Chapter 1

Breast cancer: classification based on molecular etiology influencing prognosis and prediction

Worldwide, breast cancer is the most frequently diagnosed life-threatening cancer in women and the leading cause of cancer death among women. The risk factors associated are gender, age, inherent genetic mutations at BRCA1 and BRCA2. There are different types of breast cancers on the basis of histopathological classifications with different outcome survival. Histologically similar tumors may have different prognosis and may respond to therapy differently. It is due to the differences in molecular portraits that resulted in differences in clinical behavior of same histopathological tumors. The inclusion of molecular classification of the breast cancer led to extraordinary progress in our understanding of the disease, resulting in more efficient and less toxic treatments. Increased public awareness and improved screening have led to earlier diagnosis at stages amenable to complete surgical resection and curative therapies. Consequently, survival rates for breast cancer have improved significantly, particularly in younger women. Though the classical traditional clinical and pathological parameters play an important role in high risk groups to be benefited by radio-therapy, but patients are often over treated. Molecular subtypes on the basis of receptors may provide sufficient information to allow accurate individual risk assessment to identify patients who might benefit from receiving post mastectomy radiotherapy. This chapter addresses the etiologic, clinical presentation, diagnosis, surgical and medical treatment, and prognosis of breast cancer with respect to different classification systems.

INTRODUCTION

1.1 Breast cancer

Cancer is a group of diseases that leads to uncontrolled cell division and eventually forms a lump or mass called a tumor. They are classified and named after the part of the body where the tumor originates. Breast cancer begins in breast tissue, which is made up of glands for milk production, called lobules, and the ducts that connect lobules to the nipple. The remainder of the breast is made up of fatty, connective, and lymphatic tissue. On the basis of origin, it is of two types (i) ductal and (ii) lobular. Ductal carcinoma constitutes 80-90% and lobular carcinoma constitutes 10-20% breast cancer cases.

Breast cancer is one of the most frequently diagnosed cancers in women worldwide, comprising 16% of all female cancers cases. It is estimated that this disease will affect one in eight females in America during their lifetime. It is estimated that occurrence of female breast cancer is 28% from all sites in U.S.A, and the relative risk of ever developing breast cancer is 0.125 (1 in 8) (American Cancer Society, 2009). Although breast cancer is thought to be a disease of the developed world, a majority (69%) of all breast cancer deaths occurs in developing countries (WHO Global Burden of Disease, 2004) and relative survival is poor in underdeveloped and developing countries (Coleman et al., 2008). The relative risk of developing breast cancer in the lifetime of women in the developed and developing countries is 0.048 (1 in 21) and 0.018 (1 in 56) respectively. In India, breast cancer is the leading cancer among women (Fig. 1.1) and the relative risk is 0.033 (1 in 30) (NCRP, 2008).

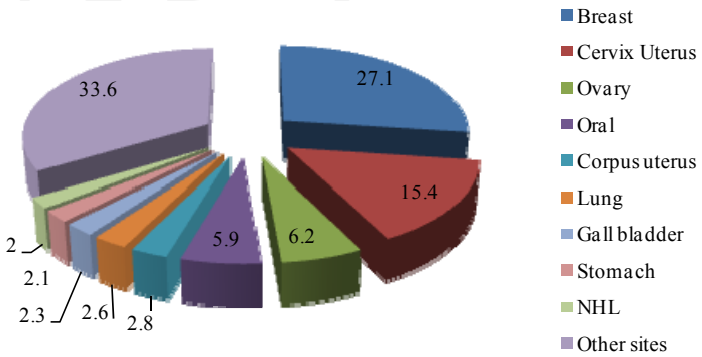


Figure 1.1: Demographic profiles of cancer cases in Indian females. Based on 2004-2005 data for Bangalore, Barshi, Bhopal, Chennai, Delhi, Mumbai, Ahmedabad and 2005 data for Kolkata.

