



## Breast cancer surgery in the elderly women: A review

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### Abstract

#### Introduction

The population of the elderly in the United States is increasing. Between 2000 and 2010 the population of women aged 65 and over increased by 11.3% with those 70 and over increasing by 6.4%. According to the Surveillance Epidemiology and End Results (SEERs) database, from 2000 to 2009 the median age for breast cancer diagnoses in the USA was 61 years of age. Approximately 41% were diagnosed above the age of 65, of which 21% were above the age of 75. As the USA population of women over 65 increases, breast cancer in older individuals is becoming more and more prevalent. The aim of our study is to discuss on the epidemiology, the risk factors, the signs and the symptoms, and finally, the current approach in the care of breast cancer in the elderly.

#### Conclusion

Knowledge of molecular biology and development of targeted therapies is the key to breast cancer treatment. It is essential elderly patients to be included in new clinical trials for individualized treatment recommendations.

### Introduction

#### Breast Anatomy

The breasts are composed of fatty tissue which contains glands responsible for milk production in the late pregnancy and after childbirth<sup>1</sup>.

Within each breast, there are about 15 to 25 lobes formed by groups of lobules, the milk glands. Each lobule is composed of grape-like clusters of acini (also called alveoli), the hollow sacs that make hold breast milk<sup>2</sup> (Figure 1).

The lobules are arranged around ducts which funnel milk to the nipples. About 15 to 20 ducts come together near the areola (dark, circular area around the nipple) to form ampullae – cavities that store the milk before it reaches the nipple surface.

Montgomery's glands are small oil glands that are located around each areola. They release a lubricant that protects the nipples during nursing.

The breasts sit over the pectoralis major muscle and usually extend from the level of the 2nd rib to the level of the 6th rib anteriorly. The superior lateral quadrant of the breast extends diagonally upwards towards the axillae and is known as the tail of Spence. A thin layer of mammary tissue extends from the clavicle above to the seventh or eighth ribs below and from the midline to the edge of the latissimus dorsi posteriorly. (For further explanation, see anatomical terms of location.)

The arterial blood supply to the breasts is derived from the internal thoracic artery (formerly called the internal mammary artery), lateral thoracic artery, thoracoacromial artery, and posterior intercostal arteries. The venous drainage of the breast is mainly to the axillary vein, but there is some drainage to the internal thoracic vein and the intercostal veins. Both sexes have a large concentration of blood vessels and nerves in their nipples. The nipples of both women and men can become erect in response to sexual stimuli, to touch, and to cold.

The breast is innervated by the anterior and lateral cutaneous branches of the fourth through sixth intercostal nerves. The nipple is supplied by the T4 dermatome.

#### Lymphatic System

Lymph is a clear, tan fluid that contains lymphocytes (white blood cells that fight disease). Lymph is drained from the breast tissues by a

rich supply of vessels. Such lymphatic vessels connect with a network of lymph nodes that are located around the breasts' edges or in nearby tissues of the armpits and collarbone. The breasts' lymph nodes are not linked in a straight line. Instead, they are staggered and fixed within fat pads – an arrangement that complicates lymph node removal during breast cancer surgery.

Lymph nodes play a central role in the spread of breast cancer. The axillary (underarm) lymph nodes are particularly important, as the are among the first places that cancer is likely to be found if it metastasizes (spreads) from the breast. This lymph node cluster is often referred to as the "tail", or Level I nodes. Level II nodes are located underneath the pectoralis minor muscle, and Level III nodes are found near the center of the collarbone (Figure 2).

#### Shape and Support

Breasts vary in size, shape and position on a woman's chest, and their external appearance is not predictive of their internal anatomy or lactation potential. The natural shape of a woman's breasts is primarily dependent on the support provided by the Cooper's ligaments and the underlying chest on which they rest (the base). Cooper's ligaments, also known as the suspensory ligaments of Cooper, suspend the breasts from the clavicle and the clavi-pectoral fascia. As their fibers run around and through the breast, these ligaments support the breasts in its position on the chest wall and maintain their normal shape. Some breasts are high and rounded, and protrude almost horizontally from the chest wall. Such high breasts are common for girls and women in early stages of development. The protruding or high breasts are anchored to the chest at the base, and the weight is distributed evenly over the area of the base of the approximately dome- or cone-shaped breasts<sup>3</sup>.

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The breast is also attached at its base to the chest wall by the deep fascia over the pectoral muscles. In a small number of women, the frontal ducts (ampullae) in the breasts are not flush with the surrounding breast tissue, which causes the sinus area to visibly bulge outward<sup>4</sup>.

Pregnancy and nursing cause further increases in breast size. As a woman ages, the fatty tissue of the breasts may become more prominent than the glandular tissue, and the breasts may feel softer. The breasts gradually atrophy (shrink) after menopause (the end of menstruation). The aim of our study is to discuss on the epidemiology, the risk factors, the signs and the symptoms, and finally, the current approach in the care of breast cancer in the elderly.

## Discussion

### Breast Cancer

Breast cancer refers to cancers originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk. Cancers originating from ducts are known as ductal carcinomas; those originating from lobules are known as lobular carcinomas. There are many different types of breast cancer, with different stages (spread), aggressiveness, and genetic makeup; survival varies greatly depending on those factors. Computerized models are available to predict survival<sup>5</sup>. With best treatment and dependent on staging, 10-year disease-free survival varies from 98% to 10%<sup>6</sup>. Treatment includes surgery, drugs (hormonal therapy and chemotherapy), and radiation.

