An overview of risk factors for recurrent breast cancer

A Mannell

Department of Surgery, University of the Witwatersrand

Corresponding author: *Aylwyn Mannell (mannell@mweb.co.za)*

Summary: The multidisciplinary management of Breast Cancer (BC) has evolved over the past 50 years: the patient is offered a choice of surgical procedures with or without radiation therapy, cytotoxics and treatments targeting the nuclei of the cancer cells. This has resulted in a reduction of disease recurrence and a significant increase in 5-year survival. But these good results deteriorate over time and almost 20% women with early stage, oestrogen-receptor (ER) positive BC will suffer recurrent cancer at 10 years. The aim of this review is the identification of risk factors for the recurrence of BC, to examine pathogenic pathways leading to BC and to report on modifications to lifestyle, surgical procedures and treatment regimes which can reduce the recurrence of BC. Patient factors associated with increased risk included the extremes of age, ethnicity, genetic inheritance obesity and alcohol ingestion. Human Immunodeficiency Virus (HIV) was not identified as a cause of BC. Treatment-related factors included microscopically positive excision margins, delay in initiation of adjuvant chemoradiation and lack of compliance with endocrine therapy. Reclassifying BC according to molecular subgroups more accurately identifies patients at risk for recurrence and aids in the appropriate selection of therapy targeted to the primary and lymphatic metastases.

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Introduction

The management of breast cancer (BC) has evolved over the past 50 years into a multidisciplinary approach involving local and systemic therapies. In a well-resourced centre the patient with early stage breast cancer[1] (clinical stage 1, IIA and the T2N1 subset of stage IIB) will have breast surgery (either lumpectomy or mastectomy) with or without radiation, a sentinel lymph node biopsy is used to assess the axilla either in place of or before axillary lymph node dissection. These local treatments are most often combined with systemic therapies including cytotoxics and those targeted to receptors in or on the nucleus of the cancer cells.

These multimodal treatments have resulted in a decline in the incidence of recurrent BC. For patients undergoing surgery for early BC in the 1990s, the rate of locoregional recurrence (LRR) at 5 years was approximately 10%.[2] By 2005, LRR at 5 years had declined to about 6% and by 2010 this had fallen to 3 to 4%.[2]

However, these good results do deteriorate with time: the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) found that women who had undergone conservative breast surgery with radiation had a 10-year risk of first recurrence of 19.3% with similar results for those having had a mastectomy.[3] This review examines factors which increase the risks of BC recurrence and that of cancer-specific mortality.

These risks are discussed under patient factors, treatment regimes and tumour biology. Detailed management options for patients with BC recurrence are beyond the scope of this overview.

Patient factors

Age

Although the incidence of BC in young women is small, age at diagnosis has a significant impact on outcome. Young age is a risk factor for LRR and death from BC.[4] This has been attributed to the association of young age with aggressive features carrying a poor prognosis. This association was investigated by Mahmood et al.[5] in a study of 14 714 women diagnosed with early stage BC between 1990 to 2007 and registered on the US Cancer Surveillance, Epidemiology and End Results (SEER) data base. A multivariable analysis of outcomes in this cohort adjusting for grade, stage, size and nodal states revealed age as an independent predictor of cancer-specific and overall survival (OS).

Patients carrying high penetrance genetic mutations namely BrCa 1/2, TP53 and PTEN commonly present as a young age.[6] When compared to sporadic BC, these cases have an increased risk of LRR, contralateral BC and other malignancies. For these reasons all patients with a suggestive family history and the very young patient (≤ 35 years) should be referred to a counsellor for discussion of genetic profiling and genetic-directed treatments.[6,7]

Obesity

Defined as a Basal Metabolic Index (BMI) of ≥ 30%,[8] obesity increases the risk of BC. Androstenedione and testosterone are converted to oestrone in adipose tissue and it is likely that this pathway underlies the increase in exposure of the breasts to oestrogen in the obese.