1.2 Risk factors of breast cancer

Every woman is at risk for developing breast cancer. Several relatively strong risk factors for breast cancer that affect large proportion of the general population have been known for some time. However, the vast majority of breast cancer cases occur in women who have no identifiable risk factors other than their gender and age (Kelsey and Gammon, 1990). The other established risk factors are previous family history, age at first full-term pregnancy, early menarche, late menopause, genetic and breast tissue density. These factors are not easily modifiable and classified under unmodified factors. However, other factors associated with increased breast cancer risk are postmenopausal obesity, hormone replacement therapy (HRT), alcohol consumption, and physical inactivity, no breast feeding are modifiable and classified under modified factors. The relative risk of various factors responsible for breast cancer are shown in Table 1.1 (Hulka and Moorman, 2001).

Table 1.1: Factors that increase the Relative Risk for Breast Cancer

Relative Risk	Factor
>4.0	Female Age (65+ vs. <65 years, although risk increases across all ages until age 80) Certain inherited genetic mutations for breast cancer (BRCA1 and/or BRCA2) Two or more first-degree relatives with breast cancer diagnosed at an early age Personal history of breast cancer High breast tissue density or 75% dense
2.1-4.0	Biopsy-confirmed atypical hyperplasia One first-degree relative with breast cancer High-dose radiation to chest High bone density (postmenopausal)
1.1-2.0 Factors that affect circulating hormones	Late age at first full-term pregnancy (>30 years) Early menarche (<12 years) Late menopause (>55 years) No full-term pregnancies No breast feeding Recent oral contraceptive use Recent and long-term use of HRT Obesity (postmenopausal) Personal history of endometrial or ovarian cancer
1.1 -2.0 Other factors	Alcohol consumption Height (tall) High socioeconomic status

Hulka BS, and Moorman PG 2001. Maturitas 2008; 38:103-113

1.3 Classification of breast cancer

1.3.1 Histopathological classification

Each breast has 15 to 25 sections called 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 and hold breast milk. The lobes and lobules are connected by thin tubes, called ducts that deliver milk to nipple (Fig. 1.2). The pink or the brown pigmented region surrounding the nipple is called areola. Connective and fatty tissue fills the remaining space in between the lobes and ducts. The most common type of breast cancer is ductal cancer. It is found in the cells of the ducts. Cancer that starts in lobes or lobules is called lobular cancer. It is more often found in both breasts than other types of breast cancer. Rarely breast cancer can begin in the connective tissue that's made up of muscles, fat and blood vessels. Cancer that begins in the connective tissue is called sarcoma. It accounts for less than 5% of all soft tissue sarcomas and less than 1% of breast cancer (Moore and Kinne, 1996). Phyllodes tumor and angiosarcoma are two common forms of sarcoma. Cancers are also classified as non invasive (in situ) and invasive (infiltrating). The term in situ means “in its original place” and refers to cancer that has not spread past the area where it initially developed. Invasive breast cancer has a tendency to spread (invade) to other tissues of the breast and/or other regions of the body. A less common type of breast cancer is inflammatory breast cancer characterized by general inflammation (red and swollen) of the breast (Fig. 1.3).

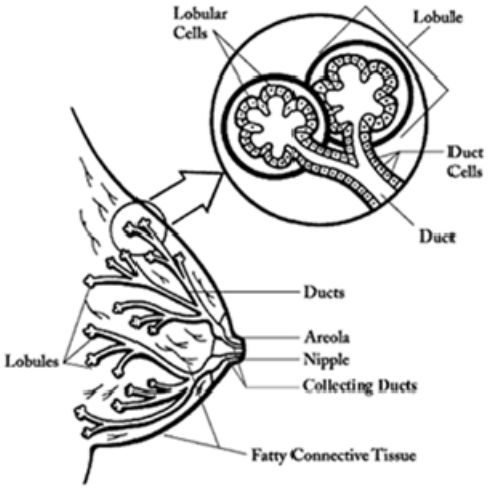


Figure 1.2: Anatomy of female breast.