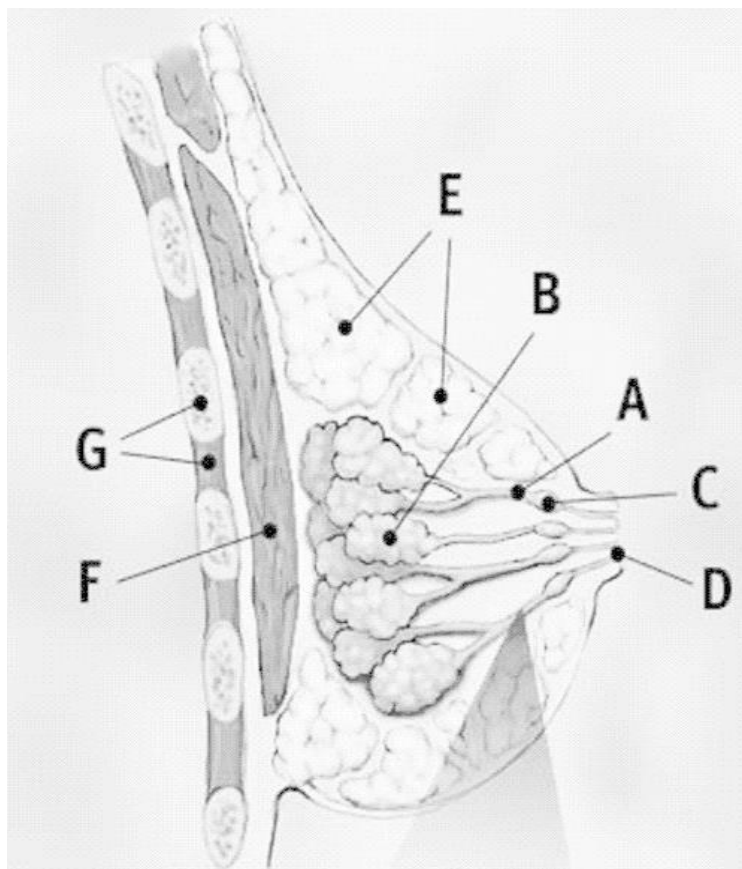
### Epidemiology

Worldwide, breast cancer is the most common cancer in women, after skin cancer, representing 16% of all female cancers<sup>7</sup>. The rate is more than twice that of colorectal cancer and cervical cancer and about three times that of lung cancer. Mortality worldwide is 25% greater than that of lung cancer in women. In 2004, breast cancer caused 519,000 deaths worldwide (7% of cancer deaths; almost 1% of all

deaths). The number of cases worldwide has significantly increased since the 1970s, a phenomenon partly attributed to the modern lifestyles<sup>8,9</sup>.

The incidence of breast cancer varies greatly around the world: it is lowest in less-developed countries and greatest in the more-developed countries. In the twelve world regions, the annual age-standardized incidence rates per 100,000 women are as follows: in Eastern Asia, 18; South Central Asia, 22; sub-Saharan Africa, 22; South-Eastern Asia, 26; North Africa and Western Asia, 28; South and Central America, 42; Eastern Europe, 49; Southern Europe, 56; Northern Europe, 73; Oceania, 74; Western Europe, 78; and in North America, 90<sup>10</sup> (Figure 3).

Breast cancer is strongly related to age with only 5% of all breast cancers occur in women under 40 years old. However, it can occur in younger women.



**Figure 1:** Breast Anatomy A: Ducts B: Lobules C: Dilated section of duct to hold milk D: Nipple E: Fat F: Pectoralis major muscle G: Chest wall / Rib cage  
Enlargement A: Normal duct cells B: Basement membrane C: Lumen (center of duct).

### United States

The lifetime risk for breast cancer in the United States is usually given as 1 in 8 (12.5%) with a 1 in 35 (3%) chance of death. A recent analysis however has called this estimate into question when it found a risk of only 6% in healthy women.

The United States has the highest annual incidence rates of breast cancer in the world; 128.6 per 100,000 in whites and 112.6 per 100,000 among African Americans<sup>11</sup>. It is the second-most common cancer (after skin cancer) and the second-most common cause of cancer death (after lung cancer). In 2007, breast cancer was expected to cause 40,910 deaths in the US (7% of cancer deaths; almost 2% of all deaths). This figure includes 450-500 annual deaths among men out of 2000 cancer cases.

In the US, both incidence and death rates for breast cancer have been declining in the last few years in Native Americans and Alaskan Natives<sup>11</sup>. Nevertheless, a US study conducted in 2005 indicated that breast cancer remains the most feared disease, even though heart disease is a much more common cause of death among women. Many doctors say that women exaggerate their risk of breast cancer.

### Racial disparities

Several studies have found that black women in the U.S. are more likely to die from breast cancer even though white women are more likely to be diagnosed with the disease. Even after diagnosis, black women are less likely to get treatment compared to white women.

Scholars have advanced several theories for the disparities, including inadequate access to screening, reduced availability of the most advanced surgical and medical techniques, or some biological characteristic of the disease in the African American population.

