is only slightly higher than that of Korea (52.1) and Japan (51.5).[3] (Table 2)

Table 2 Age-standardised incidence and mortality of different countries or cities in the world (estimates in 2012)

Country/City	Age-standardised Incidence (per 100,000)	Age-standardised Mortality (per 100,000)
Japan	51.5	9.8
South Korea	52.1	6.1
Hong Kong*	56.7	8.6
Singapore	65.7	15.5
Canada	79.8	13.9
Australia	86.0	14.0
Germany	91.6	15.5
USA	92.9	14.9
United Kingdom	95.0	17.1

Source: GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer; 2013.
**Hong Kong Cancer Registry 2012 actual figures.*

Indeed, breast cancer is the commonest cancer among females in Hong Kong, with more than 3,500 new breast cancers diagnosed in 2012.[1] The median age of diagnosis was 54, and it was the commonest cancer in the age groups ranging from 20 to 74. Among the different age

groups, increases in the number of new breast cancers have been most noticeable in the age groups of 45 – 54 and 55 – 64. Based on the trends of age-specific breast cancer incidences and the anticipated age distribution of the Hong Kong female population according to the Hong Kong Census Department, the Hong Kong Cancer Registry is projecting a record number of around 6,000 new breast cancers to be diagnosed in year 2030.

Breast cancers accounted for more than 600 deaths in 2012, the median age at death being 59.[1] Fortunately, despite an increase in ASI at 2.4% per year over the past 20 years, the age-standardised mortality (ASM) has remained largely stable over the same period. The observation is also mirrored by the Surveillance, Epidemiology and End Result programme (SEER) report of an improvement in overall survival in breast cancer patients in the US.[4] There are a number of good reasons contributing to the apparent survival improvement in Hong Kong – introduction of more effective treatments accessible to the majority, better medical supportive therapy, more early stages at presentation due to frequent opportunistic screening and public awareness, and better health condition and improving longevity of the Hong Kong population at large.

We reported in 2011 survivals of 7,500 patients with breast cancer diagnosed from 1997 – 2001 in the population of Hong Kong.[5] The 5 year relative survival, cause-specific survival and disease-free survival were 84%, 85.2% and 81.2% respectively. Stage 1 and stage 2 patients' 5 year relative survivals (97% & 89% respectively) were far better than those of stage 3 and stage 4 patients (68% & 19% respectively), underscoring the importance of early diagnosis. In a subsequent analysis of another 10,600 patients diagnosed in the years 2002 – 2006, the 5 year relative survival of the whole group was around 86%. (unpublished data) The 85.6% 5 year relative survival observed for the whole group of ~18,100 patients diagnosed over the 10 year period from 1997 – 2006 in Hong Kong was similar to the 5 year survivals reported by the cancer registries of Taiwan and Korea (82.9% and 88.5% respectively) and SEER (87.1%) over the same period.[6-8]

With a view to elucidating the clinical profiles of the breast cancers diagnosed in Hong Kong in recent years to understand the epidemiology and their relevance to survival outcomes, the Hong Kong Cancer Registry has started collecting key clinical data since about 10 years ago. In a cohort of more than 9900 patients diagnosed in Hong Kong during the period of 2010 – 2012, two-thirds were diagnosed of stage I or II cancers, 21% presented with stage III or IV cancers while 12.2% had unconfirmed stages. Among those patients, hormonal and/or human epidermal receptor-2 (HER-2) status were unknown in about 9%; 68% had oestrogen-receptor (ER) positive cancers, 53% had progesterone (PR) positive cancers, and 23% had HER2 positive cancers. With regard to the treatments delivered, 24% of those ~8,800 patients in whom the clinical data of both chemotherapy and radiotherapy treatments could be confirmed received neither chemotherapy nor radiotherapy after surgery. On the other hand, 39% patients had received both chemotherapy and radiotherapy, while 16% and 22% patients had received chemotherapy and radiotherapy alone respectively. (unpublished data)

In the foreseeable future, breast cancer will still be the most common cancer in Hong Kong females, posing a significant threat to the female population and the health care providers in both the public and private sectors despite a noticeable improving survival. The Hong Kong Cancer Registry of the Hospital Authority will be scaling up its strenuous efforts in collecting accurate and clinically relevant cancer-related data of all breast cancers diagnosed in Hong Kong, with a view to serving its role in cancer control in accordance with the International Association of Cancer Registries (IACR) of which we are a voting member, providing timely data to planners of health care strategies for breast cancer control, and collaborating with researchers in epidemiology and outcome studies.

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Hereditary Breast Cancer

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There are many environmental and epidemiological factors which will increase the risks of breast cancer and ovarian cancer such as the adaptation of a Western lifestyle and hormonal related factors. Around 15-20% of women who develop breast cancer have a family history, in what is known to be "familial" and another 5-10% a true genetic predisposition, that is "hereditary". Although it is not the most common cause, there is no other risk predictor which is as strong as an inherited mutation such as tumour-suppressor genes BRCA 1 and BRCA 2 being the most common hereditary genes related to breast cancer. A mutation in one of the BRCA genes can significantly increase the lifetime risk of breast cancer to 40-80%, and that of ovarian cancer from 11-40%. Men carrying such mutations would have 1-10% lifetime risk of getting breast cancer and up to 39% may also have prostate cancer. Apart from BRCA 1 and BRCA 2 mutations, several less penetrant genes and less common genes such as PTEN, TP53 and recently PALB2 have been identified, which when mutated, result in a significant increased risk of breast cancer as well as other cancers such as sarcoma, leukaemia and brain tumour for TP53, and thyroid cancer for PTEN. Such genes follow the autosomal dominant pattern of transmission, hence alterations in these genes can be passed down from either the paternal or maternal side. The probability of an offspring carrying the mutation is therefore 50 percent and genotypically there cannot be any "skip generations" in the inheritance. Knowing the genetic risk is as important as the environmental risks, as it is the interactions of the risks predisposed by these mutated genes with environmental and lifestyle modifiers that result in the phenotypic presentation of cancer.

Timely identification and periodic screening of high risk individuals may allow early detection of breast and other cancers, improve prognosis and treatment outcomes. There is growing evidence that breast and ovarian cancers are preventable in women with a *BRCA1* or *BRCA2* mutation. Although to date there is no supporting evidence on the benefits in the overall survival, prophylactic mastectomy is known to reduce the risk of breast cancer by 80% in women with a family history of breast cancer and by 89% risk reduction in women with a *BRCA1* or *BRCA2* mutation. Prophylactic salpingo-oophorectomies not only reduce the risk of ovarian/fallopian/peritoneal cancers by ~80% in women with a *BRCA1* or *BRCA2* mutation but it has also been shown to reduce the risk of breast cancer. For women who had preventive surgeries before age 40, a 50% risk reduction in breast cancer has been observed. Moreover, a prophylactic salpingo-oophorectomy has been found to reduce ovarian and breast cancer related mortality and all cause mortality in BRCA mutation carriers. The effectiveness of tamoxifen for primary prevention of breast cancer in BRCA1 carriers is not yet proven and its use in this setting is not widespread. However, tamoxifen has been shown to reduce the risk of contralateral breast cancer in both BRCA1 and BRCA2 carriers by 50%. Other agents which have been used for prevention of breast cancer include Raloxifene and there are ongoing studies on the use of aromotase inhibitors and other agents in the prevention setting being performed. If an individual does not opt for active prevention measures, she may be offered alternate screening interventions, including the choice of intensive breast surveillance (MRI breasts in addition to standard breast imaging such as mammography and ultrasonography) and ovarian screening including ovarian ultrasonography, CA125 and pelvic examination.

Table 1 NCCN Management of the hereditary breast and/or ovarian cancer syndrome
(Adapted from the NCCN guidelines, version 2.2014)

Hereditary breast and/or ovarian cancer syndrome management (NCCN guidelines)
• Breast screening
› Annual breast MRI screening or mammogram for aged 25-29y/ breast MRI screening and mammogram for aged ≥35-70y/individual consideration for aged >70y
• Risk-reducing mastectomy
› Counselling may include a discussion regarding degree of protection, reconstruction option and risks
• Risk-reducing salpingo-oophorectomy is recommended for those aged 35-40y and upon completion of child bearing
› Counselling may include a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms
• Address the psychosocial, social and quality-of-life aspects
• For those who have not selected risk-reducing salpingo-oophorectomy, consider concurrent transvaginal ultrasound and CA-125 monitoring starting at 30y or 5-10y before the earliest age of first diagnosis of ovarian cancer in the family
• Consider chemoprevention for breast cancer and ovarian cancer
• Consider investigational imaging and screening studies

Moreover, apart from the option of taking preventative measures, for breast cancer patients, knowing her risk status will aid decision treatment options, such as the consideration of mastectomy instead of breast conservation surgery, options of contralateral prophylactic mastectomy and more recently the choice of chemotherapy as primary treatments such as the use of carboplatin as a neoadjuvant agent and the evolvement of the use of targeted therapies, such as PARP inhibitors in the near future.

The assessment of an individual's risk for breast cancer is therefore complex. Moreover, it is important to give sufficient information to patients to aid them in the choice of management when the individual is found to be a mutation carrier. Therefore, the most important emphasis for high-risk individuals should not be put on getting the patients to be tested alone but to include genetic counselling as an essential part of the consultation. Genetic counsellors and clinical geneticist/surgeons should enable the patients to weigh the consequences and benefits in the context of his/her life and subjective values, providing a reassuring environment and counselling that leads to autonomous choice suitable for the individual.

Other hereditary breast cancer susceptibility genes and multigene panels

There are other low penetrant genes that are found to be associated with hereditary breast cancer which are less commonly tested such as *STK11*, *CDH1* and *MMR* genes, being responsible for Peutz-Jeghers and Hereditary Diffuse Gastric Cancer and Lynch syndrome respectively. Some moderate penetrance genes such as *CHEK2, ATM, BRIP1, RAD51C, RAD51D, BARD1, MRE11, RAD50, NBS1* and *FANCM* have also been recognised as breast cancer susceptibility genes. Recent development of multi-gene testing and advanced technology in Next-generation sequencing enable simultaneous analysis of specific panel of genes, and have allowed a flux of multi-gene panel kits being created and sold commercially. Although they are likely to be beneficial in contributing to prevention and possible guidance to drug management in future, there are still limited outcome data on clinical interventions particularly in lower penetrance gene mutation related breast cancers. Therefore results of multigene panels may pose difficulty in interpretation and clinical decisions and are best left for research settings and use of these panels in clinical settings should be decided upon in a case to case basis.

The Hong Kong Hereditary Breast Cancer Family Registry

The Hong Kong Hereditary Breast Cancer Family Registry was developed in March 2007 as a charitable organisation to subsidise those who are underprivileged to have the opportunity to undergo genetic testing. The Registry has also been collecting data from high risk families with consent, to study the mutation spectrum in the Chinese population. Together with the Hong Kong Hereditary High Risk Breast and Ovarian Cancer Programme which is a joint effort of University of Hong Kong, Hong Kong Sanatorium and Hospital and Stanford University School of Medicine, the programme has supported over 1800 families to date for genetic testing for risk assessment. Moreover a multidisciplinary team of genetic counsellors, nurses, surgeons, oncologists and research scientists have contributed to the programme to improve the knowledge of hereditary breast, ovarian and prostate cancers in our locality. Breast cancer patients and/or ovarian cancer patients and more recently prostate cancers can now be referred to join the programme and where suitable, the testing costs can be subsidised. Patients can also contact the registry directly to ask for more information about genetic testing and trained personnel would be able to guide individuals if their genetic testings are suitable and refer them to high risk clinics where appropriate. The testing criteria are similar to that of international guidelines with some adaptations to our locality. Breast cancer patients who (1) have at least one 1st or 2nd degree relative with breast cancer and/or ovarian cancer; (2) aged 45 years old and below; (3) have bilateral breast cancers; (4) have triple negative breast cancer; (5) have at least 1 relative with BRCA mutation related cancer; (6) are ovarian cancer patients with/without a family history of breast cancer; (7) have male breast cancer are suitable for testing for the BRCA mutations. For families with breast cancer and also other types of cancers, their family history will be assessed and recommendation of the type of genetic testing will be given. Each individual is given a genetic counselling process apart from the testing to ensure the implications for genetic testing was understood. The gold standard technique *BRCA1* and *BRCA2* mutations by bi-directional Sanger sequencing of all coding exons and multiplex ligation-dependent probe amplification (MLPA) were initially performed but since 2011 the use of next-generation DNA sequencing to expedite analysis workflow and expand gene panel to include *TP53* and *PTEN* for sequencing has been implanted. The mutation screening result of a 4-gene panel *BRCA1, BRCA2, TP53* and *PTEN* in our recruited patients revealed that 9% carried such mutations. To date, a number of recurrent and founder mutations have also been identified and the Registry has now taken the testing strategy similar to that used in Ashkenazi Jews which have three known founder mutations and full genes are only tested when the recurrent and founder mutations are not detected. This has increased the efficiency of our testing so that more individuals can benefit from risk assessment.

Conclusion

Hereditary Breast and Ovarian Syndrome only comprises 10-15 % of all breast and ovarian cancers. However with the significant increased risk of cancer, available prevention and surveillance strategies, and also targeted therapies to mutation carriers being increasingly available, it is a syndrome where clinicians should look out for and refer to further investigations.

Appendix: For more information of referrals for genetic testing please contact Hong Kong Hereditary Breast Cancer Family Registry on www.asiabreastregistry.com or email: enquiries@asiabreastregistry.com

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Update in Breast Imaging - Digital Breast Tomosynthesis (3D Mammogram)

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Introduction

Breast imaging is an integral part in the management of patients with breast diseases and is a recognised method for breast cancer screening. The common imaging tools include mammogram, breast ultrasound and magnetic resonance imaging (MRI) of the breasts. There has been a long history in using mammography as screening for breast cancers and diagnostic evaluation of breast symptoms. With technological advancement, the newer generation mammography with tomosynthesis has shown improvements in cancer detection.

Mammography

Mammography is an X-ray examination of the breast. The breast is compressed between two compression plates to flatten the breast and spread the fibroglandular tissue. Two standard views are usually obtained in each breast, namely, the cranio-caudal (CC) and medial-lateral oblique (MLO) views. One projection image per breast is obtained from each compression in conventional 2D mammogram. Additional views such as spot compression may be required to clarify any suspicious mass or distortion and a magnified view is required for better morphologic characterisation of microcalcifications. The entire procedure of bilateral mammography would take about 5-10 minutes.

Mammography Development

Mammography has been used for more than 50 years. In the old days, mammography was performed using film screen mammography. Early results in the 1960s were promising and had a true positive rate of 79% and a false negative rate of 21%. Since then, multiple randomised control trials (RCT) had proved mammography screening is effective in early detection of breast cancers and in reducing the mortality range to 20-32%.