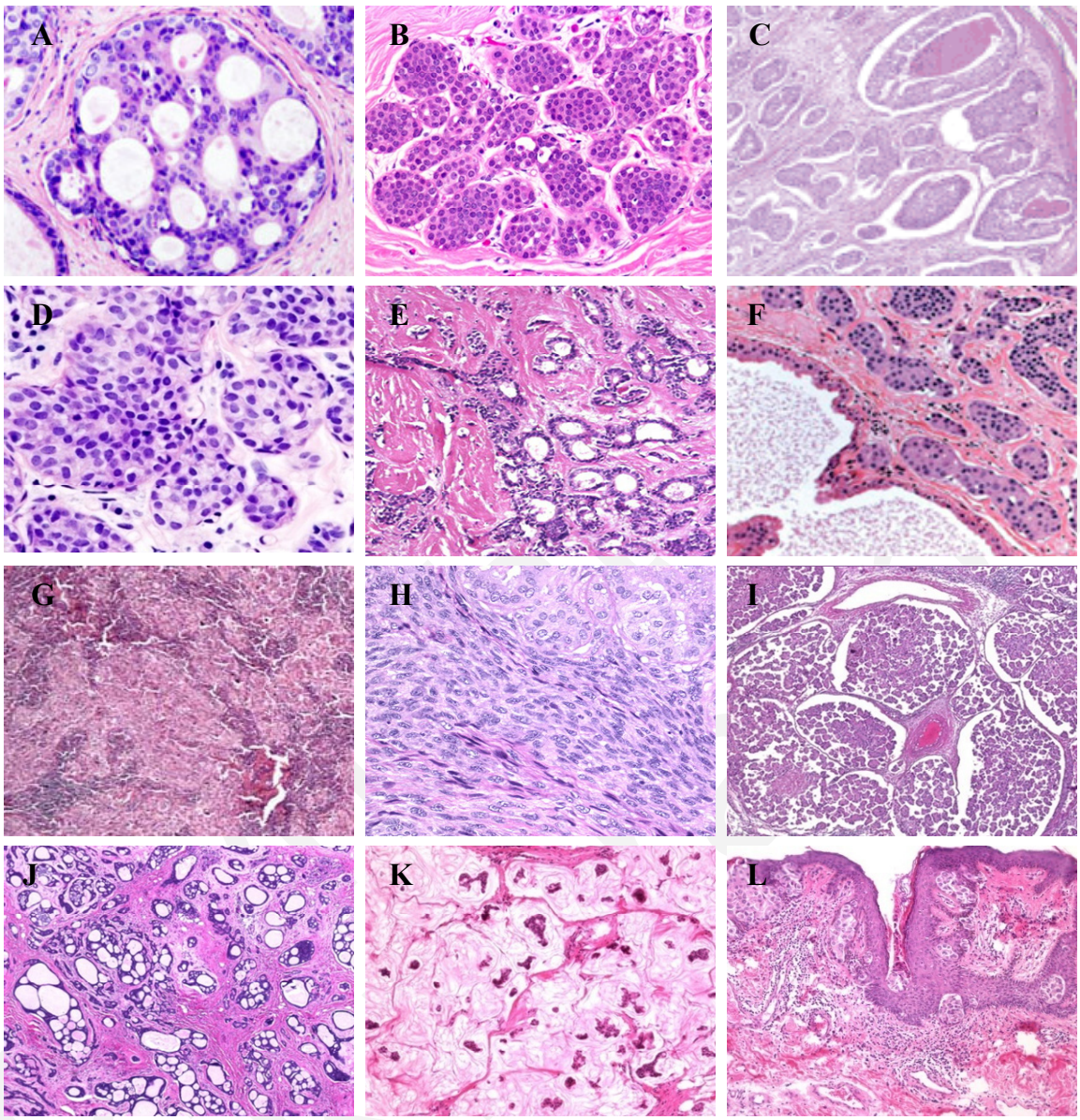


Figure 1.3: Histology of breast carcinoma. Breast carcinoma is classified into Ductal (A), Lobular carcinoma (B) and Inflammatory carcinoma. (C). It can be further classified into non-invasive (A-B) and invasive carcinoma (C-L). Invasive cancer includes Inflammatory (C), Invasive lobular (D), tubular (E) apocrine (F), medullary, (G) metaplastic (H), micropapillary, (I) adenoid cystic (J), mucinous carcinoma (K), and paget disease (L).