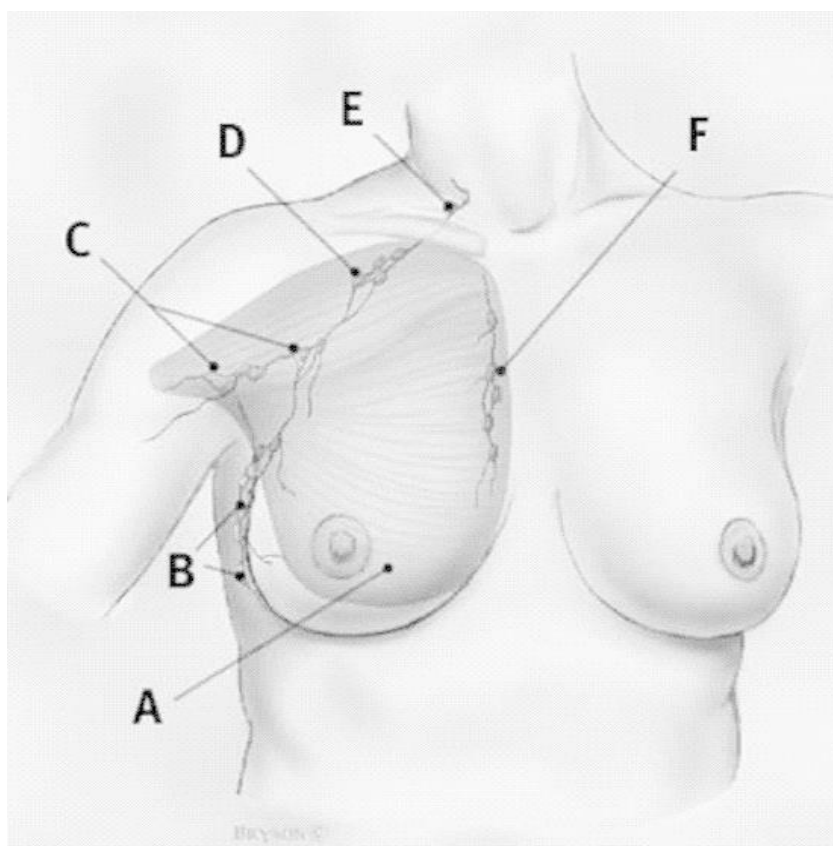
Some studies suggest that the racial disparity in breast cancer outcomes may reflect cultural biases more than biological disease differences. However, the lack of diversity in clinical trials for breast cancer treatment may contribute to these disparities, with recent research indicating that black women are more likely to have oestrogen receptor negative breast cancers, which are not responsive to hormone treatments that are effective for most white women. Research is currently ongoing to define the contribution of both biological and cultural factors<sup>12</sup>.

### UK

45,000 cases diagnosed and 12,500 deaths per annum. 60% of cases are treated with Tamoxifen, of these the drug becomes ineffective in 35%<sup>13</sup>.

### Developing countries

As developing countries grow and adopt Western culture they also accumulate more disease that has arisen from Western culture and its



**Figure 2:** Axillary Lymph Nodes A: Pectoralis major muscle B: Axillary lymph nodes: levels I C: Axillary lymph nodes: levels II D: Axillary lymph nodes: levels III E: Supraclavicular lymph nodes F: Internal mammary lymph nodes.

habits (fat/alcohol intake, smoking, exposure to oral contraceptives, the changing patterns of childbearing and breastfeeding, low parity). For instance, as South America has developed so has the amount of breast cancer. "Breast cancer in less developed countries, such as those in South America, is a major public health issue. It is a leading cause of cancer-related deaths in women in countries such as Argentina, Uruguay, and Brazil. The expected numbers of new cases and deaths due to breast cancer in South America for the year 2001 are approximately 70,000 and 30,000, respectively." However, because of a lack of funding and resources, treatment is not always available to those suffering with breast cancer.

### Classification

Breast cancers can be classified by different schemata. They include stage (TNM), pathology, grade, receptor status, and the presence or absence of

genes as determined by DNA testing<sup>14,15</sup>.

### Risk Factors

The primary risk factors that have been identified are sex<sup>16</sup>, age<sup>17</sup>, lack of childbearing or breastfeeding, and higher hormone levels.

In a study published in 1995, well-established risk factors accounted for 47% of cases while only 5% were attributable to hereditary syndromes. Genetic factors usually increase the risk slightly or moderately; the exception is women and men who are carriers of the breast cancer susceptibility gene mutations, BRCA1 and BRCA2, are at a very high lifetime risk for breast and ovarian cancer, depending on the portion of the protein where the mutation occurs.

Instead of a 12 percent lifetime risk of breast cancer, women with one of these genes have a risk of approximately 60 percent. In more recent years, research has indicated the impact of diet and other behaviours on breast cancer.

**Table 1: Morbidity and Mortality of Mastectomy in the Elderly.**

Study	Age(years)	No.	Operative mortality(%)	Complications
Hunt	>65	94	1.0	20
Schottenfield	>65	437	0.2	NS
Singletary	>69	157	1.9	24
Kessler	>70	82	1.2	11
Berg	>70	242	2.0	NS
Kraft	>75	75	4.5	NS
SEER 1967-1973	>75	NS	0.9	NS
Davis	>80	96	3.0	7
NS, not stated				

These additional risk factors include a high-fat diet, alcohol intake, obesity, and environmental factors such as tobacco use, radiation, endocrine disruptors and shift work. Although the radiation from mammography is a low dose, the cumulative effect can cause cancer.