At all ages there is a significant reduction in the distant disease-free interval (DDFI) and in cause-specific OS of obese BC patients when compared to the non-obese. A study of 2 843 young British women found that in those with oestrogen receptor (ER) positive BC, obesity was a significant and independent predictor of distant disease with a worse prognosis.[8]

In South Africa (SA), obesity in women has reached epidemic proportions: one out of 3 women is either overweight (BMI ≥ 25%) or obese.[9] Public Health measures to educate all women to the risk of BC from an increasing BMI are urgently required. However, when the diagnosis of BC is made in overweight patients, a window of opportunity exists to motivate them to change their dietary habits, emphasizing the importance of maintaining a normal weight to reduce the risk of recurrence. Counselling and encouragement from those caring for these patients can promote adherence to a healthy life style.

Alcohol

Many epidemiological studies have linked alcohol to BC. A meta-analysis of 53 individual case-control and cohort studies reported a direct relationship between the amount of alcohol taken on a regular basis and the risk of BC: every 10 gm of alcohol ingested on a regular basis led to a 7% increase in the risk of BC.

There are 2 principal pathways by which alcohol consumption can lead to breast cancer: acetaldehyde, byproduct of ethyl alcohol ('alcohol') has a toxic effect on DNA. In addition, alcohol ingestion in postmenopausal women is associated with increased adrenal secretion of precursor androgens, aromatised in peripheral tissues to oestrogen.[11] In a study of premenopausal women in Norway, alcohol ingestion was shown to increase the levels of 17β-oestradiol in saliva and serum: there was a positive association between alcohol and mammographic density in this group.[12]

Exposure of the breast to increased levels of endogenous oestrogen appears to be the final link between alcohol and an increased risk of BC at all ages.

Alcohol represents an important modifiable life-style factor, highly relevant to women in areas where alcohol is socially acceptable and freely available.

Race

Black women with BC have a higher risk of death than white women with disease of similar stage and grade. This observation applies equally to Afro-American women to Sub-Saharan women and to black women in the United Kingdom (UK).[13]

Many observers in the USA have identified disparities in access to health care, treatment options, insurance coverage and medical education as explanations for this difference. However, a recent study of patients entered on the SEER program examined the effect of race on survival. It was noted that race is an independent predictor of survival after BC.[13] Agboola et al.[14] compared the survival of 302 Nigerian women matched by stage grade and treatment to a cohort of British women of Caucasian descent in Nottingham, UK. The Nigerian women had a poorer OS.

A recent analysis of 2 915 young patients with available ethnicity data was performed as part of the 5-year Prospective Study of Outcomes in Sporadic and Hereditary Breast Cancer (POSH) Study.[15]. All of these young patients were diagnosed and treated by the National Health Service (NHS) in the UK. Despite equal access to health care, the OS and DDFS were significantly worse in the young black women.

In all 3 studies detailed above, race was a significant independent predictor of prognosis.

HIV

Of the 25 million people in Sub-Saharan Africa infected with Human Immunodeficiency Virus (HIV), 6 million live in South Africa.[16] Prior to the development of effective antiretroviral treatment (ARV) the common malignancies affecting HIV positive patients were viral related: cervical carcinoma, non-Hogkin's Lymphoma, Kaposi Sarcoma and anal carcinoma.[17] As the life-expectancy of HIV positive patients on ARVs has improved, more patients in SA are presenting with common epithelial malignancies such as breast cancer (BC). An earlier study of BC patients in Soweto, a low to middle income black residential area south of Johannesburg, found that 19.7% of patients tested for HIV were positive, reflecting the incidence of HIV in the female population of the community.[18]

The HIV positive patients were younger than HIV negative BC cases but there was no association of HIV status with stage or grade of tumour at diagnosis.

While there is no firm evidence that HIV increases the risk of breast cancer, this infection poses specific problems for clinicians managing BC. HIV is commonly associated with tuberculosis and both conditions require prompt initiation of treatment before chemotherapy.[16]

Long-term outcome studies of newly diagnosed BC patients from areas with a high prevalence of HIV have been commenced at the Tertiary (University) Hospitals serving these areas.[19] Accrual of 3 000 patients with 5 years of intensive follow-up is planned. This will help to identify the impact of HIV on the incidence of recurrent BC and the Disease Specific Survival (DSS).