Invasive ductal carcinoma is the most common breast cancer and it accounts more than 75% of breast cancer cases. Most are invasive ductal carcinoma not otherwise specified (IDC NOS), and remaining IDC includes Inflammatory breast cancer, medullary carcinoma, metaplastic, apocrine and tubular carcinoma. Medullary carcinoma accounts <5% of breast cancers diagnosed, and takes its name from its color, which is

close to the color of brain tissue, or medulla. It is an invasive breast cancer that forms a distinct boundary between tumor tissue and normal tissue. Metaplastic breast cancer is a form of invasive ductal cancer, meaning that it forms in the milk ducts and then moves into other tissues of the breast. Metaplastic breast carcinomas constitute a heterogeneous group of neoplasms, accounting for less than 1% of all invasive mammary carcinomas (Reis-Filho et al., 2005), such as squamous (skin) or osseous (bone) cells. The other groups of invasive breast cancers are invasive lobular carcinoma, adenoid cystic carcinoma, micropapillary carcinoma, mucinous carcinoma (formed by the mucus-producing cancer cells), etc.

1.3.2 Molecular classification

Breast cancer is a clinically heterogeneous disease. Histologically similar tumors may have different prognosis and may respond to therapy differently. It is believed that these differences in clinical behavior are due to molecular differences between histologically similar tumors. DNA microarray technology, Immuno-histochemistry (IHC), Fluorescent in situ hybridization (FISH), and quantitative reverse transcription polymerase chain reaction (RT-PCR) are ideally suitable techniques to reveal molecular differences among the same or different groups of histopathological specimens. Each of these molecular techniques has the potential for proper prognosis and prediction of human cancers, including breast. IHC was developed more than 30 years back and it is used for classification of breast cancer into ER positive and ER negative tumors. FISH was developed 20 years back and is used to classify breast tumors into *HER-2* amplified or non amplified categories. Breast cancer cells generally overexpress estrogen receptor (ER)/ progesterone receptor (PR), and human epidermal growth factor-2 (HER-2) receptor for breast tumor formation and progression. Thus, breast cancer can be classified into three sub-groups (i) ER/PR positive (ii) ER negative or HER-2 positive and triple negative (ER, PR and HER-2 negative) on the basis of receptor status. The classification of breast cancer on the basis of ER status improves the prognosis and clinical outcome of ER+ tumors as ER+ cancer cells depend on estrogen for their growth, and the treatment of patients with anti-estrogen agents (e.g. tamoxifen) will inhibit the effect of estrogen and thus improves the treatment outcome. Generally, HER-2+ had a worse prognosis,

however HER-2+ cancer cells respond to drugs such as the monoclonal antibody, trastuzumab, (in combination with conventional chemotherapy) and this has improved the prognosis and pathological complete response significantly (Chang et al., 2010). Triple-negative breast cancer is a high risk breast cancer that lacks the benefit of specific therapy that targets these proteins. It can be categorized in basal subtypes (Rakha et al., 2007). It is found in 10-20% of breast cancer cases and mostly diagnosed in younger women with BRCA1 and BRCA2 mutations (Dent et al., 2007; Dawood et al., 2009). The rate of recurrence is very high, and it reaches its peak within first 3 years and then declines after that. Patients with triple negative breast cancer are most likely to die within 5 years than patients with other breast cancers. All deaths due to breast cancer in patients' with triple-negative cancer occurred within 10 years of diagnosis.

A novel molecular classification of breast cancer based on gene expression profiles segregates breast cancer into four types (i) luminal, (ii) basal, (iii) HER-2 and (iv) normal type (Perou et al., 2000; Sotiriou et al., 2003; Tamimi et al., 2008) (Fig. 1.4).