In addition to the risk factors specified above, demographic and medical risk factors include:

**Personal history of breast cancer:** A woman who had breast cancer in one breast has an increased risk of getting cancer in her other breast.

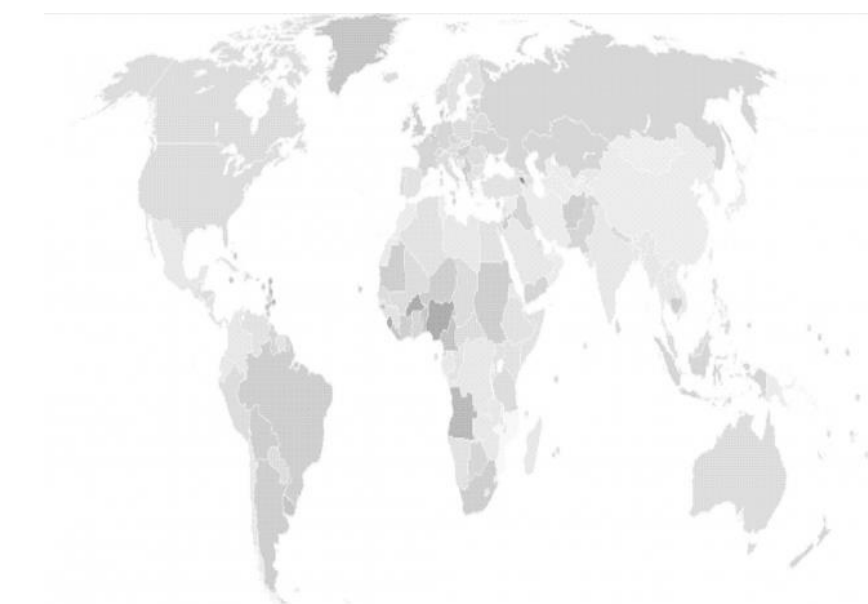
**Family history:** A woman's risk of breast cancer is higher if her mother, sister, or daughter had breast cancer. The risk is higher if her family member got breast cancer before age 40. Having other relatives with breast cancer (in either her mother's or father's family) may also increase a woman's risk.

**Certain breast changes:** Some women have cells in the breast that look abnormal under a microscope. Having certain types of abnormal cells (atypical hyperplasia and lobular carcinoma in situ [LCIS]) increases the risk of breast cancer.

**Race:** Breast cancer is diagnosed more often in Caucasian women than Latina, Asian, or African American women.

**Abortion** has not been found to be a risk factor for breast cancer. The breast cancer abortion hypothesis, however, continues to be promoted by some pro-life groups.

The United Kingdom is the member of International Cancer Genome Consortium that is leading efforts to map breast cancer's complete genome.



**Figure 3:** Age-standardized death from breast cancer per 100,000 inhabitants in 2004



### Signs and Symptoms

The first noticeable symptom of breast cancer is typically a lump that feels different from the rest of the breast tissue. More than 80% of breast cancer cases are discovered when the woman feels a lump. By the time a breast lump is noticeable, it has probably been growing for years. The earliest breast cancers are detected by a mammogram. Lumps found in lymph nodes located in the armpits can also indicate breast cancer.

Indications of breast cancer other than a lump may include changes in breast size or shape, skin dimpling, nipple inversion, or spontaneous single-nipple discharge. Pain ("mastodynia") is an unreliable tool in determining the presence or absence of breast cancer, but may be indicative of other breast health issues (Figure 4).

When breast cancer cells invade the dermal lymphatics—small lymph vessels in the skin of the breast—its presentation can resemble skin inflammation and thus is known as

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inflammatory breast cancer (IBC). Symptoms of inflammatory breast cancer include pain, swelling, warmth and redness throughout the breast, as well as an orange-peel texture to the skin referred to as *peau d'orange*.

Another reported symptom complex of breast cancer is Paget's disease of the breast. This syndrome presents as eczematoid skin changes such as redness and mild flaking of the nipple skin. As Paget's advances, symptoms may include tingling, itching, increased sensitivity, burning, and pain. There may also be discharge from the nipple. Approximately half of women diagnosed with Paget's also have a lump in the breast<sup>18</sup>.

Occasionally, breast cancer presents as metastatic disease, that is, cancer that has spread beyond the original organ. Metastatic breast cancer will cause symptoms that depend on the location of metastasis. Common sites of metastasis include bone, liver, lung and brain<sup>19</sup>. Unexplained weight loss can occasionally herald an occult breast cancer, as can symptoms of fevers or chills. Bone or joint pains can sometimes be manifestations of metastatic breast cancer, as can jaundice or neurological symptoms.

These symptoms are "non-specific", meaning they can also be manifestations of many other illnesses<sup>20</sup>.

Most symptoms of breast disorder do not turn out to represent underlying breast cancer. Benign breast diseases such as mastitis and fibroadenoma of the breast are more common causes of breast disorder symptoms. The appearance of a new symptom should be taken seriously by both patients and their doctors, because of the possibility of an underlying breast cancer at almost any age<sup>21</sup>.