Treatment regimes

Surgery

Choice of procedure. – For women with early BC, there is essentially a choice between 2 procedures: mastectomy or breast conserving surgery with radiation (BCT). The standard management of the axilla is axillary lymph node dissection (ALND) for clinically positive nodes or following a sentinel lymph node biopsy (SLND) which has identified lymph node metastases.

The European Organisation for Research and Treatment of Cancer (EORTC) published the 10-year results of a study (EORTC 10801)[20] involving patients accrued from the United Kingdom (UK), Europe and South Africa comparing these 2 procedures, BCT/ALND with modified radical mastectomy (MRM). Locoregional recurrence was greater in the BCT/ALND than in the MRM (20% versus 12%). But when the EORTC 10801 trial investigators examined the 20-year follow-up data[21] there was no significant difference in OS, DFS and DDFS between the two groups. Distant metastases and death were independent of the choice of surgical procedure.

However, a reduction in LRR following BCT has been achieved by the University of Texas MD Anderson Cancer Centre[22] for 2 331 patients managed from 1987 to 2005. These patients had Stage I and II disease, the majority of whom received adjuvant treatment. Complete surgical excision with tumour-free margins of 2 mm was accomplished in 96% cases.* This compares favourably with the results of the EORTC 10801 trial where 48% of patients had microscopically involved margins and a LRR of 20%.* The 10-year LRR in the MD Anderson group was < 5% with DFS of 94%.

Proliferative activity, as measured by Ki67% is greatest in the advancing edge of the tumour[23] and highlights the importance of an excision margin which is clear of cancer cells, i.e. 'no tumour on the ink'.[24]

The description of an appropriate negative excision margin as "no tumour on the ink" derives from a consensus guideline on margins for conservative breast surgery with whole breast irradiation (BCT) issued by the American Society of Clinical Oncology and the American Society for Radiation Oncology in 2014.[24] The guideline was based on the findings of a meta-analysis of 21 studies of BCT from well-resourced centres in Australia, UK and USA which reported local recurrence (LR) in relation to final microscopic margins.[25] This report confirmed that positive or close (< 1 mm) margins significantly increased the risk of LR, compared to negative margins of 1 mm. For the patients who received whole breast irradiation, a boost dose to the tumour bed and endocrine therapy for oestrogen receptor positive cancers, increasing the excision margins beyond 1 mm did not appear to influence the risk of LR.

However, in a subset of patients not given an additional boost dose of radiation and where a smaller proportion received tamoxifen there was a trend to significance in reduction of the odds of LR when the excision margins increased from 1 to 5 mm.

This observation can be applied to the resource-poor areas of Africa where access to radiotherapy is limited and availability of systemic treatments erratic: achieving negative margins of $\geq$ 5 mm without compromising cosmesis is acceptable in these circumstances. A South African study[26] of patients undergoing BCT identified ductal carcinoma in situ (DCIS) at the periphery of 50% of ductal cancers: current guidelines[27] for the excision of DCIS now recommend a 2 mm margin in place of 'no tumour on the ink'.

Radiation

Radiation is an essential part of BC management. Earlier trials comparing BCS with and without whole breast radiation therapy (RT) showed that omitting RT led to local recurrence (LR) rates of up to 35%.[3] Observational studies have identified delay between surgery (S) and RT as a cause of increased risk of recurrence. In a retrospective analysis of 18 000 older women who had BCT with chemotherapy, Punglia et al. demonstrated a continuing relation between the S – RT interval and LR.[28] This relationship was confirmed by prospective study of 7 800 women with early stage BC undergoing BCT in 4 Yorkshire centres, UK. After adjusting for stage and age and adjuvant chemotherapy, outcome data identified an association between increasing S – RT delay and poorer survival.[29]