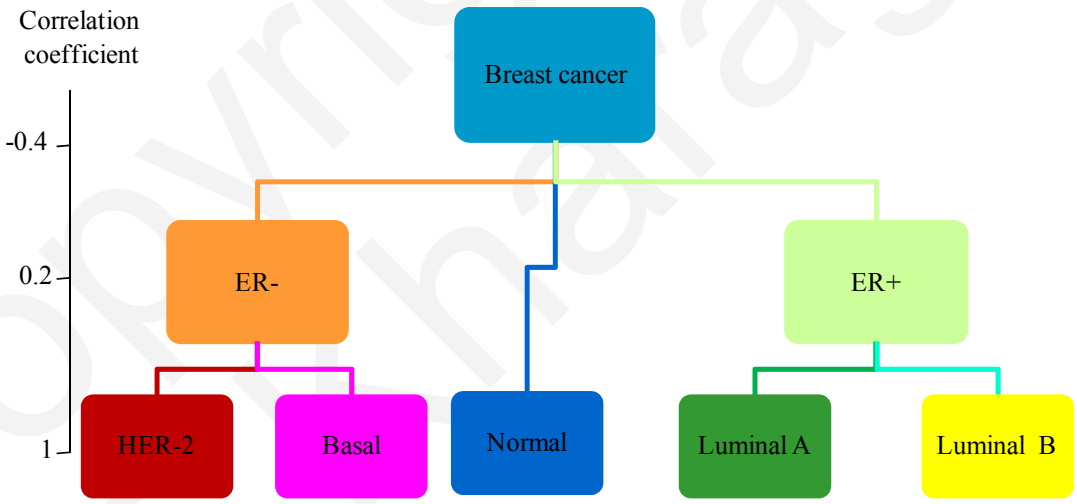


Figure 1.4: Dendrogram of breast cancer. The tumors were separated into two main groups mainly associated with ER status as analyzed by hierarchical cluster analysis generated by using gene profile data. The dendrogram is further branched into smaller subgroups within the ER+ and ER- classes based on their basal and luminal characteristics: HER-2 subgroup, dark red; basal-like 1 subgroup, pink; luminal-like A subgroup, green; luminal-like B subgroup, yellow; and normal-like breast subgroup, blue.

Luminal express keratin 8/18, ER, GATA binding protein, X-box binding protein 1, annexin XXXI, cytochrome P450 and Basal type express keratin 5, keratin 17, Integrin

β4, matrix metalloprotease 14, laminin α3, basonuclin and mutated *TP53* gene. Luminal type is further classified into luminal A and luminal B. Luminal B expresses HER-2 along with ER where as luminal A doesn't express HER-2. HER-2 subtype express ERB-2, growth factor receptor bound protein 7, TNF Receptor-associated Factor IV, GRB 7. Normal–breast-like group showed the highest expression of many genes known to be expressed by adipose tissue and other non-epithelial cell types. These tumors also showed strong expression of basal epithelial genes and low expression of luminal epithelial genes. It expresses CD36 antigen collagen type I, glycerol 3 phosphate dehydrogenase I, lipoprotein lipase A, alcohol dehydrogenase 2 (Sorlie et al., 2001). The molecular subclasses show difference in clinical outcome as per as overall survival (OS) and relapse free survival (RFS) is concerned as shown in Table 1.2. There was a significant difference in overall survival between the subtypes with basal and HER-2 is as associated with worse outcome and shortest survival time.

Table 1.2: Breast cancer outcomes in molecular types of breast cancer

Molecular types of breast carcinoma	Frequency (%)	5-year OS^{+} (%)	5-year RFS* (%)	10-year OS (%)	10-year RFS (%)
Luminal A	50-60	85-95	80-90	75-85	75-85
Luminal B	5-10	70-80	65-75	55-65	54-64
Basal	10-20	63-73	60-70	57-67	45-55
ERB-2	10-20	55-65	15-20	45-55	15-30
Normal-like	10-15	84-94	80-90	75-85	72-82

RFS: The percentage of people without any further symptoms of breast cancer during the interval elapsed between the date of breast surgery and the date of diagnosed further episode of breast cancer, whether the breast cancer was classified as a recurrence or second primary, and whatever the histology. OS: The percentage of people survived during the interval elapsed between the date of breast surgery and the date of breast cancer-related or un-related death (documented from hospital records)