### Local therapy of breast cancer

The choice of the local treatment for the elderly women is still a controversial issue. In the past local therapy depended almost exclusively on simple mastectomy, but nowadays breast conserving surgery and axillary dissection has emerged. Other alternatives such as tamoxifen, an

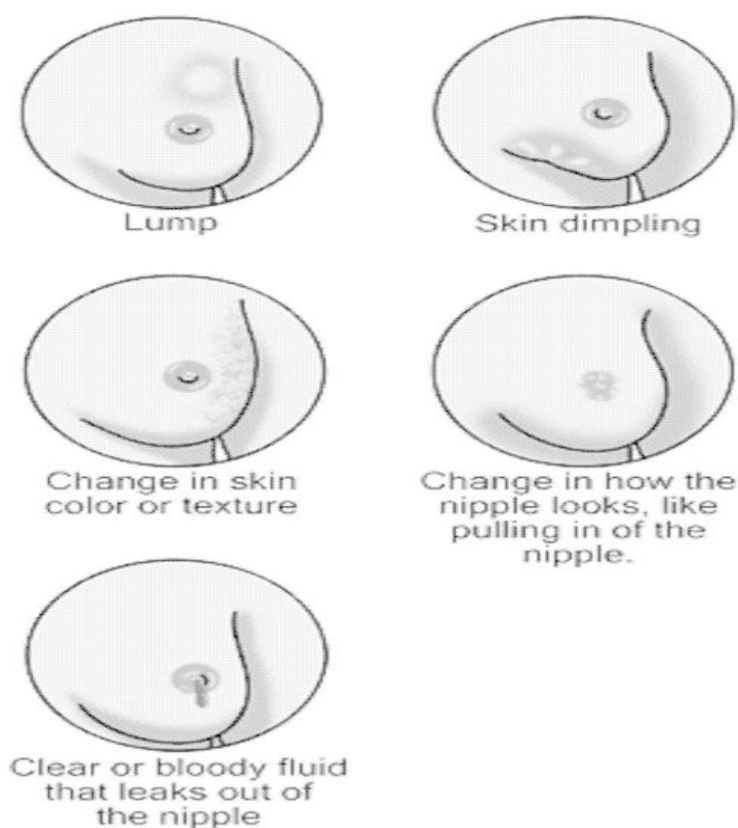


Figure 4: Early signs of Breast Cancer.

anti-tumour agent and local irradiation have increased the available options for local treatment in this population. In the process of making the decision of the appropriate local therapy is important to evaluate not only the morbidity and mortality of treatment but also the efficacy of the therapy in maintaining local control. Current options for the local management of breast cancer in the elderly include modified radical mastectomy, breast conserving surgery, axillary dissection, tamoxifen and the auxiliary use of irradiation.

### Modified radical mastectomy

The standard radical mastectomy had been employed relatively more often in the late 1970's. Since the 1980's there has been a movement toward modified radical mastectomy. A modified radical mastectomy includes removal of breast tissue, the underlying pectoralis fascia and the axillary lymph nodes.

Modified radical mastectomy is the treatment of choice for tumours

Table 2: Contraindications to Breast-Conserving Therapy with Irradiation.

- Two or more primary tumors in separate quadrants of the breast
- Diffuse malignant-appearing microcalcifications
- Prior therapeutic irradiation to the breast region that requires retreatment to an excessively high total radiation dose
- Persistent positive margins after reasonable surgical attempts

Table 3: Morbidity of Axillary Dissection.

Morbidity	Incidence (%)
Pain	15-33
Numbness	70-80
Reduced strength / decreased ROM	10-20
Lymphedema	2-30
Breast edema surgery using	15-50
General anesthesia	100

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unsuitable for conservation such as T3 tumours or multi focal tumours. It is also indicated for those patients who decline or are not fit for postoperative breast radiotherapy. Post-operative mortality and morbidity rate is low and the procedure is physically well tolerated. Singletary et al. reported perioperative mortality rate of 1.6% and wound complications of 7.6% in a study of 184 women diagnosed after the age of 69, 82% of whom underwent modified radical mastectomy<sup>22</sup>. Deaths were related to myocardial infarction and post-surgical complications were infection 9.4%, haematoma 4% and minor flap necrosis 5%. Well Berg reported five operative deaths in a series of 148 radical mastectomies in patients over 70 years of age<sup>23</sup>. Davis et al. reported a 3% mortality rate for women aged 80 or older treated by mastectomy and a 7% incidence of major complications<sup>24</sup>. Hunt et al., in a study of 94 patients reported a complication rate of 20% in elderly patients, but the operative mortality was only 1%.

Most of the implications were related to the operative wound such as wound infection, wound seroma and skin necrosis. Kessler and Seton found cardiovascular and neurological problems as the most common cause of postoperative morbidity in their series. Data on the morbidity and mortality of mastectomy in the elderly are summarized in table 1.

In conclusion, modified radical mastectomy is an excellent method for achieving local control of breast cancer and elderly people should not be denied the benefits of surgery strictly on the basis of age.