In the 1990s, Computed Radiography (CR) was used as a transition technology from analogue output to digital. However, the higher radiation dose associated with CR systems without significant benefits over diagnostic accuracy makes this technology less acceptable. Chiarelli et al in her study showed that CR systems were significantly less likely to detect cancers by 21% compared with film screen mammography.

In the digital era in the 2000s, although Full Field Digital Mammography (FFDM) had a similar overall diagnostic accuracy for screening of breast cancers compared with film mammography, digital mammography had been shown to be more accurate in women under the age of 50 years, women with radiographically dense breasts and premenopausal or perimenopausal women as demonstrated in the Digital Mammographic Imaging Screening Trial (DMIST).

Digital Breast Tomosynthesis

Mammogram is the only method of screening for breast cancers proven to have mortality benefits by RCT as well as a key diagnostic tool for evaluating breast symptoms. Its accuracy is, however, limited by the overlapping dense fibroglandular breast tissue. Small breast cancers or cancers having a similar density with the normal breast tissue may be obscured in traditional 2D mammography. There isare also concerns of false positive recalls and unnecessary biopsies from tissue superimposition by overlapping tissues that mimic pathology in screening mammography.

Digital breast tomosynthesis (3D mammogram) is a revolutionary new screening and diagnostic tool designed for detecting early breast cancers. 3D tomosynthesis data set virtually eliminates detection challenges associated with overlapping structures in the breast, being the primary drawback of conventional 2D analog and digital mammography. In addition, breast tomosynthesis increases lesion and margin visibility, help in localising lesions in the breast, reduce false positive recalls, and increasescancer detection.

Breast tomosynthesis is a form of limited angle tomography. Multiple projection images of the breasts are obtained from different angles of the rotating X Ray tube at a low radiation dose through the compressed breast. Images are reconstructed into multiple slices of 1mm thickness, viewed by trained radiologists through a dedicated monitor which is approved for tomosynthesis. Structures in each plane of the tomosynthesis slice are more clearly visible without the structure noise from overlapping tissues in front or behind the plane of interest.

First and Second Generation Digital Breast Tomosynthesis (3D Mammogram)

Although tomosynthesis has the advantages of

removing overlapping tissues, it is essential for radiologists to read the 3D mammogram together with a 2D mammogram. 2D mammogram is essential in the assessment of side to side symmetry, to assess for interval changes, to detect calcifications which are usually distributed in different slices on Tomosynthesis, and to recognise the distributional aspect of the features. In 2011, the U.S. Food and Drug Administration (FDA) approved the use of the first tomosynthesis machine to do 3D Mammogram for screening and diagnostic purposes, given that an additional 2D mammogram has to be performed. Since then, many studies had shown that there were marked improvements in cancer detection and lower false positive recalls with implementation of tomosynthesis compared with 2D mammography alone.

Despite the advantages of better cancer detection in the first generation tomosynthesis, the technology was not widely used as people were concerned about the additional 2D mammogram exposure and the discomfort associated with the longer compression duration.

Advantages of Second Generation Digital Breast Tomosynthesis

With advancements of technology, the second generation tomosynthesis utilises the 3D dataset to synthesise or reconstruct a 2D mammogram image without an additional exposure of 2D mammogram. Its use was approved by the U.S FDA in late 2013. The synthesised 2D Mammogram has image quality comparable to a FFDM and has been established in the Oslo Screening trial.

Without the need for additional 2D Mammogram exposure, the radiation dose used in the second generation tomosynthesis can be half of that in the first generation and the breast compression duration can be shortened.

By eliminating the overlapping tissues, tomosynthesis can assess the lesion margin more accurately (Fig 1) and detect better morphological details (Fig 2). More cancers can be detected be it in dense breasts or fatty breasts (Fig 3 & 4). It can also eliminate the need for additional spot compression views as clarification of false positive tissue superimposition and detection of distortion can be readily seen by reading through the tomosynthesis slices. There is no need for additional tangential views to establish whether a nodule or calcifications are skin lesions by identifying the lesions at the top or bottom slices of the set of tomosynthesis images. (Fig 5) It may also offer another benefit of applying less compression force in tomosynthesis without compromising image quality.

Multiple researches have reported on the clinical performance of breast tomosynthesis and found increased sensitivity (cancer detection) and specificity (reduction in false positive result). It was also reported that tomosyntheis can have a 40% increase in the detection of invasive cancers and a 15% drop in the recall rate.

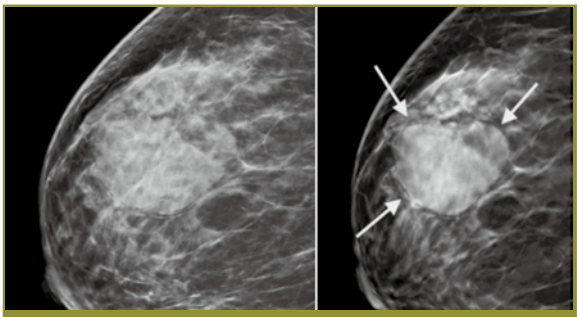

Fig 1: Lesion margin assessment is more accurate. In 2D image, the margin is partially obscured by overlapping glandular tissue (a). In tomosynthesis, the overlapping tissue is removed, resulting in sharper lesion margin (b).

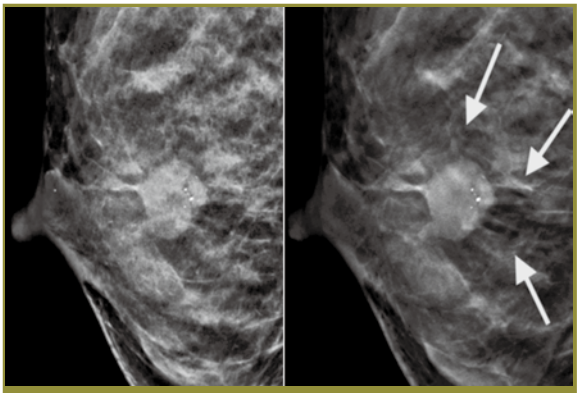

Fig 2: Spiculations are more obvious in tomosynthesis slice. In 2D image, the mass appears circumscribed (a). In tomosynthesis, it is obvious that it is a spiculated mass. (b)

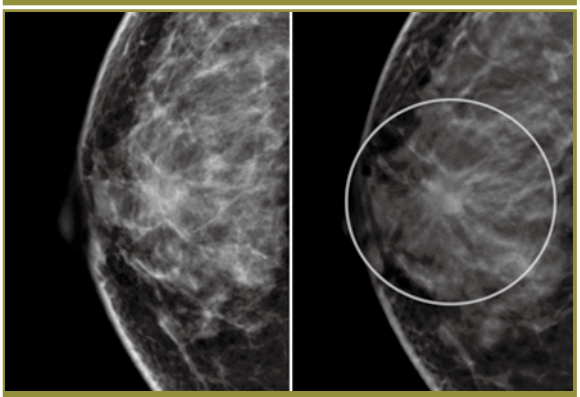

Fig 3: Right breast cancer can be missed in 2D mammogram. The spiculated mass is mammographically occult on 2D mammogram (a). The cancer is obvious in tomosynthesis (b).

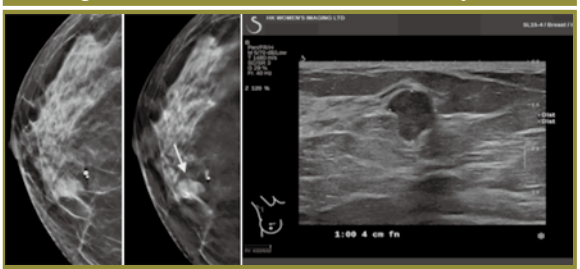

Fig 4: Tomosynthesis can identify lesions that can be missed in 2D mammogram. An oval mass is obscured in 2D mammogram (a). The mass is obvious in tomosynthesis (b). Ultrasound shows that it is a non-parallel lesion and subsequent biopsy confirms that it is an invasive ductal carcinoma (c).

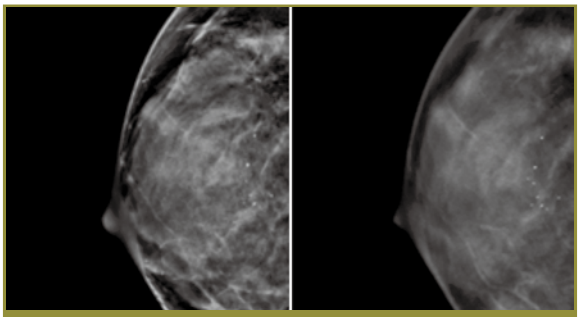

Fig 5: Tomosynthesis can preclude the use of a tangential view. 2D mammogram shows calcifications, without knowledge whether they are inside the breast or skin calcifications (a). The calcifications are shown to be at skin layer by identifying the calcifications at the top slice of the tomosynthesis dataset (b).

In the Screening with Tomosynthesis or Standard Mammography (STORM) trial, the cancer detection rate increased from 5.3 per 1000 screens with 2D mammogram to 8.1 per 1000 screens when tomosynthesis was combined with 2D mammography and an estimated 17% reduction in recalls.

The first large-scale population-based study in the U.S. published in 2013 found that breast tomosynthesis was associated with a significant increase in breast cancer detection rates (up 35% for overall cancers and 53% for invasive cancers).

A recent study involving more than 450,000 examinations published in 2014 reported that with the addition of tomosynthesis there was a 41% increase in the detection of invasive breast cancers, a 49% increase in positive predictive value (PPV) for recalls and a 21% increase in PPV for biopsies. There was also a 15% reduction in recalls.

Radiation Dose

For the first generation tomosynthesis (3D mammogram and additional 2D exposure), the mean glandular dose(MGD) for a 5cm thick 50% glandular breast is 2.5mGy, which is less than the Mammography Quality Standards Act limit for a two view screening mammography study. For the second generation tomosynthesis, the only exposure is for the 3D dataset and the dose is 1.3mGy which is about half of the first generation. Tomosynthesis study, which generates a lot more images, can be performed within the range of that for standard 2D mammography (1.2mGy).

It has to be stressed that while worrying about the radiation dose of tomosynthesis study which gives a lot more information from the images, the CR system and the older generation film screen mammography did have much higher radiation doses compared with digital mammography. As less additional views would be required in tomosynthesis, the radiation dose for second generation tomosynthesis with synthesised 2D mammogram can have much lower levels of radiation than a 2D mammogram utilising CR systems or film screen mammography with or without additional views.

Tomosynthesis guided Biopsy

The tomosynthesis technology can be extended to the biopsy platformThe target mammographic lesion can be visualised clearly on tomosynthesis slices without the need for doing stereo-pair images that may sometimes be difficult for lesions that can only be seen in one view or corresponding targets in stereo-pair images cannot be confidently localised, such as in patients with multiple scattered and grouped microcalcifications. This not only speeds up the biopsy procedure by easier and accurate lesion targeting but also offers biopsy of those lesions that are only detected on tomosynthesis.

Disadvantages of Digital Breast Tomosynthesis

The capital cost and maintenance cost are increased, not only for the machine but also the need for a dedicated workstation approved for tomosynthesis. It also requires a larger storage size for the large amount of digital images generated. There is a learning curve for radiologists to master images reading and the reading time is much increased to as much as 1.5 to 2.3 times compared to conventional digital mammography as there are more images required to be read. Moreover there are still some limitations in the detection of calcifications. Italso requires the provision of a tomosynthesis guided biopsy option for patients with lesions that are only visible on tomosynthesis.

Digital breast tomosynthesis cannot replace an ultrasound study which is a primary imaging modality to evaluate a breast mass. For a mass detected by tomosynthesis, there is no way to tell whether it is cystic or solid, or the vascularity or stiffness of the lesion without a supplementary ultrasound study.

ACR Statement

In 2014, the American College of Radiology (ACR) issued a Statement on Breast Tomosynthesis which stated that breast tomosynthesis has been shown to be an advanceover digital mammography, with higher cancer detection rates and fewer patient recalls for additional testing. Tomosynthesis has been shown to improve key screening parameters compared to digital mammography. This technology is now used in clinical practice and is no longer investigational.

Conclusion

Digital Breast tomosynthesis (3D mammogram) not only has better accuracies in terms of increased cancer detections and reduced false positive results, it can also be performed more comfortably for women with fewer additional spot compression views and less compression can be applied than that in traditional 2D mammograms with no evident difference in image quality. However there are still some limitations and hence case selection is important. With increased knowledge and experience, Digital Breast tomosynthesis is likely to be the future standard of care in breast imaging.

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Updates in surgical treatment of breast cancer

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Introduction

With the increase in public awareness of breast cancer and increasing use of breast imaging, there are more screen detected and non-palpable breast cancers. Surgery remains the mainstay of treatment for breast cancer, the goals of which include complete resection of the tumour, with negative margins in order to reduce the local recurrence and to obtain the pathological staging so as to provide the prognosis and subsequent adjuvant treatment. For the primary tumour, there are two main types of surgery, namely mastectomy and breast conserving therapy. For the axillary part, either sentinel lymph node biopsy or axillary dissection would be done. For mastectomy patients, reconstruction could be performed as an immediate procedure or performed at a delayed stage.

Pre-operative diagnosis for breast cancer

For breast cancer patients, it is preferable that histological confirmation of malignancy is available before definitive surgery. This is usually done by large bore needle core biopsy. In this way, better planning (including need for axillary surgery and options of immediate reconstruction) can be discussed in detail. In addition, intraoperative frozen section confirmation and re-operation can be avoided. Pre-operative histological confirmation is preferred in addition, as cytology can associate with false positive results. Apart from confirmation of malignancy, immunohistochemical staining on large bore needle core biopsy specimens also provides information on tumour grading, ER and PR status, overexpression for c-erbB2 oncoprotein and Ki 67 status. This information together with the clinical staging, will help to select patients who will benefit from neoadjuvant treatment. Such information is also paramount in the decision of post-operative adjuvant therapy.

Surgical management of breast cancer patients

Surgery involving the primary tumour would either be in the form of breast conservation therapy or mastectomy.

For breast conservation therapy, we have to localise the tumour before the operation. Accurate localisation will enable achievement of negative margins with the minimum excision volume. There are several ways to do the localisation, namely by palpation, ultrasound, stereotactic technique by inserting a hook wire or injection of isotopes. In suitable cases, endoscopic assisted breast conserving surgery would be done. For those non-palpable lesions, prior localisation is usually performed by a radiologist on the day of the operation. Intraoperatively, we resect the target lesion with the help of a hand held gamma detector probe or with the guidance of a hook wire. The specimen would then be sent to the radiology department for specimen mammogram and scintigraphy to ascertain that all the targets are removed during the operation.