1.4 Clinical outcomes of breast cancer in association with clinical, histopathological and molecular classification

Breast cancers can be classified by different schemata. Classification aspects include clinical (age, tumor, node), histopathological (grade, ER and HER-2 status, ductal,

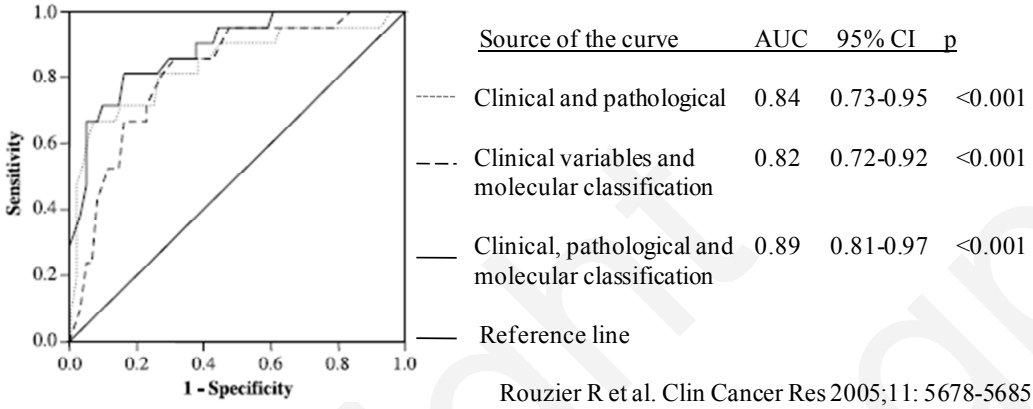
lobular, invasive) and molecular (normal-like, luminal, basal, HER-2) values. Every aspect influences treatment response and prognosis as shown in Table 1.2 and Table 1.3.

Table 1.3: Frequency and outcome of histological types of invasive breast cancer

Histopathological type of invasive breast carcinoma	Frequency (%)	10-year OS (%)
Invasive ductal carcinoma not otherwise specified (IDC NOS)	50-60	35-50
Inflammatory carcinoma	1-6	30-40
Apocrine carcinoma	1–4	Like IDC NOS
Medullary carcinoma	5–7	50–90
Metaplastic carcinoma	<5	Unknown
Micropapillary carcinoma	1-2	Unknown
Tubular carcinoma	1–2	90–100
Invasive lobular carcinoma	5–15	35–50
Adenoid cystic carcinoma	0.1	85–100
Mucinous carcinoma	<3	85–95
Neuroendocrine carcinoma	2–5	Unknown
Mammary Paget disease	1-4	40-50

The true prognostic or predictive value of the various molecular classes is unknown because there is a strong correlation between molecular class and conventional histopathologic variables (ER status, grade). For example, in one study, all luminal-type cancers were ER-positive and 63% of these were also low or intermediate grade, in contrast to 95% of basal-like cancers that were ER-negative, 91% of which were high grade (Pusztai et al., 2003). These associations partly explain the different clinical outcome observed in different molecular classes. Rouzier et al. studied the pathological outcomes of different molecular subclasses of breast cancer patients. They obtained tumor tissue biopsies from 82 patients with newly diagnosed breast cancer before they were given a commonly used chemotherapy (Taxol/5-fluorouracil, doxorubicin, and cyclophosphamide). Patients with basal-like and erbb-2+ subgroups were found to have the highest rates (45% each) of a pathological complete response, while only 6% of luminal tumors had a complete response. Among the normal-like cancers, no response was seen (Rouzier et al., 2005). None of the 61genes associated with pathologic CR in the basal-like group were associated with pathologic CR in the erbB2+ group, which suggest that the mechanisms of chemotherapy sensitivity may vary across the subtypes.

As molecular classification was not independently associated with pathologic CR, the predictive accuracy of the logistic regression models including (a) clinical + pathologic variables, (b) clinical variables + molecular classification, and (c) clinical + pathologic variables + molecular class (Fig. 1.5) was measured by constructing Receiver Operating Characteristics curve.