### Breast-conserving surgery

Breast conservation treatment, consisting of breast-conserving surgery (lymphectomy or partial mastectomy) and postoperative radiotherapy, is now recommended as the standard of care for patients of all ages with early disease. Large randomized studies have clearly shown that breast conservation treatment has similar efficacy to mastectomy. Differences in disease-free survival or overall survival were

similar between the two approaches, although a significant increase in local recurrences was seen in the breast conservation treatment groups.

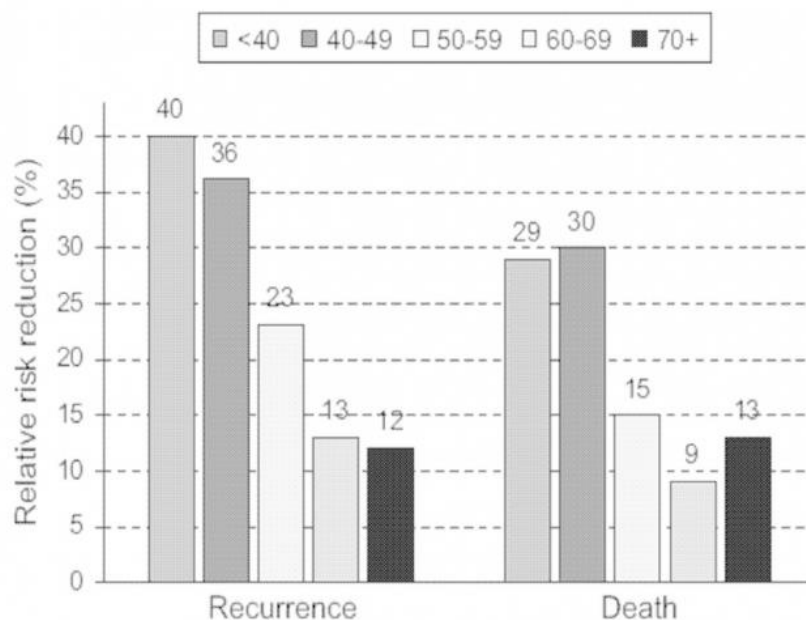
Most elderly women with primary breast cancer are candidates for breast conservation treatment. However available data suggests that older patients are less likely to receive such treatment<sup>25</sup>. Small studies involving patients aged 70 years or older have documented that breast conservation treatment, in comparison with mastectomy, is associated with better quality of life<sup>26</sup> and is preferred by most elderly patients<sup>27</sup>.

Several studies have suggested that elderly women may have a lower rate of breast recurrence after partial mastectomy and radiotherapy than their younger counterparts. Fourquet et al. reported a 97% rate of control at 10 years for women over age 55 compared to 85% for women aged 33-45 and 71% for women age 32 or younger in a series of 518 patients.

Veronesi et al. and Clark et al. have also reported a decreasing frequency of breast recurrence with increasing age. Local recurrence rates can be affected by a number of treatment factors, such as the extent of surgical

resection, the status of the surgical margin and the use of adjuvant tamoxifen. Many retrospective studies have reported a significantly increased rate of breast tumor recurrence in those who received radiotherapy with positive microscopic resection margins compared with those with negative margins. Several factors have been associated with a low risk for breast tumour recurrence in patients with positive margins. In some series, a positive margin that is characterized as focal has been associated with a lower risk of breast tumour recurrence when compared with more extensively involved margins<sup>28,29,30</sup>.

Postoperative radiotherapy after breast conserving surgery has been shown to achieve reduction in absolute risk of 5-year local recurrence from 25.9% to 7.3% ( $p < 0.0001$ ) and a reduction in 15-year absolute breast cancer mortality risk from 35.9% to 30.5% ( $p=0.0002$ )<sup>31</sup>. A slight but noticeable increase in non-breast cancer mortality in women who received radiotherapy (mainly heart disease and lung cancer) was probably related to the use of older suboptimum radiotherapy regimens and technique. Despite the benefits, elderly patients continue to receive radiotherapy less



**Figure 5:** Relative recurrence and mortality reduction per age group with adjuvant polychemotherapy according to the 2005 overview of the Early Breast Cancer Trialists' Collaborative Group.



frequently after breast-conserving surgery than younger patients<sup>32</sup>. A number of randomized trials, usually limited to an upper age limit of 70 years, show a significant reduction in risk of local recurrence from postoperative breast irradiation, but no effect on overall survival. Some trials found age to be a factor that predicts for a lower risk of local recurrence after whole breast irradiation compared with conservative surgery alone<sup>33,34,35,36,37,38,39</sup>.

Postoperative breast irradiation should therefore be considered in all elderly patients undergoing breast-conserving surgery. The standard contraindications to breast conserving therapy with radiation are shown in table 2.

Breast irradiation has been shown to be well tolerated in elderly population. A tolerance study by Wyckoff and colleagues demonstrated that radiation dose, duration of therapy, number of treatment interruptions and toxicities were no different in women over the age of 65 compared to women younger than 65<sup>40</sup>. Even patients over 80 years tolerate breast irradiation.

Some teams have proposed different modalities of partial breast irradiation, thus decreasing the total length of postoperative treatment while taking into account the potential sub-clinical disease in the tumour bed. Several techniques of partial breast irradiation have been described. Low dose<sup>41,42</sup>, and high dose rate<sup>43,44,45,46,47</sup>, perioperative brachytherapy or external beam RT<sup>48,49</sup> and more recently, per-operative radiotherapy<sup>50,51,52</sup> achieved a recurrence rate of between 0 and 4.4%, with a median follow up varying between 8 and 72 months, associated with cosmetic results comparable to those achieved with conventional external-beam. The advantage of this concept of adjuvant treatment is to perform both lymphectomy and irradiation of the tumour bed during the same admission, all in about 10 days<sup>53,54</sup>.