For patients undergoing mastectomy, it is mandatory to have a histological confirmation prior to the operation. Currently, mastectomy variations include simple mastectomy, skin sparing mastectomy, nipple areolar sparing mastectomy and areolar sparing mastectomy. The choice depends on the size, site of the primary tumour, presence of skin involvement and reconstruction decisions. Skin sparing mastectomy, nipple areolar sparing mastectomy and areolar sparing mastectomy are suitable for patients who undergo immediate reconstruction. Reconstruction can be performed by using autologus myocutaneous flaps, or implants. The most common myocutaneous flaps used are the TRAM (Transverse rectus abdominis flap) and the latissimus dorsi flap. There is also an option of an DIEP flap (deep inferior epigastric perforator flap) if plastic surgical expertise is available. The prosthesis used is usually either a saline or silicone gel prosthesis. For some cases where a two staged approach is anticipated, a temporary expander of all the above mastectomy and reconstruction options, oncological clearance is still the first priority.

The chief aim of axillary procedure is for nodal staging which dictates subsequent adjuvant treatment. For clinical T1 or 2 N0 tumours, a sentinel lymph node (SLN) biopsy is the standard procedure. SLN could either be localised by blue dye, isotope or both. The blue dye would be injected by the surgeon after anaesthesia while the Tc-99m sulphur colloid isotope would be injected by a radiologist/nuclear medical specialist at the radiology/nuclear medicine department. The harvested SLNs would be sent immediately to the pathology department for frozen section. If the SLN is positive for metastasis, level 1 & 2 axillary dissection would be performed in the same operation. Pre-operative counselling would include the false negative rate of the frozen section as this is higher when the size of the metastasis is smaller than 0.2mm. The decision on reoperation should be individualised if the paraffin section confirms LN metastases which were not diagnosed during frozen section.

Axillary management for ductal carcinoma in situ warrants special consideration. As DCIS is usually confined within the breast, level 1 & 2 axillary dissection

is not indicated. However, if the preoperative diagnosis is established by core biopsy, there is a chance of under diagnosis as invasive foci may be missed by the initial biopsy. Therefore in selected cases (i.e. high grade DCIS, mass forming DCIS, patient undergoing mastectomy) SLN biopsy is advisable. However, intraoperative analysis by frozen section may not change intraoperative management decision and therefore can be omitted and further planning can be made when final pathology results are available.

The surgical management of breast cancers has evolved from more radical resections to a more conservative approach both in the breast and axilla. There is also an increased use of neoadjuvant therapy and oncoplastic surgical techniques which have increased the spectrum of women who would be able to choose breast conservation surgery as an option. Cosmetic outcomes after oncoplastic surgery and reconstructive surgery have increased the choice of surgery to achieve cosmetically sound results and yet not compromising oncological care.

Follow-up protocol

Follow-ups of breast cancer patients can detect local recurrence, systemic metastases, contralateral breast cancer and complications from previous treatment (e.g. lymphoedema, amenorrhoea, osteoporosis, keloid scar…). Regular full body imagings such as the use of CT scan, PET CT scans and tumour marker analysis is not considered standard of care at present as their use will not prolong survival. Regular surveillance mammogram with options of ultrasonography as a compliment is recommended to detect ipsilateral breast tumour recurrence and contralateral cancer. As recurrence may occur >5 years after completion of definitive treatment, breast cancer patients should have extended clinical follow-ups.

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Physiotherapy Management in Breast Cancer

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A. Lymphoedema Management

1. Introduction

Lymphoedema is an abnormal accumulation of protein-rich fluid in the interstitial space caused by obstruction of the lymphatic drainage system. The condition causes chronic inflammation and reactive fibrosis of the tissue and may progress to elephantiasis.

Breast cancer related lymphoedema (BCRL) is a type of secondary lymphoedema complicated by cancer treatment such as surgery or radiation therapy, which would damage the lymph system. One in five women breast cancer patients develops arm lymphoedema. Extensiveness of lymph nodes excision, radiation therapy, obesity, infection and genetic predisposition are the risk factors for BCRL.

2. Stages of Lymphoedema

The staging of the lymphoedema published by the International Society of Lymphology is as follow:

Stage 0: Latent or subclinical
Swelling is not yet evident; impaired lymph transport; subtle changes in tissue fluid and/or composition; change in subjective symptoms e.g. feeling heaviness

Stage 1: Reversible
Oedema regresses with limb elevation; early accumulation of fluid that is relatively high in protein content; pitting oedema may be present

Stage 2: Irreversible
Irreversible oedema with fibrosis, hyperpigmentation

Stage 3: Lymphostatic elephantiasis
Trophic skin changes; extensive fibrosis may cause hardening of tissues and disfigurement, easy infection of skin; uncontrolled buildup may develop elephantiasis

3. Assessment of Lymphoedema by Bio-impedance measurement

It is hard to cure lymphoedema. Hence, preliminary evidence is to advocate early detection and expedite intervention so as to prevent the condition from deteriorating. Bio-impedance spectroscopy (BIS) can aid early detection and early intervention.

Bio-impedance spectroscopy (BIS)
Bio-impedance is the measurement of tissue resistance to an electrical current. BIS is used to measure differences of extracellular fluid in an arm or leg using the unaffected arm or leg as a reference presented as a ratio. The standardised cut-off value to demonstrate the presence of lymphoedema is determined by the ratio greater than a mean ratio plus three standard deviations observed in a comparable healthy population. The BIS device score (Diagram 1), which indicates whether the extracellular fluid is within normal range or beyond the ratio threshold, can be an early sign of lymphoedema. It aids in detecting sub-clinical unilateral lymphoedema Periodic monitoring with BIS reduces the incidence of clinical lymphoedema from 36.4% to 4.4%.

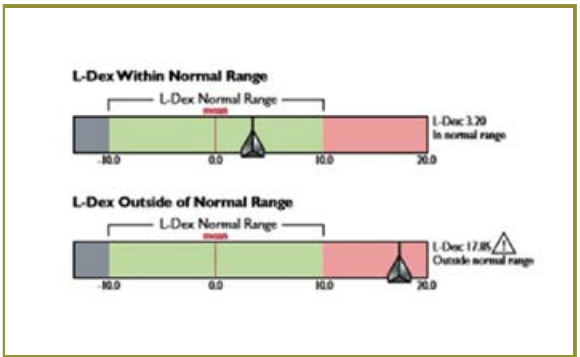


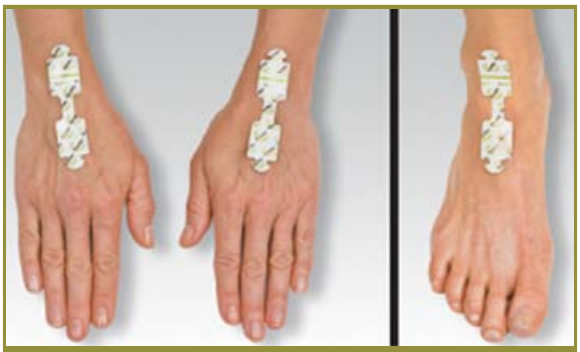
Diagram 1: (above) a score within normal range; (below) a score outside the normal range implying early sign of lymphoedema5.

3.1. When to perform a BIS?
It is advised to do a preoperative baseline assessment followed by periodic BIS measurements with 3 – 6 months intervals is suggested. . Effective prevention of lymphoedema helps to improve quality of life and reduces the health care costs.

3.2. How is a BIS performed?
Measurements are performed with the patient in a supine position. Electrodes are attached to the standard anatomical positions (Picture 1) by a trained nurse or physiotherapist.

3.3. Limitations

BIS has limitations in bilateral swelling since there is no "normal side" for comparison. In such patients, circumference measurements would be a better choice for monitoring. The pre and post-surgery circumference measurements provide affordable, convenient and yet reliable information but sub-clinical lymphoedema may be undetectable.



Picture 1: Electrodes placed in standardized anatomical position at wrist and ankle

Picture 2: Multilayer bandaging

Picture 3: (above) commercially-made compression sleeve; (below) tailor-made flat-knitted compression sleeve and glove

4. Treatment of Lymphoedema

4.1. Combined Decongestion Therapy (CDT)

CDT is an effective way to manage lymphoedema and consists of the following components:

4.1.1.Manual Lymph Drainage (MLD)

MLD promotes the lymph flow by stretching and releasing of the skin. This rhythmic massaging of the skin helps to stimulate the lymphatic flow and its return to the blood circulation to the desired directions of flow. Therefore in unilateral BCRL, lymph fluid is redirected from the affected limb and axilla to the unaffected axillary lymph nodes and ipsilateral side of the inguinal nodes. For bilateral BCRL, the lymph fluid of the bilateral axilla will be directed to the bilateral inguinal nodes.

4.1.2. Compression Therapy

Compressive bandaging or compressive garment is used. Multilayer bandaging (Picture 2) of the upper limb is done such that high pressure is applied distally with gradual decrease in pressure proximally. Short stretch bandage provides low resting pressure while the arm is in a static position and provides high pressure when the arm is in motion. This enables adequate swelling control at rest while increasing effectiveness when muscles are contracting. Bandages can also soften fibrosis.

A compressive sleeve is relatively easier to wear and therefore more convenient when used in daily life. A compression force of 20-30 mmHg is suggested. Multilayer bandaging has an advantage over commercially-made compressive sleeves (Picture 3) as it provides better pressure support to the changeable and irregular shape of the arm compared to the latter.

Tailor-made flat-knitted pressure garment is also recommended as it provides optimal pressure over the narrow part of the arm as well as the widest part of the arm and hand.

For lymphoedema stage 0 and 1, a compressive sleeve will be used to stabilise the swelling and prevent deterioration. For lymphoedema stage 2 and 3, compressive bandaging will be the predominate choice for reducing the volume of the swollen arm.

4.1.3. Skin Care

Compressive bandages and garments may absorb the moisture and oil of the skin and stress the skin. Regular application of a pH-neutral cream can maintain hydration of the skin.

4.1.4. Therapeutic exercise and breathing exercise

Muscle and joint movements will increase passive lymph transport in intramuscular, intracapsular and intraligamentary lymph collectors.

Abdominal breathing changes the intra-abdominal pressure which acts as a pump to the deep lymph ducts and promotes the lymph flow.

4.2 Treatment phases for CDT

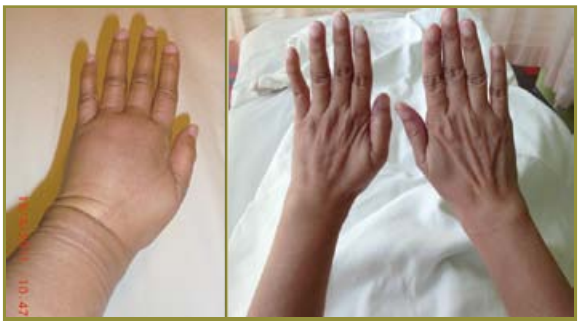
Phase 1 Decongestive phase

This is the intensive treatment phase. A daily treatment for 4-6 weeks according to the severity of the lymphoedema is recommended. Daily MLD and bandaging is applied with instructions for exercises. Compression bandage should be worn 24 hours if tolerable. There should not be any numbness or pain. The aim is to achieve the maximum volume reduction and once volume reduction has plateaued, phase 1 treatment will be weaned off and the patient can be progressed to the maintenance phase.

However, most patients are unable to comply with a daily treatment regimen for 4 weeks and for less severe cases 2 weeks is acceptable.

Phase 2 Maintenance Phase
Patients and their caregivers will be trained with self-MLD and bandaging techniques at home during phase 1. Tailor-made pressure garment is suggested when patients are discharged from physiotherapy. The goal of this phase is to maintain themselves to what has been achieved in Phase 1. (Picture 4)

Patients will be educated on how to handle changes in lymphoedema condition and taught how to strengthen their arm without making the lymphoedema worse. They are guided to modify daily life to avoid overstress of the arm. They should be confident in self-home management of their condition upon discharge.



Picture 4: (left) before treatment; (right) after treatment

5.Conclusion
Lymphoedema is a progressive condition if it is untreated and can be disabling. Patients should be equipped with the knowledge and skills to prevent and manage this secondary sequela from cancer treatments. Physiotherapists provide pre-operative examinations, educations, ongoing monitoring, early identification and specialised CDT intervention. Proactive prevention and effective management can enhance the life quality on their road to recovery.

B. Physical Fitness Training

1. Background Information
Cancer patients very often experience side effects that limit their physical ability during treatment and afterwards. Overall physical function is generally diminished because of loss of aerobic capacity, muscle tissue, flexibility, body composition and neuromotor function. Exercise is an important treatment for the recovery and rehabilitation of cancer survivors.

Cancer-related fatigue is indeed the most common symptom in breast and other cancer survivors. It often causes significant disruption in functioning and affects quality of life. The medical origin such as anaemia, cachexia and dehydration should be treated first. If the level of fatigue persists with unrelated recent changes in activity level, patients are advised to undergo a supervised exercise programme for improving physical fitness and cognitive behavioural therapy for lifestyle adjustment. An early-supervised exercise programme can have positive effects on cancer-related fatigue, submaximal cardiorespiratory fitness and muscle strength.

Supervised exercise also improves overall quality of life. Most breast cancer survivors are overweight obese which contributes to a worse prognosis among breast cancer patients. Exercise helps to maintain or reduce weight.

Evidence has shown that breast cancer survivors have an increased risk of heart failure and coronary artery disease, which may be related to chemotherapy and radiation induced cardiac toxicity. Exercise rehabilitation reduces such risks.

2. Exercise Testing
Measurement of physical fitness is a common practice in rehabilitative exercise programmes. The test helps to provide data in the development of individualised exercise regimes, collect baseline and follow-up data for evaluation of progress and to establish fitness goals.

There are a few considerations prior to exercise testing and designing the exercise programme

- Evaluation for peripheral neuropathies and musculoskeletal morbidities secondary to treatment If there has been hormonal therapy and/or known metastatic disease to the bone, risk of fracture needs to be assessed
- Assessment of likelihood of cardiac toxicity
- Evaluate shoulder morbidity prior to upper body exercise
- Evaluate health history, comorbid chronic diseases and any exercise contraindications
- Evidence- based literature indicates 1RM testing is safe among survivors of breast cancer
- Use a leg ergometer rather than treadmill for exercise testing (for overweight and obese patients)
- Begin the test at a low initial workload and small increments per testing stage (for overweight and obese patients)
- No exercise testing is required to start a light intensity walking, progressive strength training, or flexibility programme

3. Exercise Programme
Survivors of cancer should avoid inactivity during and after treatment. Patients should return to normal daily activities as quickly as possible after surgery.