Rouzier R et al. Clin Cancer Res 2005;11: 5678-5685

Figure 1.5: Receiver Operating Characteristic curves for logistic regression models. Three different prediction models were compared including clinical plus histopathologic variables (model 1), clinical variables plus molecular classification (model 2), and clinical plus histopathologic plus molecularclassification (model 3). All three models were similarly done.

The three models yielded similar area under curve (AUC). This indicates that the molecular class alone can replace histopathological characteristics (estrogen receptor, HER-2 status, or grade) for prediction of pathologic CR but provides little additional information when these characteristics are included. The basal-like and HER-2 tumors were predominantly high nuclear grade and the basal-like tumors were almost all estrogen receptor negative and 80% of HER-2 molecular class expresses HER-2. These characteristics are known to be associated with higher likelihood of pathologic CR to preoperative chemotherapy (Rouzier et al., 2002; Abrial et al., 2005; Gennari et al., 2008). Because of this association, incorporation of molecular class into a logistic regression–based predictor of response did not improve the prediction accuracy compared with using routine clinical and pathologic variables only. Therefore, it is likely that more focused gene signature–based predictors will need to be developed through supervised

outcome prediction methods that are differentially expressed between cases of pathologic CR and residual disease.

1.5 Screening and detection of breast cancer

Screening uses test/techniques to check people who might have that disease (breast cancer) and to allow it to be treated at an early stage when a cure is more likely. Breast cancer screening is done by mammography (low dose x-ray technique to visualize the internal structure of the breast). On average, mammography will detect about 80-90% of the breast cancers in women without symptoms. Testing is somewhat more accurate in postmenopausal than in premenopausal women (Michaelson et al., 2002). It can reduce breast cancer mortality by 20-30% in women over 50 yrs old in high-income countries when the screening coverage is over 70% (IARC, 2008). MRI, or magnetic resonance imaging, is a technology that uses magnets and radio waves to produce detailed cross-sectional images of the inside of the body. MRI does not use x-rays, so it does not involve any radiation exposure. Breast MRI is not recommended as a routine screening tool for all women as MRI screening results in more false positives results. However, it is recommended for screening women who are at high risk for breast cancer, usually due to a strong family history and/or a mutation in genes such as BRCA1 or BRCA2. It is also used for gathering more information about the suspicious area found on mammogram and ultrasound and also used for monitoring recurrence after treatment. Positron emission tomography (PET) scan creates computerized images of chemical changes that take place in the tissue. PET scans may play a role in determining whether a breast mass is cancerous. However, PET scans are more accurate in detecting larger and more aggressive tumors than they are in locating tumors that are smaller than 8 mm and/or less aggressive. They may also detect cancer when other imaging techniques show normal results. PET scans may be helpful in evaluating and staging recurrent disease. Clinical breast examination (CBE) is recommended for average risk asymptomatic in the age group of 20-30 to observe any changes in shape, texture, and location of lumps (situated in skin or deeper tissues). The breasts should also be inspected for skin changes (e.g., dimpling, redness) and asymmetry. The area under both arms will also be examined. CBE is also an opportunity for a woman and her health care provider to discuss changes in her

breasts, early detection testing, and factors in the woman's history that might make her more likely to develop. All women should become familiar with both the appearance and feel of their breasts to detect any changes and report them promptly to their physician. A woman who chooses to perform breast self-exams (BSE) should receive instructions and have her technique reviewed by a health care professional who performs clinical examinations. Finding and reporting breast changes early offers women the best opportunity for improving breast cancer treatment and reducing breast cancer deaths. Mammotome® is a vacuum assisted breast biopsy that uses image guidance such as stereotactic x-ray, ultrasound, MRI and/or molecular imaging to perform breast biopsies. Mammotome offers a full array of tissue markers to mark the biopsy site for follow-up observations. There have been no reports of serious complications resulting from the Mammotome breast biopsy system. Ductal lavage is another screening and investigational technique for collecting samples of cells from breast ducts for analysis under a microscope. A saline (salt water) solution is introduced into a milk duct through a catheter (a thin, flexible tube) that is inserted into the opening of the duct on the surface of the nipple. Fluid, which contains cells from the duct, is withdrawn through the catheter. The cells are checked under a microscope to identify changes that may indicate cancer or changes that may increase the risk for breast cancer. The procedure is used to identify precancerous cells, called atypical cells. Ductal lavage is currently performed only on women who have multiple breast cancer risk factors to detect breast cancer before it starts. Ductal lavage appears to have low sensitivity and high specificity for breast cancer detection, possibly because cancer-containing ducts fail to yield fluid or have benign or mildly atypical cytology (Khan et al., 2004).