An explanation for the deleterious effects of delaying RT may lie in the inflammatory response with increase in growth factors in the area of excision.[30] These changes can promote proliferation of atypical cellular elements and neoplastic progression during a prolonged S – RT interval. Two observations support this hypothesis: 75% of LRs occur in the same quadrant as the primary cancer and a radiation boost of 16 gy to the tumour bed will significantly reduce local relapse.[31] Whether devascularisation of the tumour bed with tissue hypoxia impairs the response to RT is under investigation in the Preoperative Accelerated Partial Breast Irradiation (PAPBI)* trial of neoadjuvant radiation therapy.[32]

Mastectomy is a standard procedure for patients at high risk of local recurrence: postmastectomy radiation therapy (PMRT) has decreased the risk of LRR and of breast cancer mortality in patients with lymph node metastases.[33] But not all BC is equally radiosensitive. Nguyen et al.[34] classified BC according to the receptor profile (ER, PR, Her2) and studied the response of each molecular subtype to radiation therapy. Those cancers lacking hormonal receptors (triple negative) had a greater incidence of local recurrences with a serious impact on survival[34] while RT is most effective for breast cancers of the luminal A subtype.[35]

Chemotherapy

Neoadjuvant or primary chemotherapy has the advantage of increasing surgical options by down-sizing a cancer and of identifying patients with a complete response which

*European Organization for Research and Treatment of Cancer.

will improve prognosis. An equivalent survival value of adjuvant chemotherapy for early BC has been established by randomized controlled trials (RCT).[36] But postoperative delay in commencing chemotherapy may have an adverse effect on outcome.

Gagliato et al.[37] reviewed the survival of 6 827 patients with non-metastatic BC who received adjuvant chemotherapy at the MD Anderson Cancer Centre. When time to initiation of chemotherapy (TTC) was greater than 60 days, OS was adversely affected. Patients with BC displaying aggressive phenotypes (triple negative, Her 2 positive receiving trastuzumab) as well as those with Stage III disease had significantly worse OS compared to those with a TTC of ≤ 30 days.

A recent meta-analysis of over 15 000 patients with BC found that for every 4-week increase in TTC there was a 6% increase in the risk of death.[38] Vandergrift et al.[39] assessed time to adjuvant chemotherapy (TTAC) in the management of 6 622 women with non-metastatic BC at nine National Comprehensive Cancer Network (NCCN) centres and examined factors associated with delay. The mean TTAC was 12 weeks: the most frequent cause of delay were immediate postmastectomy reconstruction, re-excision for positive margins and use of the 21-gene reverse transcription polymerase chain reaction assay.

Surgery promotes the invasive capacity and dispersion of free malignant cells.[30] In addition, cell-mediated immunity is suppressed in the postoperative period increasing likelihood of metastatic spread.

Avoidance of delay to initiate chemotherapy or endocrine therapy may be critical for patients with Stage II and III disease who have a high risk of micrometastases.

Endocrine therapy

Almost 70% of BCs are oestrogen receptor (ER) alpha positive. In these tumours, oestrogen stimulated growth and spread of the cancer can be inhibited by a selective oestrogen receptor modulator (tamoxifen), by immobilization and degradation of the ER (fulvestrant) and by irreversible steroid inhibition (aromatase inhibitor, AI). Antioestrogen adjuvant therapy for hormone sensitive BC reduces risk of recurrence and increases survival by 39% and 31% respectively.[40]

However, there are problems associated with endocrine therapy which can increase the risk of recurrence. These include tumour-related factors of oestrogen resistance and ER change as well as the patient-related factors of non-adherence and non-compliance. Even among well motivated, well monitored trial patients on endocrine therapy, one out of five women will discontinue treatment over time. The rate of nonadherence outside a trial can be as high as 50%.[41]

The Breast International Group B1G 1-98 trial randomized 6 193 postmenopausal women to a double blind trial of tamoxifen, letrozole alone or in sequence and studied the impact of treatment adherence on Disease Free Survival (DFS). It was found that 19% patients stopped treatment early, usually due to side effects. Multi variable analysis revealed that low adherence was linked to reduction in DFS: the risk of recurrence was 35 – 36% greater when compared to patients who completed the 5-year course of antioestrogen therapy.[42]

There is mounting evidence that increasing the duration of endocrine therapy in women with ER positive cancers from 5 to 10 years improves outcomes. In the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial,[43] approximately 13 000 women with nonmetastatic BC who had completed 5 years of tamoxifen (TMX) were randomly allocated to either TMX to 10 years or to stop (controls). The risk of recurrence during years 5 – 14 after diagnosis was 21.4% for women continuing tamoxifen compared to 25% for controls.