The exercise programme recommended by ACSM is as illustrated: 1:

Type	Aerobic training, resistance and flexibility exercise
Frequency	Aerobic: 3 – 5 days per week and gradually increase to ≥5 days per week to maximise caloric expenditure Resistance: 2 – 3 days per week Flexibility: Daily
Intensity	• Exercise tolerance may be highly variable during active treatment. Survivors who have completed treatment may increase intensity slowly for all physical activities. • Heart rate may be less reliable for monitoring intensity for cancer survivors. Therefore, it is advised to use self-rated perceived exertion (RPE) instead. However, heart rate reserve (HRR) method is potentially the most feasible method for clinical use4. Therefore, both methods would be taken into consideration. • If the patient is able to tolerate the exercise without adverse effects, the exercise intensity needs not differ from healthy populations: Aerobic: moderate intensity (40% - < 60% HRR/ VO_2R, RPE 12- 13 / 20) and eventual progression to vigorous intensity (60% - 80% HRR/ VO_2, RPE 12 – 16/ 20) Resistance: Start with a very low resistance, progress resistance at small increments. No upper limit on the amount of weight to which survivors can progress. Watch for any lymphoedema symptoms and change accordingly. Flexibility: To the point of tightness or slight discomfort. Not to exceed ROM restrictions resultant to surgery and/or radiation therapy.
Time	Aerobic: A minimum of 30 minutes per day progressing to 60 minutes per day Accumulation of intermittent exercise of at least 10 minutes short bouts is an effective alternative to continuous exercise at the beginning Resistance: At least 1 set of 8 – 12 reps Flexibility: 10 – 30 seconds hold of a static stretch for 2 – 4 reps (a total of 60s per joint is recommended)
Progression	Slow progression for cancer survivors. If the exercise leads to an increase in fatigue or other common adverse symptoms, the programme should be reduced to a level that is better tolerated. Changes in arm/shoulder symptoms or swelling should result in reductions or avoidance of upper body exercise until after appropriate medical evaluation and treatment.

4. Conclusion

Every individual with cancer can have a unique experience and response. Therefore, whilst using standard guidelines, we should implement our clinical judgements to provide a suitable fitness training programme for breast cancer survivors.

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Before prescribing, please consult full prescribing information which is available upon request.

Reference: 1. Sovaldi Hong Kong Prescribing Information (EUJAN14HKFEB14). 2. Kris V Kowdley et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicenter phase 2 trial. Lancet 2013 Mar. 3. AASLD & IDSA. Recommendations for Testing, Managing, and Treating Hepatitis C. 2014 Dec. 4. European Association for the Study of the Liver (EASL). EASL Recommendations on Treatment of Hepatitis C 2015. Journal of Hepatology. 2015 Mar.

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HKSVD0006

Adjuvant and neoadjuvant therapy for breast cancer

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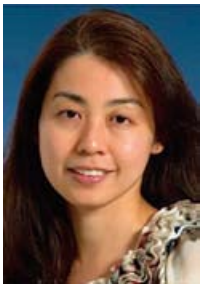
Dr Joanne CHIU


Dr Henry SZE

In Hong Kong, breast cancer is the most prevalent female cancer with an incidence of more than 3500 new cases diagnosed every year[1]. According to the American Joint Committee on Cancer staging system, breast cancers can be categorised into one of the 4 stages (I to IV) based on the size of the tumour, involvement of lymph nodes, and spread of tumour outside of the breast (a term called metastasis). Without distant metastases, most breast cancers are potentially curable.

The primary treatment modality for early breast cancers is surgical excision with mastectomy (removal of the whole breast) or lumpectomy (removal of the tumour plus surrounding tissue). The addition of adjuvant therapy has been proven to significantly enhance long-term survival after surgery[2].

Adjuvant therapy

Even in the early stage, a small amount of cancer cells might break away and be carried to distant sites. They are not detectable by imaging but could become the potential source of recurrence in the future. Adjuvant therapy is the treatment given after surgery to decrease recurrence and to improve long-term survival. Commonly used modalities include systemic therapies such as chemotherapy, targeted therapy, or hormonal therapy, and localised treatment with radiation therapy.

Chemotherapy

Chemotherapy is well recognised to decrease tumour recurrence. Commonly used regimens nowadays include anthracycline, which is often combined with cyclophosphamide with or without fluorouracil. In the long run anthracycline-based chemotherapy could effectively decrease mortality by 20-38%[2]. For more advanced node-positive disease, additional taxane is often given for its extra survival benefit[3,4].

These treatments are administered by intravenous infusion in cycles, and delivered as an outpatient. Depending on regimens, adjuvant chemotherapy usually lasts for 4-6 months. Most patients tolerate treatment with supportive medication and complete all cycles. Although anthracycline can cause more nausea and vomiting, these symptoms are fairly well controlled with effective anti-nausea medication in the modern days. Hair loss is common but it is transient. Treatment-specific toxicities include anthracycline-induced cardiac problems and potential secondary cancer, and taxane-induced peripheral neuropathy. With combination chemotherapy, the chances of bone marrow suppression leading to compromised immunity is high so patients need to be vigilant about their increased risk of infection. Since chemotherapy can permanently damage the function of the ovaries, many women develop menopause after chemotherapy and issues of family planning need to be addressed especially if the patient has not completed a family.

Who should receive adjuvant chemotherapy?

Although adjuvant chemotherapy is commonly used, it is associated with undesirable side effects. All tumours are different, and the benefit of chemotherapy depends on the inherent risk of recurrence. In general, the higher the stage of a tumour, the higher the risk for recurrence and there would be more benefit of using adjuvant chemotherapy. Besides staging, a number of tumour factors can also help determine the use of adjuvant chemotherapy. For instance, a tumour with high proliferative capacity tends to respond better to chemotherapy. Younger patients whose tumours are often more aggressive and might have more survival benefit from chemotherapy. Tumours carrying hormone receptors or HER2 receptors behave differently and the prognosis can be affected by adjuvant hormonal therapy or targeted therapy as well. Diagnostic tests such as MammaPrint® or Oncotype DX® are useful tools using additional information of gene signatures to predict the risk of recurrence when the use of chemotherapy is doubtful[5,6]. These can help identify patients who could be spared from chemotherapy and the associated side effects.

Hormonal therapy

Some breast tumours carry oestrogen or progesterone receptors. Female hormones can trigger these hormonal receptors and stimulate tumour growth. Adjuvant hormonal therapy is taken everyday orally, and is an effective means to decrease recurrence of these tumours. Tamoxifen is a commonly used hormonal therapy. It antagonises the action of oestrogen, and can be given to both pre- and post-menopausal women. Five years of adjuvant tamoxifen can significant lower the risk of recurrence and death from breast cancer by more than 30%[7]. The benefit can be further increased when the use is extended to 10 years[8]. However, prolonged use of tamoxifen can increase the chances in blockage of blood vessels (a term called thromboembolic events) and endometrial cancer. The metabolism of this drug can also be interfered by a class of psychiatric medication called selective serotonin receptors inhibitors, which are used for management of depression and peri-menopausal symptoms.

Post-menopausal women have another choice of hormonal therapy. Aromatase is an enzyme that converts other hormones into oestrogen. Aromatase inhibitors (AI) decrease the residual oestrogen levels, further lower hormonal stimulation of the tumour and decrease death from breast cancer[9]. Among AIs are anastrozole, letrozole, and exemestane. Women can take AI for 5 years, or start with tamoxifen then switch to AI after 2 years for a total treatment duration of 5 years. Most women tolerate the drug well for the whole duration of adjuvant treatment. The more common side effects are joint pain, muscle pain, and menopausal symptoms such as hot flashes and night sweats. Since the drug can lead to osteoporosis, preventive measures such as use of bisphosphonates or denosumab might be needed to improve bone health and prevent premature fracture. All women on AI should maintain a good habit of regular exercise to strengthen bone density and take adequate amounts of calcium and vitamin D in their diet.

Targeted therapy

About 25-30% of breast cancers express a surface receptor called HER2. Activation of these receptors triggers tumour cell growth and we now have medication that targets HER2 to turn off the growth signal. Trastuzumab (Herceptin®) is the first drug of its class. This drug has a selective action on tumour cells and has minimal adverse effects on normal tissue. For women with HER2-positive breast cancer, addition of the adjuvant trastuzumab to chemotherapy decreases the risk of recurrence by 50% compared with chemotherapy alone[10,11]. This drug is given intravenously usually every 3 weeks, for a total of 1 year after primary surgery. Although this drug is very well tolerated, about 5% of patients develop heart failure so patients on this drug should have regular monitoring of heart function by 2-dimensional echocardiography or radionuclide ventriculography. This cardiotoxicity usually improves once the drug is stopped[12].

Radiotherapy (RT)

Adjuvant RT given after surgery has been shown to reduce the incidence of locoregional recurrence and breast cancer deaths[13-14]. It is an integral part of breast-conserving therapy (BCT), which has become the most acceptable standard of care for the majority of women with early stage invasive breast cancer with the advantage of achieving the most optimal cosmetic results. For patients with mastectomy performed, adjuvant RT is recommended for patients with large tumour size or lymph node metastases[15]. Traditionally, RT is given as a daily treatment, 5 days a week over 5 weeks to deliver 50Gy in 25 fractions. Modern hypofractionated RT schemes using fewer treatments (13-15 fractions) and shorter overall treatment time (2.5-3 weeks) can achieve equivalent treatment outcome and are more convenient to our patients so that they can resume their usual daily activities earlier[16-18]. Thanks to the advances in technology, it is increasingly common to use more sophisticated techniques including 3D conformal RT (3DCRT) or intensity-modulated RT (IMRT) to deliver adjuvant RT for breast cancer[19-20]. These rapidly evolving techniques make it possible to direct the radiation more accurately to the breast/chest wall and the regional lymphatics including the axilla and the internal mammary chain. The radiation dose to the surrounding normal structures especially the heart and the lungs can be markedly reduced (Figure 1) and thus long term side effects can be minimised.

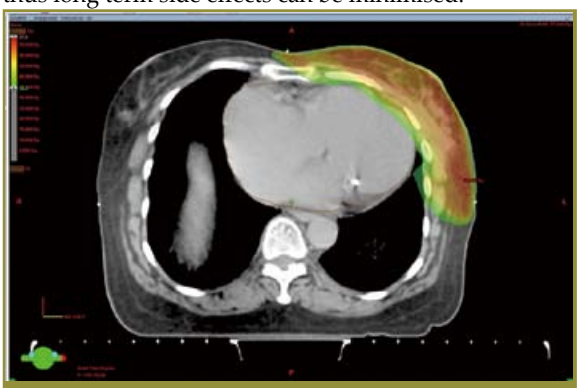

Figure 1. RT to the left breast using advanced RT technique. The left breast receives a high radiation dose while the heart is well protected.

Neoadjuvant therapy

Sometimes a breast cancer grows to a size too big to be removed surgically, or it is fairly big relative to the normal breast tissue so breast conservative therapy is not possible. Upfront systemic therapy, a term called neoadjuvant therapy, can be used to shrink the tumour so it becomes operable or makes breast conservative therapy possible. Neoadjuvant therapy can be combination chemotherapy, targeted therapy, or even hormonal therapy. In certain institutions the waiting time for surgery can be long, neoadjuvant therapy has an added benefit of avoiding any delay in treatment. Neoadjuvant therapy also has the advantage of assessing the response to treatment directly. For certain subtypes of breast cancer, a complete clearance of the tumour by treatment at the time of surgery (pathological complete response (pCR)) is linked to better long-term survival outcome. This characteristic has made neoadjuvant therapy an attractive platform for evaluation of novel drug regimens. For instance, pertuzumab is a new drug targeting HER2 receptors. Addition of pertuzumab to the existing regimen of trastuzumab and docetaxel boosted the rate of pCR from 21 to 39%[21]. As a result of this study, the drug was granted accelerated approval by the U.S. Food and Drug Administration for use in the neoadjuvant setting. The practice of neoadjuvant therapy requires close collaboration between oncologists and surgeons and therefore it is usually adopted in more established units.

Summary

Early breast cancer is a potentially curable disease. Multiple modalities are available to improve the long-term outcome by cutting down tumour recurrence. Chemotherapy, hormonal therapy, targeted therapy, and radiotherapy can be the integrated parts of treatment. Even for locally advanced tumours that are not amenable for primary surgical resection, neoadjuvant therapy can help shrink the tumour and makes surgery possible. Treatment for breast cancer is a rapidly growing field and we are looking forward to more effective therapies with less toxicity.

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*Treatment of physician's choice (TPC) or capecitabine. TPC was defined as any single-agent chemotherapy or hormonal or biological treatment approved for the treatment of cancer and to be administered according to local practice; radiotherapy; or symptomatic treatment alone. 61 (7.6%) vinorelbine; 46 (5.7%) gemcitabine; 592 (73.8%) capecitabine; 38 (4.7%) taxanes; 24 (3%) anthracyclines; 25 (3.1%) other chemotherapies; 9 (1.1%) hormonal therapy.[1,2]

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Management of Metastatic Breast Cancer (MBC)

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Introduction

Despite improvements in adjuvant treatment for early-stage breast cancer, up to 25-30% patients will still develop recurrences and metastases. Moreover, around 5-10% breast cancer patients are found to have metastatic diseases at presentation. Although metastatic breast cancer (MBC) is a highly treatable disease, it is still generally incurable. New targeted therapy agents, chemotherapeutic drugs and hormonal agents have been developed in recent years but the progress is relatively slow and the median overall survival is still only 2-3 years. It should be noted that the range is wide in this highly heterogeneous group and up to 30% may survive for 5 years.

The goals of treatment are to lengthen the survival, minimise the associated symptoms and hence improve their quality of life (QOL). The balance between treatment benefits and toxicities is most important. With the escalating cost of new cancer treatment, funding and resources are increasingly the prime concern in the choice of therapies.

General Principles

In view of the great variations of disease status in advanced breast cancers, a multidisciplinary and individualised approach is critical. The patients should be included in all steps of the decision-making process and their preferences should be duly respected. The treatment strategy should be tailored according to individual priorities and disease status with consideration of their physical, functional, psycho-social and spiritual needs.

Although occasional patients with isolated secondary or oligometastases may benefit from aggressive local ablative therapies and achieve complete remissions and long survivals, metastatic breast cancer is essentially a systemic disease that requires systemic treatment.

There are three main systemic inventions: hormone therapy, chemotherapy and biologic agents (especially anti-HER-2 agents). These can be used sequentially or concurrently in various scenarios. There are different breast cancer subtypes, clinically classified according to their ER (Oestrogen Receptor), PR (Progesterone Receptor) and HER-2 (Human Epidermal Receptor 2) status (Figure 1); hormonal therapies and anti-HER2 therapies are only relevant to tumours having respective positive receptor tests in the immunohistochemical tests.

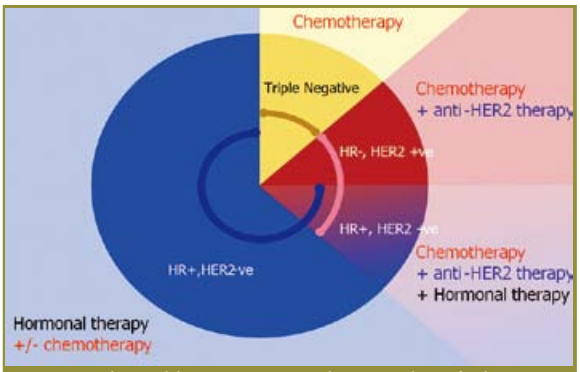

Figure 1. Clinical breast cancer subtypes, classified according to commonly available immunohistochemical tests. Hormone receptor (HR) is considered positive if ER (Estrogen Receptor) and/or PR (Progesterone Receptor) is positive.