After discharge from hospital, the patient can start adjuvant systematic treatment without delay if necessary.

Partial breast irradiation also aims at sterilizing the surrounding tumour-bed area. All authors propose a target volume with a safety margin of 2 cm outside the excision cavity, including 1 cm superficial and 1 cm deep in the cavity, if possible<sup>55,56,57</sup>.

Irradiation is well tolerated in the elderly population and chronologic age alone is not an indication for its omission from breast-conserving therapy. In patients who do not undergo breast irradiation, a wider surgical resection (quadrantectomy) appears to decrease the risk of local recurrence.

### Axillary Dissection

Axillary lymph node dissection should be done in patients with clinical evidence of the involvement of axillary lymph nodes. This has been the gold standard treatment for many years and despite its high morbidity results in excellent staging and local disease control. Before the sentinel lymph node procedure, older patients with breast cancer were less likely to undergo axillary lymph node dissection than the younger patients for several reasons<sup>58,59</sup>.

First, although generally considered a safe procedure, it can be associated with postoperative numbness, paraesthesia, pain and muscle weakness, which could contribute to a subsequent reduction in quality of life<sup>60,61</sup> (Table 3). One study, however, has shown that older patients experience fewer axillary lymph node dissection-related arm symptoms than do younger patients<sup>62</sup>.

Second, axillary lymph node dissection is considered a staging rather than a therapeutic procedure for breast cancer, and is used to determinate pathological local involvement and, therefore, to dictate need for adjuvant treatment.

Third, several studies have shown no difference in outcome in older patients with small tumours without palpable lymph nodes when axillary lymph node dissection was omitted<sup>63,64</sup>. In elderly patients in whom the results of an axillary lymph node dissection will not affect adjuvant chemotherapy decisions,

including those with small tumours and low risk of nodal involvement, it might be appropriate to omit axillary lymph node dissection.

It is likely that many frail, older women may gain no benefit from axillary surgery, which could be replaced by axillary radiotherapy.

Axillary radiotherapy as a sole treatment may give good local control and survival rates but is associated with similar rates of shoulder stiffness and lymphoedema as axillary surgery. There is little or no survival difference between radiotherapy and axillary dissection<sup>65,66,67</sup>. Local disease control rates are acceptable with axillary radiotherapy, varying between 0.5% and 12%<sup>68</sup>. Again few studies have focused on older women where rates of axillary disease are lower<sup>69</sup> and life expectancy is shorter.

Although there has been a trend toward eliminating axillary dissection, particularly in the elderly population, knowledge of the status of the axillae is still the most important predictor of breast cancer outcome. The emergence of a sentinel lymph node biopsy is an alternative therapeutic option that is particularly attractive for the elderly patient: It eliminates the need for an axillary dissection in patients found to have a negative sentinel node while identifying node-positive patients who may benefit from further surgical intervention.

### Sentinel Lymph Node Biopsy

The sentinel node is defined as the first draining lymph node of a particular cancer and, if correctly identified, accurately predicts the histologic status of the lymphatic basin. The sentinel node is an accurate predictor of the status of the remaining nodes of in the axillae in 97-100% of cases. Sentinel lymph node biopsy is the targeted removal of one or two lymph nodes, which are identified by the injection of blue dye and radioisotope into the breast. Sentinel lymph node biopsy compared to "standard axillary therapy" was the subject of the recently published ALMANAC trial which found reduced morbidity, better quality of life and no difference in mortality or local recurrence in the axilla<sup>70</sup>. The sentinel

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biopsy is an alternative option for the elderly because it has lower morbidity, can be performed under local anesthetic<sup>71</sup>, and only those women with positive nodes will need definite therapy which can be either axillary dissection, radiotherapy or in frail elderly women with ER positive tumours, endocrine therapy.

Many elderly patients are not offered axillary staging because the complications outweigh the potential benefits of the procedure. The sentinel node biopsy is a promising alternative and may allow all patients to undergo axillary staging, providing accurate prognostic information with minimal morbidity.

## Systemic Therapy

### Adjuvant treatment

Adjuvant therapy has come to play a large role in breast cancer management. Tamoxifen is well established as an effective therapy for postmenopausal, oestrogen receptor-positive women with node-positive or node negative breast cancer. An overview analysis<sup>72</sup> of 37,000 women treated with adjuvant tamoxifen demonstrated a 47% reduction in the risk of breast cancer recurrence and a 26% reduction of breast cancer death in treated women. With tamoxifen treatment for longer than 2 years, even greater benefits are observed. For the subgroup of women aged 70 and older, the reductions in the odds of recurrence and death were 54% and 34% respectively.

An EBCTCG meta-analysis of randomized trial done before 1995 showed substantial benefits of adjuvant chemotherapy in postmenopausal women in all age groups compared with no chemotherapy<sup>73</sup>. The gain was larger in those aged under 50 years of age compared with those over 50 years. (Figure 5). Two independent studies using the SEER database<sup>74,75</sup> have shown that adjuvant chemotherapy improves overall survival in elderly patients with oestrogen-receptor-negative tumours and that benefit was similar for women above and below the age of 70 years. However safety concerns should be considered.