On the ATLAS Study, compliance with tamoxifen for extended period was estimated to be 80%. It is expected that full compliance with 10 years at tamoxifen will reduce LRR and BC mortality for up to 20 years after diagnosis of BC.

Tumour biology

Clinicopathological data in patients with BC will identify most cases at increased risk of recurrent disease. These clinical indices of aggression include size of tumour, nodal metastases, high Bloom-Richardson histological grading, lymphovascular invasion and an extensive intraduct component.[44] However, adverse histopathology does not accurately define prognosis. For example, 20% of node negative BCs recur and more than 30% node positive BC remains disease free for 15 years.[3]

Reclassifying BC according to molecular subgroup more accurately identifies patients at increased risk of relapse and can guide the selection of adjuvant therapy. These molecular subtypes are defined by the presence or absence of hormone receptors (ER, PR), Her2 and the proliferative marker, Ki67.[45]

However, BC is an heterogeneous disease in which different clones of cancer cells within a primary tumour may vary in metastatic potential. Recent studies of biological markers in primary BC paired with their lymph node metastases have demonstrated receptor discordance in more than one third of patients,[46] the lymph nodes exhibiting a more aggressive phenotype. The usual finding is a negative discordance of PR receptors where the loss of these reduces the response to antioestrogen therapy and is coupled with an increase in the proliferative marker Ki67.[44] Her2 expression in metastatic nodes is most often constant with a few studies identifying increased gene amplification.[48,49]

In patients with positive lymph nodes, it is likely that these metastases will have the greatest impact on distant relapse and prognosis: it has been suggested that adjuvant therapy should be determined by the receptors profile of the lymph node metastases rather than that of the primary tumour.[50]

Conclusions

Age, race, genetic inheritance and tumour biology are irrevocable. But awareness of the risks associated with extremes of age at diagnosis, the receptor profiles in different ethnic groups, the genetic and familial background as well as histopathological evidence of malignant aggression will facilitate appropriate management.

One of the most obvious factors that could be corrected to reduce the risks of BC is obesity. This requires public and individual recognition that an increasing BMI is associated with both increasing risk of BC as well as a worse outcome. National campaigns to educate all women to the dangers of obesity are urgently required and counselling overweight patients with BC will help to reduce recurrence.

Regular intake of alcohol increases endogenous production of oestrogen and the risk of BC. Alcohol is a critically important modifiable lifestyle factor.

HIV is an unlikely cause of BC. Universal testing of women at risk and prompt initiation of antiretroviral therapy will improve the outcomes of BC management in HIV positive patients.

The first prerequisite for breast surgery is complete excision of the tumour, clear of all microscopic cancer. Although BCT and mastectomy lead to similar OS, mastectomy may be advisable where there is a high risk of local recurrence. These high risk cases include patients carrying genetic mutations and BC families.

Radiation is a critical part of regional BC management and the risks of delaying this are well established. Careful planning is needed to minimize the S-RT interval. The importance of the boost dose in BCT and of postmastectomy RT have been confirmed by long-term follow-up.

Delay in initiation of adjuvant systemic therapies leads to measurable increases in cancer-specific mortality. Patients with Stage II and III BC have a high risk of micrometastatic disease. Therefore, prompt administration of adjuvant chemotherapy and endocrine treatments can be critical to OS.

For women with ER positive cancers the benefits of antioestrogen therapy can only be achieved by compliance with the drugs prescribed. Regular patient contact and encouragement to continue these life-saving medications is important.

Molecular subtyping of BC aids the choice of systemic treatment and is a guide to prognosis. Receptor profiling of the lymph node metastases may further improve the selection of, and response to specific therapy.

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