Assessment Principles

Apart from a complete history and physical examination, the initial assessment should also include blood tests to evaluate basic organ functions and preferably serum tumour markers (e.g. CA15.3 and CEA), to facilitate disease monitoring, if elevated. PET-CT scans are increasingly used to replace the traditional CT imaging (of thorax and abdomen) and bone scan due to their increasing availability and higher sensitivity. However, a routine brain imaging (e.g. MRI brain) to exclude brain metastases in asymptomatic patients is not recommended. Evaluation of response to therapy is crucial and the imaging studies (of evaluable sites) should be done every 2-4 months; however, less frequent monitoring is acceptable for more indolent disease.

As the biological markers profile (ER, PR, HER2) may evolve in a small percentage of patients, repeating a core biopsy at the metastatic site, if clinically feasible, should be considered. If the tumour biology in the metastatic site differs from the original primary tumour, however, it is unclear which biological profile should guide the choice of treatment. It is generally recommended to consider the use of targeted therapy (hormone therapy and/or anti-HER-2 agents) when receptors are positive in at least one biopsy, regardless of timing[1].

Various factors affecting the choice of treatment are listed in Table 1. It should be emphasised that the age of the patient should not be the sole reason to withhold effective therapy in elderly patients nor to overtreat in young patients.[1]

Table 1 Factors affecting treatment choice in Metastatic Breast Cancer (MBC)

Disease-related factors	Patient-related factors
Biological markers: ER/PR/ HER-2 status	Biological age
Previous therapies : response and toxicities	Performance status
Disease-free interval	Co-morbidities (including organ dysfunction)
Tumour burden (number and site of metastases)	Menopausal status (for hormone therapy)
Need for rapid disease/ symptom control	Psychological and socioeconomic factors (particularly funding constraint)
	Patient preference

Systemic Treatment

A. Hormone therapy

For patients with hormone receptor (ER and/or PR)-positive metastatic breast cancers, hormone therapy is the initial systemic treatment of choice unless there are life-threatening components (e.g. massive liver metastases), systemic symptoms requiring immediate palliation (e.g. shortness of breath due to lymphangitis carcinomatosis of lung) or concerns about endocrine resistance (e.g. only weakly positive hormone receptors)[2]. Contrary to traditional belief, visceral involvement alone is not an indication for chemotherapy and patients with a limited visceral component can be safely treated with hormone therapy.. The benefit of second-line hormone manipulation can be up to 50% in relapsed disease and failure to benefit from an initial trial with hormone therapy correlates with subsequent failure. Common hormone agents are listed in Table 2.

Table 2 Common hormone agents

Hormone Agent	Dose and schedule	Suitability
Tamoxifen	20mg PO daily	Pre- and post-menopausal
Aromatase Inhibitors:		Post-menopausal
Anastrozole	1mg PO daily	
Letrozole	2.5mg PO daily	
Exemestane	25mg PO daily	
Fulvestrant	500mg IM monthly	Post-menopausal
Lutelinising hormone-releasing hormone (LHRH) analogue:		Premenopausal
Goserelin	3.6mg SC monthly	Alternatives include ovarian ablation by oophorectomy or radiotherapy
Leuprolide	7.5mg IM monthly	

For premenopausal patients, ovarian suppression/ ablation combined with additional hormone agents like tamoxifen or an aromatase inhibitor is often preferred. Ovarian suppression can be achieved through ovarian irradiation, LHRH analogues injection or surgical oophorectomy.

The preferred first-line hormone therapy for postmenopausal women depends the adjuvant hormone therapy regime. Options include aromatase inhibitors, tamoxifen or fulvestrant. For metastatic postmenopausal patients without prior use of any aromatase inhibitor, an aromatase inhibitor is often the first choice due to its lower cost, convenience of use (compared with fulvestrant) and higher efficacy (compared with tamoxifen).

It should be noted that the original fulvestrant dose is 250mg IMI monthly at its introduction and it has been demonstrated to have similar efficacy as aromatase inhibitors. However, a subsequent study showed that the higher dose fulvestrant (500mg IMI monthly) was equally well tolerated but would achieve a 4 month longer median overall survival. So far there are no data directly comparing fulvestrant 500mg with an aromatase inhibitor. To further complicate the issue, a recent randomised study found that the combination of anastrozole (an aromatase inhibitor) and fulvestrant was superior to anastrozole alone or sequential anastrozole and fulvestrant, despite the use of a dose of fulvestrant (250mg) that was below the current standard.[3]

For MBC patients after successful control by chemotherapy, hormone therapy is also often used as maintenance to prevent disease progression. However, concurrent use of chemotherapy and hormone therapy has not shown a survival benefit and hence should be avoided outside trial settings.

There are also two new biologic agents to enhance the effects of aromatase inhibitors in MBC: everlolimus and palbociclib. Everolimus, an oral drug inhibiting the mTOR pathway, can be added to steroidal aromatase inhibitors to prolong the disease-free survival by 5 months after failure of a non-steroidal aromatase inhibitor.[4] Palbociclib is a selective inhibitor of the cyclin-dependent kinases CDK4 and CDK6. Its approval for use was based on the results of a phase II study in which progression-free survival for patients receiving palbociclib and letrozole was 20.2 months, versus 10,2 months for those on letrozole alone. The decision to add these biologic agents should take into account of their very high cost and toxicities (particularly stomatitis by everolimus and neutropenia by palbociclib).

B. Chemotherapy

Chemotherapy is often needed for rapid disease control and may be the only available option for patients with negative hormone receptors or endocrine resistance. Combination chemotherapy gives a higher response rate and earlier onset of clinical benefit than a single agent; it may be preferred in patients with relatively fit physical conditions and life-threatening disease. However, in most other scenarios, sequential use of a single agent is often preferred so as to minimise the treatment side effects, but without jeopardising the survival.

Anthracycline- or taxane-based regimens are popular effective first-line regimens Re-challenging with anthacyclines after adjuvant treatment is often difficult due to its cumulative cardiac toxicity. However, if given in the adjuvant setting, a taxane can be re-used, especially if the disease-free interval is at least 1 year. Other effective options include capecitabine, vinorelbine, carboplatin, gemcitabine and newer agents like albumin-bound paclitaxel and eribulin. As an oral agent, the use of capecitabine is particularly attractive; it is well tolerated with minimal hair loss and only

results in mild marrow suppression. The duration of chemotherapy should be tailored to individual patients; it is usually around 6 months but can be continued till disease progression for agents.

Whilst chemotherapy should not be used concurrently with hormone agents, it can be combined with a targeted agent like anti-HER-2 agents (see below) or bevacizumab, a monoclonal antibody that blocks tumour angiogenesis by inhibiting vascular endothelial growth factor A. In contrast to the strong beneficial effect of anti-HER-2 agents, addition of bevacizumab to first or second-line chemotherapy for MBC provides only a modest progression-free survival benefit but no overall survival benefit. Considering the lack of predictive test, high cost and potential side effects, its use in MBC is controversial.

C. Anti-HER-2 Agents

Around 20% of breast cancers have over-expression of HER-2 receptors (Human Epidermal Receptor 2) and these are more aggressive disease with a higher risk of relapse and poorer survival. These anti-HER-2 agents are best used together with chemotherapy but for patients going to receive hormone therapy instead, the addition of anti-HER-2 agents can also give substantial progression-free survival benefit. Following the success of trastuzumab (a monoclonal antibody that binds to the HER-2 receptor) in both adjuvant and metastatic settings, other anti-HER-2 agents with different mechanisms have been approved for use in the metastatic setting. These include lapatinib (an oral tyrosine kinase inhibitor which interrupts the HER2-2 pathway) and pertuzumab (a monoclonal antibody inhibiting the dimerisation of HER2 with other HER receptors). In first-line metastatic settings, however, the combination of chemotherapy plus trastuzumab has been shown to be superior to chemotherapy plus lapatinib. For previously untreated HER-2 positive MBC, the addition of pertuzumab to trastuzumab (i.e. dual anti-HER-2 blockade) to chemotherapy (docetaxel), as compared with the addition of placebo, significantly improved the median overall survival to 56.5 months.[5]

T-DM1 (trastuzumab emtansine) is a new class of drugs called antibody-drug conjugates. This class of drugs combines an antibody, which is able to target certain tumour cells, with a cytotoxic agent. By delivering chemotherapy through targeted means, the cytotoxicity is confined to the tumour cells while sparing surrounding healthy tissues. Following a failure of trastuzumab-based chemotherapy, T-DM1 has been shown to provide superior efficacy than other combinations.[6]

Special Issues

Surgery of the primary tumour for patients with metastases at diagnosis

The true value of the surgical removal of the primary tumour in these patients is currently unknown and the studies are largely retrospective and conflicting. The general consensus is that surgery of the primary should not be offered as a routine practice but can be discussed on a case-by-case basis and offered to selected patients.

Oligometastatic breast cancer

A distinctive subset of MBC is oligometastatic breast cancer, characterised by a single/few detectable metastatic lesions. Available data report favourable outcomes after 'radical' local therapy (e.g. surgical resection, stereotactic body radiotherapy), in addition to systemic therapy, for limited metastatic disease. However, selection bias and the retrospective nature of data do not allow for generalisation of the results: the use of such approaches must be individualised.

Bone Metastases

Up to 70% MBC patients may develop bone metastases in their disease courses and it can markedly impair the quality of life by causing pain, pathological fractures and even spinal cord compression. Apart from titration of analgesics, palliative radiotherapy to symptomatic or strategic sites should be considered for pain relief and prevention of skeletal complications. Surgical stabilisation/fixation may also be needed for impending fractures of long bones. In cases of spinal cord compression, urgent surgical decompression can relieve neurological deficits in selected patients with limited vertebral level involvement. Apart from systemic therapy, a bone modifying agent like bisphosphonates (e.g. zoledronic acid) or a RANK-ligand inhibitor (e.g. denosumab) is now widely used to prevent skeletal-related events in patients with bone metastases. Denosumab is increasingly popular because of its ease of use (monthly subcutaneous injections) and higher efficacy; there is also no need for dose adjustment for renal impairment as in the case of zoledronic acid. Patients receiving these bone-directed therapies should be reminded to avoid invasive dental procedures to prevent the uncommon occurrence of osteonecrosis of jaw and receive calcium and vitamin D supplementation to prevent drug-induced hypocalcaemia, which can be fatal in rare cases.

Brain Metastases

Patients with extensive brain secondaries should be treated with whole brain irradiation but patients with 1-3 small brain secondaries may be treated with surgery or radiosurgery, with or without whole brain irradiation. A recently reported phase III trial (consisting mostly of lung cancer participants) found that adding whole-brain radiation therapy to radiosurgery did not significantly extend survival of patients, although it did help to control the growth of brain metastases. The risk of cognitive decline versus a longer duration of intracranial disease control after whole brain irradiation should be discussed with the patient.[7]

Conclusions

Metastatic breast cancer is a complex and heterogeneous disease which remains virtually incurable in nearly all patients. Proper choice and sequencing of systemic therapies and other supportive measures like radiotherapy and surgical intervention are crucial to lengthen the survival and maintain quality of life. Many questions remain unanswered and an individualised treatment tailoring to the patient's needs, psycho-social status and funding limitation is important.

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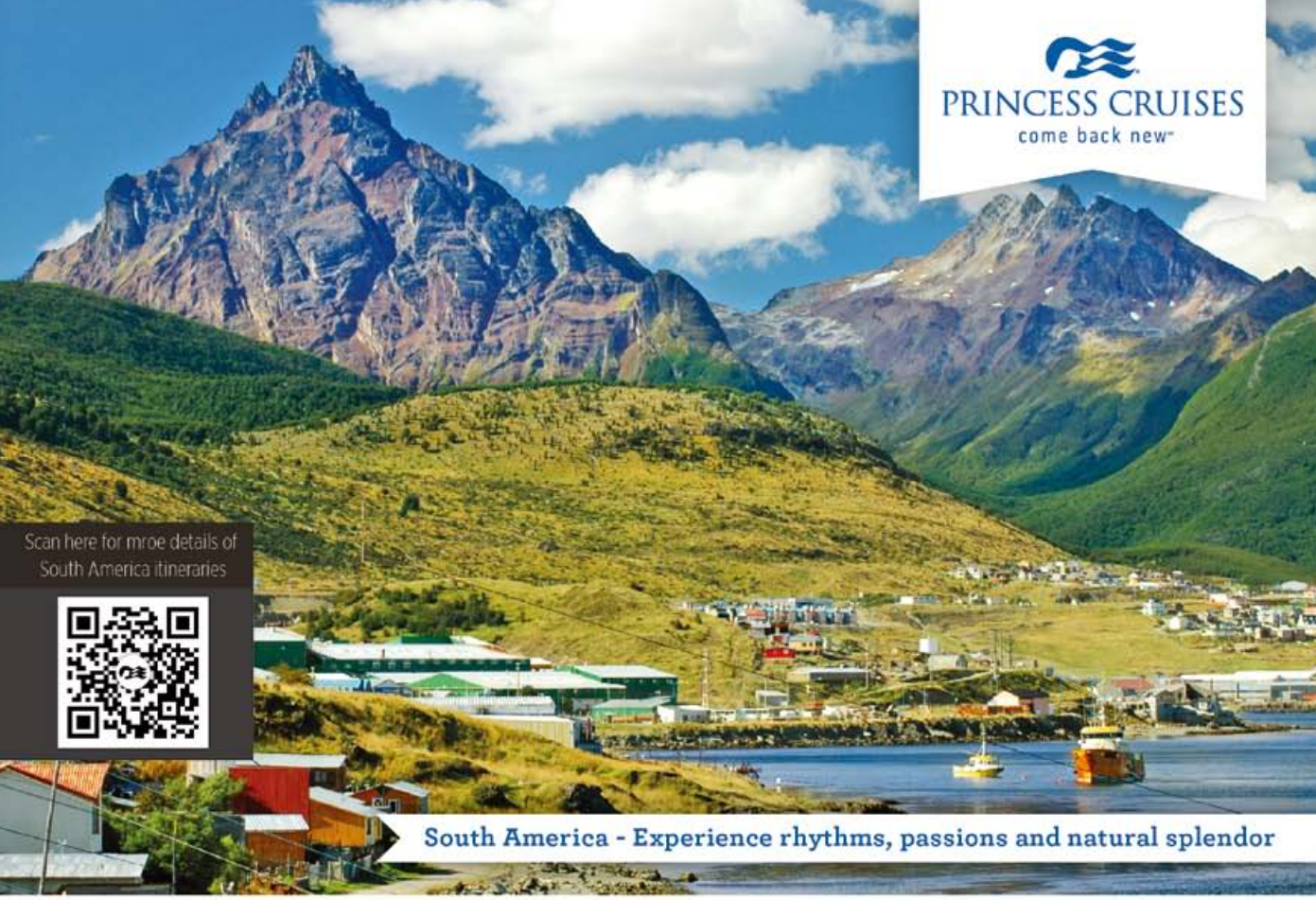

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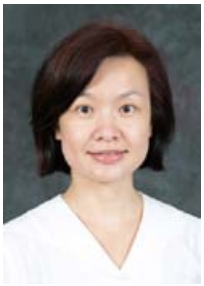
Palliative Care for Patients with Metastatic Breast Cancer – When and How?