The use of anthracycline-containing regimens has been associated with a 47% 10-year cardiac failure rate for women aged 66-70 years compared with 33% for CMF recipients and 28% for controls who received no adjuvant chemotherapy. By contrast, CMF has been shown to be less effective and is also poorly tolerated in older women<sup>76,77</sup>.

Docetaxel and cyclophosphamide might be an alternative, certainly in patients at cardiac risk<sup>78</sup>. Healthy elderly patients with node-positive breast cancer and estimated survival of 10 years or more should be considered for more aggressive chemotherapy regimens that include anthracyclines and taxanes.

Treatment with adjuvant trastuzumab, concurrent with taxanes or after chemotherapy for a total duration of 1 year, improves outcome significantly in ERBB2-positive patients<sup>79,80</sup>. In the National Surgical Adjuvant Breast and Bowel Project B31 study, age over 50 years was an independent predictor of trastuzumab-associated congestive heart failure<sup>81</sup>.

Healthy elderly patients without cardiac disease and with ERBB2-positive tumours should be considered for trastuzumab treatment. Close cardiac monitoring is essential for older patients receiving trastuzumab in the adjuvant setting.

Ganz et al.<sup>82</sup> studied the psychosocial morbidity of chemotherapy in elderly patients and found that the frequency of anxiety related to chemotherapy, before and after chemotherapy nausea, and problems with daily living resulting from treatment did not differ for young and old patients. In addition the severity of these problems seemed to be greater in the young patients. This study suggests that chemotherapy can be delivered with acceptable toxicity in the elderly.

Decisions regarding the use of chemotherapy should be made on the basis of the patient's risk of breast cancer recurrence, overall health status and current or future quality of life. In patients at high risk of local relapse, such as those with multiple positive lymph nodes and negative

oestrogen receptor status, the use of chemotherapy should be considered.

## Metastatic breast cancer

Metastatic breast cancer is treatable but not curable. Therefore, the main aims in treating elderly patients, like younger patients, with metastatic breast cancer are to maintain quality of life, minimize symptoms from disease and prolong survival without causing excessive toxicity. Older women are more likely than younger women to be diagnosed at a more advanced stage of breast cancer due to lack of screening or delays in management<sup>83,84</sup>. In selected patients with low tumour burden and metastases, especially in the bones, primary tumour removal can improve survival<sup>85,86</sup>.

Hormone treatment should be the treatment of choice for women with oestrogen-receptor-positive or progesterone-receptor-positive tumours without life-threatening disease. The superiority of aromatase inhibitors as first-line treatment over tamoxifen has been shown in the postmenopausal population<sup>87,88</sup>. Since the benefit of aromatase inhibitors over tamoxifen is mainly in terms of disease-free survival and not overall survival, tamoxifen can be valuable alternative to aromatase inhibitors if adverse events or cost are a concern. Other treatment options with "safer" profiles include tamoxifen, aromatase inhibitors, antioestrogen such as fulvestrant, progestins and high-dose oestrogens.

Women older than 70 years of age who are treated with chemotherapy for metastatic disease derive similar benefits to their younger counterparts<sup>89</sup>.

The use of chemotherapy should be considered in hormone-receptor-negative or hormone refractory patients. Preference should be given to safer chemotherapeutic drugs such as weekly taxane regimens, newer less cardiotoxic anthracycline formulations, capecitavine, gemcitabine and vinorelbine.

Monotherapy is generally favoured over combination chemotherapy since is generally associated with increased toxicity and little survival gain compared with the sequential use of





single drugs. Strict follow-up is essential in this population in particular to avoid overtreatment and debilitating side-effects. Particular attention should be paid, to supportive care, since older patients are more likely to develop neutropenia than are younger patients<sup>90</sup>, and generally have less functional reserve than their younger counterparts.

Bisphosphonates provide a supportive, expensive and no-life prolonging, benefit to many patients with bone metastases. Early intervention with bisphosphonates appears to provide the greatest potential for bone sparing benefit and palliation of bone related symptoms. Changes in renal function are important to consider when bisphosphonates therapy is contemplated, because of the possibility of renal failure.

### Conclusion

Currently, stage of disease, tumour grade, hormone-receptor status and HER2 status remain the key prognostic factors for determining prognosis and treatment in patients with breast cancer. However many studies suggest that age at breast cancer diagnosis is a major determinant of therapy received. Only minor differences in the use of mastectomy and breast-conserving therapy were reported between age groups. However, the older women are less likely than their younger counterparts to receive axillary dissection and breast irradiation. The lack of representation of older women in clinical trials makes it difficult to generalize their results to the elderly population.

The use of microarray technology, which is able to identify a limited number of specific genes that can predict disease free survival, is likely to become a better way to define prognosis and select treatment.

Gene array technology seems to be capable of identifying accurate estimates of the risk of metastases and identify low-risk patients, who would

derive little to no benefit from chemotherapy.

The explosion of knowledge of molecular biology and the development of targeted therapies is the new era for improving breast cancer treatment. It is very important that elderly patients will be included in these new clinical trials in order for individualized treatment recommendations to be developed for these patients.

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