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I. PALLIATIVE CARE & ITS INTEGRATION INTO CANCER CARE

Palliative care is a branch of medicine with the goal of preventing and relieving pain and suffering. According to WHO[1], palliative care:

- "provides relief from pain and other distressing symptoms";
- "affirms life and regards dying as a normal process";
- "intends neither to hasten or postpone death";
- "integrates the psychological and spiritual aspects of patient care";
- "offers a support system to help patients live as actively as possible until death";
- "offers a support system to help the family to cope during the patients' illness and in their own bereavement";
- "uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated";
- "will enhance quality of life, and may also positively influence the course of illness";
- "is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications".

There is always a role for palliative care at all stages of cancer diseases to reduce and control the symptoms of cancer and side effects of treatment throughout the cancer journey. It is now widely acknowledged that a palliative and supportive care approach to care should not be utilised only at the end of life, but whenever needs are identified irrespective of the stage of the cancer[2-7]. In this regard, The American Society of Clinical Oncology (ASCO)[8] and The European Society of Medical Oncology (ESMO)[9,10] recommended palliative care be offered along with treatment for patients with metastatic cancer and those who have many or severe symptoms. The physical, psychological and social needs of cancer patients are addressed by the cooperation of a multidisciplinary professional team including oncologists, physicians with expertise in palliative care, nurses, allied health care providers, home care services, social workers, chaplains and mental health care professionals. Palliative care may be offered at home, in a hospital or in a hospice.

Seven randomised controlled trials (RCTs) have demonstrated that early integration of palliative care into the standard cancer care in patients with advanced cancer maintains or improves survival and improves quality of life[8].

II. METASTATIC BREAST CANCER REQUIRES MORE THAN A MEDICAL APPROACH

According to the Hong Kong cancer registry 2012, about 6% of new breast cancers are metastatic when they are diagnosed[11]. It is expected that around 30% of women who are first diagnosed with early stage breast cancer will go on to develop metastatic breast cancer[12]. The primary goals of managing advanced breast cancer are to improve the length and quality of life. Treatment choices are dependent on the balance between the potential benefits and side effects of the therapeutic options. Although metastatic breast cancer is considered incurable, advances in oncological intervention e.g. novel chemotherapeutic and targeted therapies have provided more than ever treatment options. The disease could be controlled for extended periods of time and allows people to live with a good quality of life, and on occasions for many years[12-17]. Despite breast cancer patients can have a chance to live for years on stable medical regimens, it is inevitable that disease would get out of control and the treatment course would become arduous. The experience of profound life threat and the accompanying uncertainty become the common psychological denominator for both the affected woman and her loved ones. The challenges of maintaining life balance, as well as managing pain, fatigue, and other physical and psychological symptoms associated with the disease and treatments reflect the consensus that palliative and supportive care are essential from the point of diagnosis[18,19]. Living with metastatic breast cancer requires more than a medical approach.

Effects of Metastatic Breast Cancer on Quality of Life

Quality of life is a multidimensional construct that includes several domains of a person's life: physical functioning, psychological functioning, social functioning, sexual functioning and spiritual and existential matters[20,21]. Breast cancers can have significant impacts on these domains (see table 1). The assessment of women's needs for information and support in each of these major life domains, and how the needs could be met by existing clinical services are very important.

Table 1 Impact of metastatic breast cancer on different domains of quality of life

Physical Issues:	▪ Physical symptoms related to the cancer and treatments e.g. pain, malaise, nausea, vomiting, anorexia, dyspnoea, abdominal bloating, lymphedema, tumour fungation, bleeding etc. Doctors should be alert to the symptoms & signs associated with the cancer induced conditions that require early/urgent treatment (see table 2). ▪ Loss/disruption of routine functional performance & social roles e.g. self-care activities (feeding, dressing), mobility (move indoors/outdoors), physical activities (walking, lifting) and personal roles (household activities, work).
Psychosocial Issues:	▪ 25-50 % women would experience clinically significant anxiety & depression with breast cancer recurrence[22-23]. ▪ Distress level increases as the cancer progresses, hence the more pronounced unmet needs in terms of psychological support[24].
Social Issues:	▪ Negative impact on marital and other relationships with family and friends[25-28]. - Women may feel their partners could not appreciate & understand the devastating impact of disease progression. - Family members may be even more distressed than the woman. - Functional role impairment (see above) can restrict the ability to pursue normal social activities, limit the social contacts and interactions. ▪ Family & social support play critical roles on how the women can cope with the disease[29]. More open communication, cohesion, conflict resolution and expression of feelings are helpful in disease adjustment.
Sexual Issues:	▪ This has not been extensively researched with few descriptions in literature[30,31]. Elements affecting sexuality could be involved: - Fear of e.g. death, disfigurement, loss of partner, being a burden to loved ones. - Side effects of systemic treatment e.g. hair loss, nausea & vomiting, ovarian failure, fatigue and general loss of well-being.
Other Issues:	▪ Studies found that existential issues e.g. death, freedom, isolation and question of meaning are more important among people with advanced cancers[32,33].

Table 2 Cancer induced conditions that require early/urgent treatment

Diagnosis	Symptoms & Signs
Spinal Cord Compression	▪ unresolved back or neck pain, ▪ decreased in feeling or power in arms/legs, ▪ loss of bladder/bowel control
Superior Vena Cava Compression	▪ dyspnoea, ▪ arm/facial swelling
Brain metastasies	▪ headache, ▪ nausea, ▪ confusion, ▪ seizures, ▪ personality changes
Hypercalcaemia	▪ confusion, ▪ excessive thirst, ▪ vomiting, ▪ constipation, ▪ increased bone pain
Pulmonary Embolism	▪ dyspnoea ▪ tachyarrythmia, ▪ chest pain, ▪ cough, ▪ leg swelling
Sepsis	▪ fever, ▪ hypotension
Pleural effusion	▪ dyspnoea, ▪ chest pain, ▪ dry cough
Pericardial effusion	▪ dyspnoea, ▪ chest pain, ▪ oedema
Liver metastases	▪ jaundice, ▪ nausea, ▪ right upper quadrant pain, ▪ hepatomegaly

III. THE PALLIATIVE CARE MODEL IN HONG KONG

Integrating Palliative Medicine and Oncology in Clinical Service[34]

Picture 1: Hong Kong East Cluster Pamela Youde Nethersole Eastern Hospital Hospice Centre

The public sector is responsible for the majority of oncology and palliative care services in Hong Kong. There are six oncology centres in Hong Kong, offering clinical oncological service (both medical & radiation oncology) and palliative care. In 2007, with the support from charity funding, day hospice centres were established in all six oncology centres. A more comprehensive structure of palliative care supporting in-patient care, out-patient clinics, ambulatory and home hospice was then developed which was never before. The palliative service is led and coordinated by clinical oncologists who have obtained dual specialist qualifications of clinical oncology and palliative medicine from the training by the Hong Kong College of Radiologists. Palliative service is delivered in a multidisciplinary team approach addressing the needs of patients and their families, including bereavement counselling. In this way, oncological and palliative cares are provided in a one-stop service with an early introduction and access to palliative care. This approach is advocated by the ESMO Programme of Designated Centre of Integrated Oncology and Palliative Care[10]. Three oncology centres in Hong Kong have been accredited as ESMO Designated Centre under the programme.

Apart from clinical oncologists, palliative care specialists under the Hong Kong College of Physicians are also offering palliative care service in Hong Kong. Their service is more focused on the palliative care at the terminal phase of life. The scope of service is more extensive nowadays. The scope has expanded to cover the terminal non-malignant diseases in addition to cancers.

The collaborative model between palliative care teams of clinical oncologists and internal medicine physicians secured a continual and seamless transition of palliative care from active oncological treatment to end-of-life care. It expanded the access to palliative care service under the restraint of resource capacity. It may also mitigate the fear of being abandoned that some patients feel when referred to a palliative care service at the terminal stage of illness.

IV. SUMMARY

Metastatic breast cancers influence all aspects of the women's lives. With the advent of more options of oncological intervention e.g. targeted therapies and supportive medications, there is promise for a growing population of women living with metastatic breast cancer. Patients, family and carers should be provided with information and support/counselling regarding:

- Course of disease & associated anticancer treatments;
- Specific measures that could be available to relieve distressing symptoms;
- Knowledge and application of services available; and
- Practical needs e.g. domestic help, financial, transport, emotional/spiritual needs.

Palliative care is to improve symptom control in association with psychological, social and spiritual well-being of both the patient and the family. Palliative care is provided in a multidisciplinary team approach. It is appropriate at any age and at any stage in cancers. Early integration palliative care into the standard cancer care allows better patient and caregiver outcomes & quality of life.

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MCHK CME Programme Self-assessment Questions

Please read the articles and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 30 September 2015. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

Breast cancers in Hong Kong – an overview from the Hong Kong Cancer Registry – Dr Roger KC NGAN

1. A genuine increase in the risk of developing breast cancer as measured by a rising age-standardised incidence rate among females is the main reason for the substantial increase in the number of new breast cancer cases in Hong Kong for the past 10 years.
2. The recent surge of new breast cancer cases is mostly observed in younger patients aged 30 – 45.

Hereditary Breast Cancer – Dr Ava KWONG

3. All offsprings of a BRCA mutation carrier, male or female will carry the BRCA mutation .

Update in Breast Imaging - Digital Breast Tomosynthesis (3D Mammogram) – Dr Chun-ying LUI

4. Reconstructed or synthesised 2D Mammogram from Digital Breast Tomosynthesis in second generation 3D mammogram has image qualities comparable to a 2D Full Field Digital Mammogram.

Update in surgical treatment in breast cancer – Dr Gebevueve CY CHEUNG and Dr Miranda CM CHAN

5. Use of preoperative core biopsy can decrease the need of re-operation and use of frozen section.

Physiotherapy Management in Breast Cancer – Ms Rainbow Ka-yee LAW et al

6. Strengthening exercise of a lymphoedema-affected arm is not possible as it will make the lymphedema worse.

Adjuvant and neoadjuvant therapy for breast cancer – Dr Joanne CHIU and Dr Henry SZE

7. Adjuvant targeted therapy against HER2 in combination with chemotherapy can effectively decrease the risk of breast cancer recurrence.
8. There is a trend to increase the overall radiotherapy treatment duration beyond 5 weeks to achieve a better disease control.

Management of Metastatic Breast Cancer (MBC) - Dr Tsz-kok YAU

9. For breast cancer patients with metastases at diagnosis, surgical resection of the primary tumour should be routinely offered to improve the survival.

Palliative Care for Patients with Metastatic Breast Cancer – When and How? - Dr Inda Sung SOONG

10. Early integration of palliative care into the standard cancer care in patients with advanced breast cancer allows better patient and caregiver outcomes & quality of life.

ANSWER SHEET FOR SEPTEMBER 2015

Please return the completed answer sheet to the Federation Secretariat on or before 30 September 2015 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Name (block letters):_____ HKMA No.: _____ CDSHK No.: _____

HKID No.: __ __ - __ __ __ __ X X (X) HKDU No.: _____ HKAM No.: _____

Contact Tel No.:_____ MCHK No.: _____ (for reference only)

Answers to August 2015 Issue

A brief review and update on treatment of atopic dermatitis

1. F **2.** F **3.** F **4.** F **5.** F **6.** F **7.** F **8.** F **9.** T **10.** T

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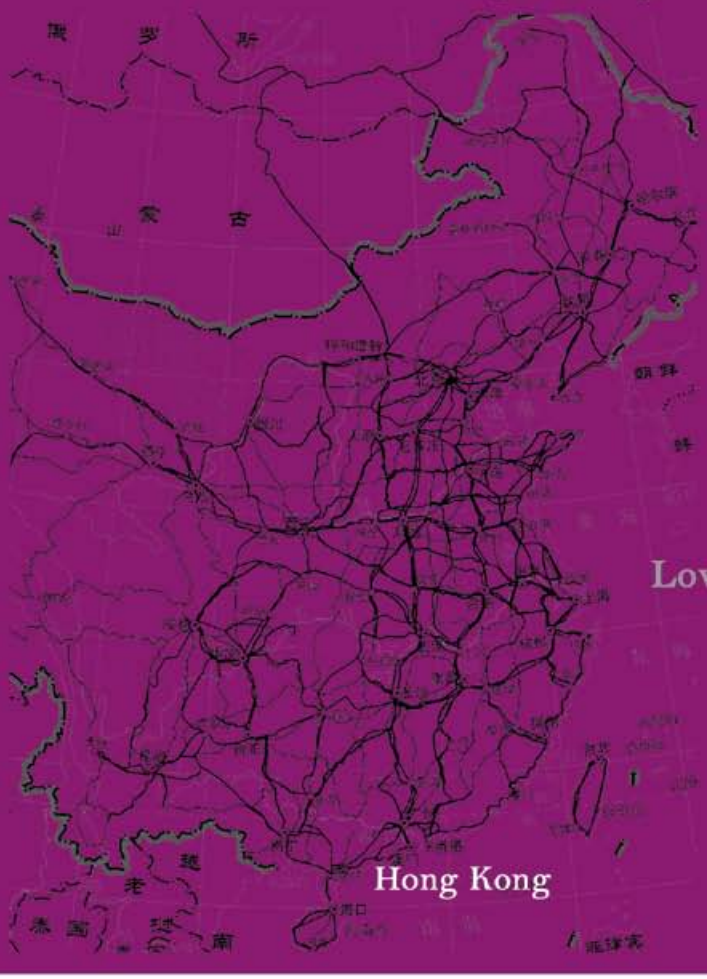

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The Galapagos …an experience of the lifetime

Dr Clement TH CHEN

MBChB (HK), FRCS (Edin), FCSHK, FHKAM (General Surgery)

Specialist in General Surgery
Associate Consultant, Division of Breast Surgery, Department of Surgery, The University of Hong Kong, Queen Mary Hospital

Dr Clement TH CHEN

The Galapagos is a group of volcanic Islands located on the Equator in the Pacific Ocean, hidden away from civilisation. Because of its isolation, it has developed its unique ecosystem that you can find nowhere else. It is within the border of Ecuador in South America. It is an exciting journey to naturalists to see the flora and fauna. And for a tourist like me, to be greeted by the friendliest birds, to dive and swim with penguins (in the Equator!), to observe the landscape evolved by nature and to see those endemic species like marine iguanas or giant Galapagos tortoises, it is like heaven on earth. No wonder, UNESCO designated Galapagos as the first World Heritage site in 1978.

To get there, you have to take a flight from Ecuador or Chile, which lasts about 2-3 hours. After you have landed, take a dinner on the waterfront while wild sea lions would just sit near accompanying you. I was astonished by their gigantic size to be pets but they are as eager to impress you with their loud howls to amuse their own kind.

The Galapagos consists of 18 main islands, located at the Galapagos triple junction. These islands move along the South American Plate at a rate of about 6cm per year. The first island was estimated to have formed at least 8 million years ago. With time, older islands would disappear into the sea. Island Isabela and Island Fernandina are relatively young and are still active with occasional eruptions. Others are ageing. Espanola, being the oldest island, is now inhabited by plants, followed by birds and reptiles gradually. The best way to explore the Galapagos is to go by sea, visiting each and every island in a period of one to two weeks. You could see a very different ecosystem on each island…It is no surprise therefore that this is where Charles Darwin was inspired and proposed the theory of Evolution.

Mr Darwin neglected his medical studies, and came here during his voyage of the Beagle. He observed that the beaks of the finches differ among islands. He contributed it to be the process of natural selection, where only the fittest survives. The bird beaks adapted and evolved.

Now, let's begin the journey of exploring this place. We shall start from the island, Santa Cruz in town of Puerto Ayora, where it has the largest human population. Alternatively, you can stay in San Cristobol, where the settlement begins. These are the usual places where materials are supplied all the way from the Latin American continent. Stay here for 1-2 days to enjoy your lovely hotel, to stroll along the street, or to sip a drink in the waterfront, and do buy some souvenirs. You can organise deep sea fishing here. Fish is abundant because of the convergence of three major oceanic currents that brings an incredible amount of marine life.

However, if you are short of time, go to the fish market in the morning instead. The presence of big fish such as the enormous tuna and other big fish is quite a scene. You will be amused by the presence of pelicans that are also there, waiting patiently to share the catch of the day without actually doing the fishing themselves.

I arranged some scuba diving sessions there. It was a busy underwater scene. Numerous schools of fish. Fast swimming penguins. Small sharks. Colourful corals. This is a first class diving spot.

You can also sail to many islands depend on your time, budget and itinerary. I chose to use the Alta because it is an elegant and cozy motor boat. It carries only 16 passengers, an ideal size that you can get to know each passenger well. The boat takes you to the major spot sights you should visit. If you are under a budget, land based island hopping would be the alternative.

Now, let's go sailing. The first island we are going to visit is Genovesa. It has the nickname of the bird island, where abundant red-footed boobies, Nazca boobies can be seen. In the nesting seasons, you can spot baby birds easily.

The next stop would be Isabela and Fernandina. The living environment here is harsh and unforgiving with larva and few vegetation. Here, you can see the land and marine iguanas. The land iguanas can be huge! The endemic Galapagos marine iguana is the only reptile that has adapted and is able to swim in the ocean. The Galapagos cormorant (flightless cormorant) may not look loving with shabby feathers, but it has adapted radically that the flying ability is lost.

Flightless cormorant | *Land iguana* | *Marine iguana and lava lizard*

Then we will sail to Bartolome, where you can appreciate the volcanic landscape. You can see the penguins living in the Equator. It is so because of the cold current belt surrounding the island. You are welcome to join the fun and do snorkelling here. Don't be surprised to find penguins dashing off like bullets beside you!

Santa Cruz hosts the largest population. Here you can appreciate the Scalesia forest. Scalesia is an endemic tree in Galapagos. There is also the Charles Darwin Research Station. Large giant tortoises are found here. The reserve centre helps hatching the tortoises' eggs to raise their population. In the Black Turtle Cove, you can see large sting rays and small sharks.

Our final stop would be remote yet the oldest island, Espanola. You can see it is richly inhabited by the various plants and animals.

Let's briefly talk about a few interesting species.

1) My favourite bird: the seabird Boobies. Like women who fancy different high heeled shoes, their feet also come in different bright colours like tortoise blue and red and elegant grey. These birds are very friendly and they are not photo shy. So have your camera ready, the birds are eager to show their cute little feet!

2) The marine iguanas. Iguanas are land animals. However, in the harsh environment filled only by lava, these iguanas get into the water to feed on green algae. There is a point to note, as they are cold-blooded animals, facing the cold sea water of about 5 degree Celsius, they have to feed faster because when the body temperature drops, they can be immobilised.

3) The Sally crabs. Unlike the green crabs we can find in Hong Kong, these are bright coloured crabs in red, orange, yellow and brown. They live along the lava shore. Besides feeding on green algae, they are also good friends to the marine iguanas by removing the ticks on their skin.

Sally crab

Sally crab and marine iguana

4) The native Galapagos tortoise. I could not imagine that tortoises can be so big. An adult one weighs up to 250kg. Lonesome George was world famous, because it was the only sub-species tortoise left to extinct. I was glad that I could say hi to him before he left the world at an estimated age of 100 in year 2012 without producing any offspring.

The late Lonesome George

5) The Galapagos penguins. They are the only wild penguins that live at the Equator. This is because of the cold current in Galapagos.

6) The plants have to adapt to the difficult environments. So bushes and cacti or cactuses grow here. The dandelion also amazingly evolved and grew into a special kind of tree called scalesia.

The human activity had shaped the endemic species. First being the sailors and pirates who arrived here since 1700, along with whalers and fur-seal hunters. Very sadly, they killed almost all of the tortoises close to the point of extinction for food and trade. Subsequently the government and NGOs put great effort to preserve the Galapagos.

In addition, the 'El Niño' phenomenon, worsened by the global warming, causing the sea temperatures to rise dramatically, altered the algae growth. It killed 70% of the marine iguanas in starving to death in 1997-98 because they feed on algae only.

Every time I visited a nature reserve, be it the Amazon or the Galapagos, I see how the global climate change and human activities have great impacts on the ecosystem. It always serves as a good reminder that we should do my best to preserve our earth. After all, there is our one and only one planet.

Dermatological Quiz

Dr Lai-yin CHONG

MBBS (HK), FRCP (Lond, Edin, Glasg), FHKCP, FHKAM (Med)
Specialist in Dermatology & Venereology

Dr Lai-yin CHONG

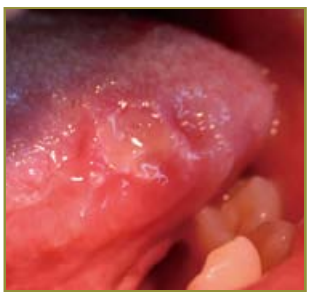

Fig.1: Painful ulcer at lateral side of tongue

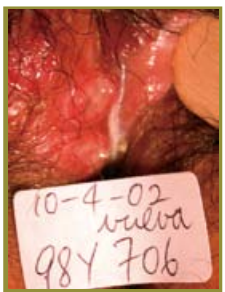

Fig.2: Painful ulcers at right labium majus

This 30-year-old Chinese female complained of recurrent painful oral and genital ulcerations for one year. There was no history of blistering before the erosions. She also recalled that once she had some painful nodules over both legs. Her past health was good. There was no significant drug history or preceding venereal exposure.

Questions:

1. What are your preliminary diagnosis and differential diagnoses?
2. What is the usual bedside test that may be useful in establishing the diagnosis?
3. What are the geographical variation in its prevalence and clinical manifestations in Southern China?
4. What are the treatment options?

(See P.40 for answers)

Calendar of Events

Date / Time	Function	Enquiry / Remarks
1 TUE 1:45 PM	**HKMA Tai Po Community Network – Advances in the Management of T2DM-Insulin Independent Mechanism** Venue: Chiuchow Garden Restaurant(潮江春) Shop 001-003, 1/F, Uptown Plaza (新達廣場), No.9 Nam Wan Road, Tai Po	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
8:00 PM	**HKMA Council Meeting** Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Christine WONG Tel: 2527 8285
2 WED 1:00 PM	**HKMA Shatin Doctors Network - Rosacea and Related Dermatoses** Venue: Jasmine Room, Level 2, Royal Park Hotel, 8 Pak Hok Ting Street, Shatin	Ms. Wendy CHENG Tel: 2824 0333
3 THU 10:00 AM	**Recreation and Sports Club for HK Professional Bodies (RSCP) Table Tennis Tournament 2015** Venue: Cornwall Street Squash and Table Tennis Centre	Mr. Ian KWA Tel: 2527 8285
4 FRI 8:00 AM	**Joint Surgical Symposium - Recurrent Hepatocellular Carcinoma** Organiser: Department of Surgery, The University of Hong Kong & Hong Kong Sanatorium & Hospital; Chairman: Prof. FAN Sheung Tat; Speakers: Prof. FAN Sheung Tat and Dr. CHOK Siu Ho; Venue: Hong Kong Sanatorium & Hospital	Department of Surgery, Hong Kong Sanatorium & Hospital Tel: 2835 8698 Fax: 2892 7511 1 CME Point (Active)
6 SUN 1:00 PM	**HKMA Badminton Tournament** Venue: MacLehose Medical Rehabilitation Centre	Miss Denise KWOK Tel: 2527 8285
8 TUE 1:00 PM	**HKMA Yau Tsim Mong Community Network - Reference Framework for Preventive Care for Older Adults in Primary Care Settings** Venue: Pearl Ballroom, Level 2, Eaton, Hong Kong, 380 Nathan Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA Kowloon West Community Network - Latest COPD Management – Dual Bronchodilation** Venue: Crystal Room IV-V, 3/F., Panda Hotel, 3 Tsuen Wah Street, Tsuen Wan, N.T.	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
6:00 PM	**1) Assessment of disease activity and damage in psoriatic arthritis; 2) Case presentation** Venue: Hospital Authority Headquarters, Room 205S	Dr. LEE Ka Lai Tel: 9229 4616 1 CME Point
9 WED 7:30 AM	**Hong Kong Neurosurgical Society Monthly Academic Meeting – Management of post irradiation ICA stenosis in NPC** Venue: M Block, Ground Floor, Lecture Theatre, QEH	Dr. LEE Wing Yan, Michael Tel: 2595 6456 1.5 CME Points
11:30 AM	**HKMA Golf Tournament** Venue: Eden Course, The Hong Kong Golf Club, Deep Water Bay	Mr. Ian KWA Tel: 2527 8285
1:00 PM	**HKMA Central, Western & Southern Community Network - The Current Management of Herpes Zoster** Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
10 THU 1:00 PM	**HKMA Hong Kong East Community Network - Overactive Bladder: Advances in Management** Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA New Territories West Community Network - Certificate Course on Men's Health (Session 1): Erectile Dysfunction** Venue: Plentiful Delight Banquet (元朗喜尚嘉喜酒家), 1/F., Ho Shun Tai Building, 10 Sai Ching Street, Yuen Long	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA Kowloon East Community Network - Rotavirus Infection in Children: Disease Burden and Prevention** Venue: V Cuisine, 6/F., Holiday Inn Express Hong Kong Kowloon East, 3 Tong Tak Street, Tseung Kwan O	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
2:00 PM	**HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2015 – Robotic Surgery for Ca Prostate** Venue: Function Room A, HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central,	HKMA CME Dept. Tel: 2527 8452 1 CME Point
12 SAT 2:15 PM	**CME Lecture - Refresher Course for Health Care Providers 2015/2016** Venue: Training Room II, 1/F, OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin, Kowloon	Ms. Clara Tsang Tel: 2354 2440 2 CME Point
14 MON 7:30 PM	**1) Local recurrence after surgery; 2) RCC in solitary kidney, and renal preservation** Venue: Multi-disciplinary Simulation and Skills Centre, 4/F, Block F, QEH	Ms. Tammy Hung Tel: 9609 6064 1 CME Point
15 TUE 1:45 PM	**HKMA Tai Po Community Network - Postmenopausal Osteoporosis Continuum: Why do We Start So Early?** Venue: Chiuchow Garden Restaurant(潮江春) Shop 001-003, 1/F, Uptown Plaza (新達廣場), No.9 Nam Wan Road, Tai Po	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
17 THU 1:00 PM	**KECN-HKCFP-UCH – Certificate Course for GPs 2015 (Session 4) – Common Skin Aging Problems** Venue: V Cuisine, 6/F., Holiday Inn Express Hong Kong Kowloon East, 3 Tong Tak Street, Tseung Kwan O	Ms. TAI / Ms. WONG Tel: Ms. TAI: 3949 3430 / Ms. WONG 3949 3087 1 CME Point
1:00 PM	**HKMA New Territories West Community Network - Certificate Course on Men's Health (Session 2): A Step Forward towards Better BPH & LUTS Management** Venue: Plentiful Delight Banquet (元朗喜尚嘉喜酒家), 1/F., Ho Shun Tai Building, 10 Sai Ching Street, Yuen Long	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
19 SAT 2:30 PM	**MPS Workshop – Mastering Shared Decision Making** Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	HKMA CME Dept. Tel: 2527 8452 2.5CME Point
20 SUN 9:00 AM	**Summer Vigor 2015** Venue: Sai Kung	Mr. Ian KWA Tel: 2527 8285
1:00 PM	**HKMA Badminton Tournament** Venue: MacLehose Medical Rehabilitation Centre	Miss Denise KWOK Tel: 2527 8285
22 TUE 1:00 PM	**HKMA Kowloon West Community Network - 6th Annual Meeting cum CME Lecture on "First 1000 Days of Life – What Matter Most?"** Venue: Panda Grand Ballroom B, 5/F., Panda Hotel, 3 Tsuen Wah Street, Tsuen Wan, N.T.	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
6:30 PM	**MPS Workshop – Mastering Your Risk** Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central	HKMA CME Dept. Tel: 2527 8452 2.5 CME Point
23 WED 1:00 PM	**HKMA Shatin Doctors Network - Update in the Management of Gout** Venue: Jasmine Room, Level 2, Royal Park Hotel, 8 Pak Hok Ting Street, Shatin	Mr. Wilson HON Tel: 3954 5003 1 CME Point
1:00 PM	**HKMA Central, Western & Southern Community Network - The Breast Mouse – A GP's Approach in 2015** Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
24 THU 1:00 PM	**HKMA New Territories West Community Network - 6th Annual Meeting cum CME Lecture on "How to Avoid being Brought to the PIC?"** Venue: Pearl Ocean (金霞殿), 1/F., Gold Coast Yacht and Country Club (黃金海岸鄉村俱樂部 - 遊艇會), 1 Castle Peak Road, Castle Peak Bay	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA Kowloon East Community Network - Diagnosis and Treatment of Axial-Spondyloarthropathy (Axial-SpA)** Venue: V Cuisine, 6/F, Holiday Inn Express Hong Kong Kowloon East, 3 Tong Tak Street, Tseung Kwan O, Sai Kung, N.T.	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
26 SAT 7:30 PM	**HKMA Tennis Tournament** Venue: Kowloon Tong Club	Miss Denise KWOK Tel: 2527 8285
27 SUN 10:00 AM	**Recreation and Sports Club for HK Professional Bodies (RSCP) Ten-Pin Bowling Tournament 2015** Venue: SCAA Bowling Centre	Mr. Ian KWA Tel: 2527 8285
28 MON 8:00 PM	**HKMACF Charity Concert for SCHSA** Venue: Concert Hall, Hong Kong City Hall, 5 Edinburgh Place, Central	Miss Ellie FU Tel: 2527 8285

Answers to Dermatological Quiz

Answer:

1. Behcet's syndrome
   This disease was first described in 1924 by Hulusi Behcet, a Turkish dermatologist, consisted of a triad of recurrent oral aphthous ulcers, genital ulcers, and uveitis.

   The diagnostic criteria of Behcet (International Study Group) include:
   Oral aphthosis (recurrent) + at least two of the following:
   Genital (ulcer), ocular (uveitis), skin (erythema nodosum-like or papulopustular eruption) and pathergy.

   The differential diagnoses are chronic inflammatory bowel diseases, collagen-vascular diseases, herpes infection and Reiter's disease. These must be excluded before the diagnosis is established.

2. Pathergy skin test
   A positive result is defined as the formation of a sterile erythematous papule or pustule that appears 24-48 hours following the injection of 0.1ml normal saline intradermally at the forearm with a sterile needle of 20 gauge or smaller. A pathergy phenomenon reflects a hyper-reactivity response of the skin to scratches & intracutaneous needle punctures. However it is not diagnostic of the Behcet's syndrome. For instance, it is also invariably positive in pyoderma gangrenosum. Unfortunately, the sensitivity of this test is very low in Southern Chinese, making it seldom of any value in this group of population.

3. The Behcet's syndrome is also known as the "Silk road disease" from the East to the Mediterranean. It is most prevalent in Turkey, Iran, Saudi Arabia, Japan, Korea and Northern China. Interestingly there were considerable geographical variation in prevalence and clinical manifestations in Southern China including Hong Kong. For example, in Southern Chinese, the prevalence is rare, the commonest skin lesion is erythema nodosum-like eruptions instead of other skin manifestations, while the ocular involvement and other systemic involvements are much less common than in the Turks and Japanese. The specificity and sensitivity of the pathergy test is also much lower in Southern Chinese versus Turks and Japanese.

4. Treatment options include colchicine, dapsone, thalidomide, systemic corticosteroids, azathioprine, etc. It is now one of the well established indications for thalidomide. In recent years, tumour necrosis factor inhibitor therapy with infliximab and etanercept has also demonstrated varying degrees of success.

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Specialist in Dermatology & Venereology

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1. Friedewald S, Rafferty E , Rose S, et al. "Breast Cancer Screening using Tomosynthesis in Combination with Digital Mammography." Journal of the American Medical Association. 2014 July;311(24):2499-2507. Epub 2014 June 24. **7.** Rose S, Tidwell A, Bujnock L, et al. "Implementation of Breast Tomosynthesis in a Routine Screening Practice: An Observational Study." American Journal of Roentgenology. 2013 Jun; 200(6): 1401-1408. Epub 2013 May 22. **14.** Bonafede M, Kalra V, Miller J et al. "Value analysis of digital breast tomosynthesis for breast cancer screening in a commercially-insured US population" ClinicoEconomics and Outcomes Research. 2015 Jan 13. [Epub ahead of print]. **15.** Kalra V, Haas B, Forman H et al. "Cost-Effectiveness of Digital Breast Tomosynthesis." (paper presented at the annual meeting of the Radiological Society of North America, Chicago, IL, November 2012).

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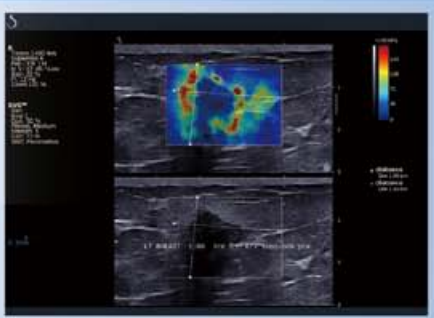

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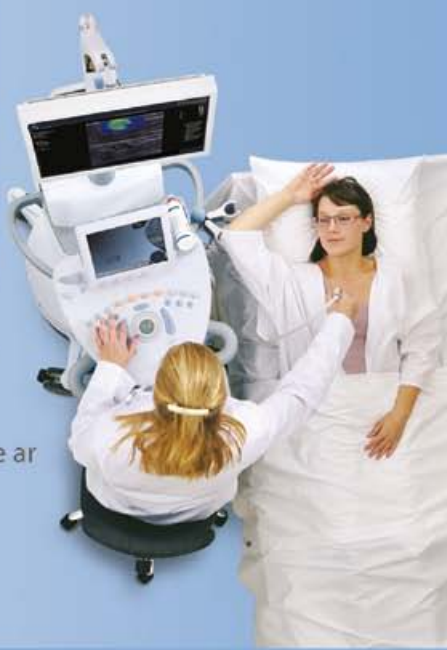

60 peer reviewed publications and a multinational study of over 1600 patients have demonstrated the clinical benefits:

- SWE™ helps Improve breast ultrasound cancer detection [1,2]
- SWE™ helps reducing negative biospsies [3-7]
- SWE™ provides quantitative ar valuable information for treatment planning and monitoring [8-10]

Consult the references HERE : http://bit.ly/1IVCrle

www.supersonicimagine.com

Contact

PRISMTECH
LEADING TECHNOLOGIES

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Break the Cycle of Conventional Therapy

AFINITOR is the ***FIRST and ONLY Targeted Therapy***
to enhance and to extend the clinical benefits of endocrine therapy in patients with HR-positive, HER-negative advanced breast cancer progression

Significant durable PFS benefits after First Recurrence on NSAI Adjuvant Treatment

– Afinitor + exemestane vs exemestane alone: 15.2 months vs 4.2 months[1]

AFINITOR® (everolimus) tablets

NOVARTIS ONCOLOGY

Novartis Pharmaceuticals (HK) Ltd
27/F, 1063 King's Road, Quarry Bay, H.K.
Tel: 2882 5222 Fax: 2577 0274

Reference: 1. Campone et al. St. Gallen Breast Cancer Conference 2013. Poster 276

Further information is available on request

Prescribing Information

Important note: Before prescribing, consult full prescribing information. **Presentation:** Tablets containing 2.5 mg, 5 mg or 10 mg of everolimus. Dispersible tablets containing 2 mg, 3 mg or 5 mg of everolimus. **Indications:** postmenopausal women with advanced hormone receptor-positive, HER2negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole.; treatment of adult patients with progressive neuroendocrine tumors of pancreatic origin (PNET) with unresectable, locally advanced or metastatic disease; treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib.; treatment of adult patients with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery.; pediatric and adult patients with tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected. **Dosage: Advanced HR+ BC, advanced PNET, advanced RCC, or renal angiomyolipoma with TSC:** 10 mg once daily with or without food. For patients with hepatic impairment, reduce the AFINITOR dose. If moderate inhibitors of CYP3A4 and/or Pglycoprotein (PgP) are required, reduce the AFINITOR dose to 2.5 mg once daily; if tolerated, consider increasing to 5 mg once daily. If strong inducers of CYP3A4 are required, increase AFINITOR dose in 5 mg increments to a maximum of 20 mg once daily. **TSC with SEGA:** 4.5 mg/m² once daily, adjust dose to attain trough concentrations of 5-15 ng/mL. Assess trough concentrations approximately 2 weeks after initiation of treatment, a change in dose, a change in co-administration of CYP3A4 and/or PgP inducers or inhibitors, a change in hepatic function, or a change in dosage form between AFINITOR Tablets and AFINITOR DISPERSIBLE Tablets. For patients with severe hepatic impairment reduce the starting dose of AFINITOR Tablets or AFINITOR DISPERSIBLE Tablets.If concomitant use of moderate inhibitors of CYP3A4 and/or PgP is required, reduce the dose of AFINITOR Tablets or AFINITOR DISPERSIBLE Tablets by 50%. If concomitant use of strong inducers of CYP3A4 is required, double the dose of AFINITOR Tablets or AFINITOR DISPERSIBLE Tablets. **Contraindications: Hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients. Warnings/Precautions:** • **Non-infectious pneumonitis:** Cases have been described in patients taking AFINITOR, some of these have been severe and on rare occasions, a fatal outcome was observed. A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as shortness of breath, pleural effusion, cough or dyspnea, and in whom infectious, neoplastic, and other nonmedicinal causes have been excluded. In some cases, management of pneumonitis may require dose reduction, dose interruption or discontinuation. The use of corticosteroids may be indicated. • **Infections:** AFINITOR is immunosuppressive. Localised and systemic bacterial, fungal, viral or protozoal infections (e.g. pneumonia, aspergillosis or candidiasis, hepatitis B reactivation) have been described in patients taking AFINITOR; some of these have been severe and occasionally fatal. Pre-existing infections should be resolved prior to starting treatment with AFINITOR. Be vigilant for symptoms or signs of infection during treatment with AFINITOR. In case of emergent infections, institute appropriate treatment promptly and consider interruption or discontinuation of AFINITOR. If a diagnosis of invasive systemic fungal infection is made, discontinue AFINITOR and treat with appropriate antifungal therapy. • **Hypersensitivity reactions** have been observed with everolimus. • **Oral ulceration:** Mouth ulcers, stomatitis and oral mucositis have been seen in patients treated with AFINITOR. Management of these adverse reactions may require dose reduction, dose interruption or discontinuation. Topical treatments are recommended, but alcohol- or peroxide- containing mouthwashes should be avoided. • **Renal failure:** Cases of renal failure, some fatal, have been observed in patients treated with AFINITOR. • **Laboratory tests and monitoring:** Renal function, blood glucose, and complete blood counts are recommended prior to initiation of and periodically during treatment. • **Hepatic impairment:** AFINITOR may be used at a reduced dose with severe hepatic impairment if desired benefit outweighs the risk. • **Vaccination:** Avoid use of live vaccines. • **Pregnancy:** AFINITOR should not be given to pregnant women unless the potential benefit outweighs the potential risk to the foetus. • **Women of childbearing potential:** Use highly effective contraception methods while receiving AFINITOR and for up to 8 weeks after ending treatment. • **Breast-feeding:** Women taking AFINITOR should not breast feed. • **Fertility:** Male fertility may be compromised by treatment with AFINITOR. Amenorrhea (including secondary amenorrhea) has been observed in female patients receiving AFINITOR. **Interactions:** • Avoid concurrent treatment with strong CYP3A4 or PgP inhibitors (e.g. ketoconazole, itraconazole, ritonavir, clarithromycin, telithromycin) • Caution with moderate inhibitors of CYP3A4 or PgP (e.g. erythromycin, verapamil, diltiazem, fluconazole, ciclosporin, amprenavir, fosamprenavir, aprepitant). Concurrent treatment with moderate inhibitors of CYP3A4 or PgP require dose reduction • Avoid concurrent treatment with strong inducers of CYP3A4 or PgP (e.g. rifampicin, rifabutin, carbamazepine, phenobarbital, phenytoin, efavirenz, nevirapine, dexamethasone, prednisone, prednisolone, St. John's Wort (*Hypericum perforatum*)) • Avoid grapefruit juice, grapefruit, star fruit, Seville oranges and other foods affecting CYP3A4 or PgP. • Caution when used in combination with orally administered CYP 3A4 substrates with a narrow therapeutic index. **Adverse reactions: BC, NET, RCC:** • Very common (≥10%): Infections, decreased appetite, dysgeusia, headache, cough, pneumonitis, epistaxis, dyspnea, stomatitis, diarrhea, nausea, vomiting, rash, dry skin, pruritus, nail disorder, fatigue, asthenia, mucosal inflammation, peripheral edema, pyrexia, weight decreased • Common (≥1 to <10%): Diabetes mellitus, exacerbation of diabetes mellitus, dehydration, insomnia, hypertension, hemorrhages, pulmonary embolism, haemoptysis, dry mouth, dyspepsia, dysphagia, oral pain, abdominal pain, acne, hand-foot syndrome, erythema, arthralgia, proteinuria, renal failure, increased daytime urination, chest pain • Uncommon (<1%): pure red cell aplasia, new onset diabetes mellitus, ageusia, congestive cardiac failure, deep vein thrombosis, acute respiratory distress syndrome, impaired wound healing, Cases of Hepatitis B reactivation and amenorrhea (including secondary amenorrhea) have been observed. **TSC with renal angiomyolipoma:** • Very common (≥10%): anaemia, leukopenia, hypercholesterolemia, stomatitis, nausea, acne, fatigue, blood lactate dehydrogenase increased • Common (≥1 to <10%): urinary tract infection, sinusitis, upper respiratory tract infection, thrombocytopenia, hypersensitivity, hypophosphatemia, hyperlipidemia, decreased appetite, iron deficiency, headache, dysgeusia, ageusia, cough, epistaxis, pneumonitis, diarrhea, vomiting, abdominal pain, flatulence, dermatitis acneiform, dry skin, papule, renal failure acute, amenorrhea, menstruation irregular, menorrhagia, vaginal hemorrhage, menstruation delayed, **TSC with SEGA:** *Phase III study M2301 (78 patients treated with AFINITOR for a median duration of 9.6 months):* • Very common (≥10%): Stomatitis • Common (≥1 to <10%): Upper respiratory tract infection, pneumonia, otitis media, gastroenteritis viral, neutropenia, anemia, hypercholesterolemia, aggression, insomnia, convulsion, cough, epistaxis, pneumonitis, oral pain, rash, amenorrhea, menstruation irregular, fatigue, irritability, pyrexia, gait disturbance, blood cholesterol increased, low density lipoprotein increased, neutrophil count decreased, blood triglycerides increased, *Additional adverse reactions observed in Phase II study C2485 (28 Patients treated with AFINITOR for a median duration of 34.2 months):* • Very common (≥10%): Sinusitis, cellulitis, gastroenteritis, pharyngitis, otitis externa, skin infection, body tinea, gastric infection, urinary tract infection, furuncle, nasopharyngitis, conjunctivitis, hypertriglyceridemia, diarrhea, dermatitis acneiform, acne • Common (≥1 to <10%): Infection, abscess limb, bronchitis viral, agitation, pharyngeal inflammation, gastritis, vomiting, proteinuria, blood immunoglobulin G decreased, The following clinically relevant ADRs were reported in a higher frequency category in the phase II study C2485 than in the phase III study M2301 (increase from common to very common): upper respiratory tract infection, otitis media, pneumonia, cough, pyrexia, hypercholesterolemia, hypertriglyceridemia and neutropenia. • Laboratory abnormalities: abnormalities were observed in some hematology and clinical chemistry laboratory tests. **Packs and prices:** Everolimus tablets 2.5mg, 5mg and 10mg (30 tablets). **Legal classification:** P1S1S3. **Ref:** US PI Aug 2012 (2012-PSB/GLC-0526-s)

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