1.6 Breast Cancer Treatment

Breast cancer treatment depends on stage, age, hormonal and receptor status. Most women with breast cancer will have some type of surgery. Surgery is often combined with other treatments such as radiation therapy, chemotherapy, hormone therapy, and/or targeted therapy.

1.6.1 Surgery

Most patients with breast cancer have surgery to remove the cancer from the breast. The types of breast cancer surgery differ in the amount of tissue that is removed with the tumor, depending on the tumor's characteristics, whether it has spread (metastasized), and patient's personal feelings. Some of the lymph nodes under the arm are usually taken out and looked at under a microscope to see if they contain cancer cells. Breast-conserving surgery or lumpectomy is done to remove the cancer cells but not the breast itself. Lumpectomy is almost always followed by about 5 to 7 weeks of radiation therapy. A woman who chooses lumpectomy and radiation will have the same expected long-term survival as if she had chosen mastectomy (Fisher et al., 2002). Simple or total mastectomy includes removal of the entire breast. Modified radical mastectomy includes removal of the entire breast and lymph nodes under the arm, but does not include removal of the underlying chest wall muscle, as with a radical mastectomy. Both lumpectomy and mastectomy are often accompanied by removal of regional lymph nodes from the axilla, or armpit, to determine the involvement of lymph nodes and spreading of the disease. Axillary lymph node metastasis is the most important prognostic factor for the disease-free and overall survival. Patients with multiple unfavorable risk factors such as positive axillary lymph nodes, high nuclear grade, young age and large tumor showed poorer local control and disease-free survival than patients without any risk factors, and so more aggressive treatment is required for these patients. Adjuvant radio- chemo- or targeted therapy has improved the prognosis of patients with higher risk factors (Lee and Chan, 1984; Kim et al., 2005).

1.6.2 Radiation therapy

Radiation therapy is a cancer treatment that uses high-energy x-rays or other types of radiation to destroy cancer cells remaining in the breast, chest wall, or underarm area after surgery, or to reduce the size of a tumor before surgery (Early Breast Cancer Trialists' Collaborative Group, 2000). There are two types of radiation therapy. External radiation therapy uses a machine outside the body to send radiation toward the cancer. Internal radiation therapy uses a radioactive substance sealed in needles, seeds, wires, or catheters that are placed directly into or near the cancer. The way the radiation therapy is

given depends on the type and stage of the cancer being treated. Using traditional clinical and pathological factors, patients can be classified into subgroups by the risk of loco-regional recurrence. In the high-risk groups the absolute benefit of irradiation is larger. However, the patients are over-treated in every subgroup. Substantial proportion of the patients remains free of loco-regional recurrence even in the absence of irradiation, and some patients develop loco-regional recurrence despite postoperative irradiation. Molecular subtypes on the basis of receptors may provide sufficient information to allow accurate individual risk assessment to identify patients who might benefit from receiving post mastectomy radiotherapy (PMRT). A significantly improved overall survival after PMRT was seen only among patients of luminal subtypes. No significant overall survival improvement after PMRT was found among patients with basal and ERB2 subtypes (Fig. 1.6). There was also smaller improvements in loco-regional recurrence of breast cancer in basal and ERB2 subtypes as compared to luminal A and luminal B (Kyndi et al., 2008). Hence, the improvement in survival resulting from the use of irradiation is more related to the prevention of local recurrences. Post-irradiation local recurrence increases the risk of mortality, but with good prognostic factors (<4 positive nodes, tumor size <2 cm, Grade 1 malignancy, ER- and PR-positive, HER-2-negative) the 10-year survival is 80-90% (Fodor, 2009).

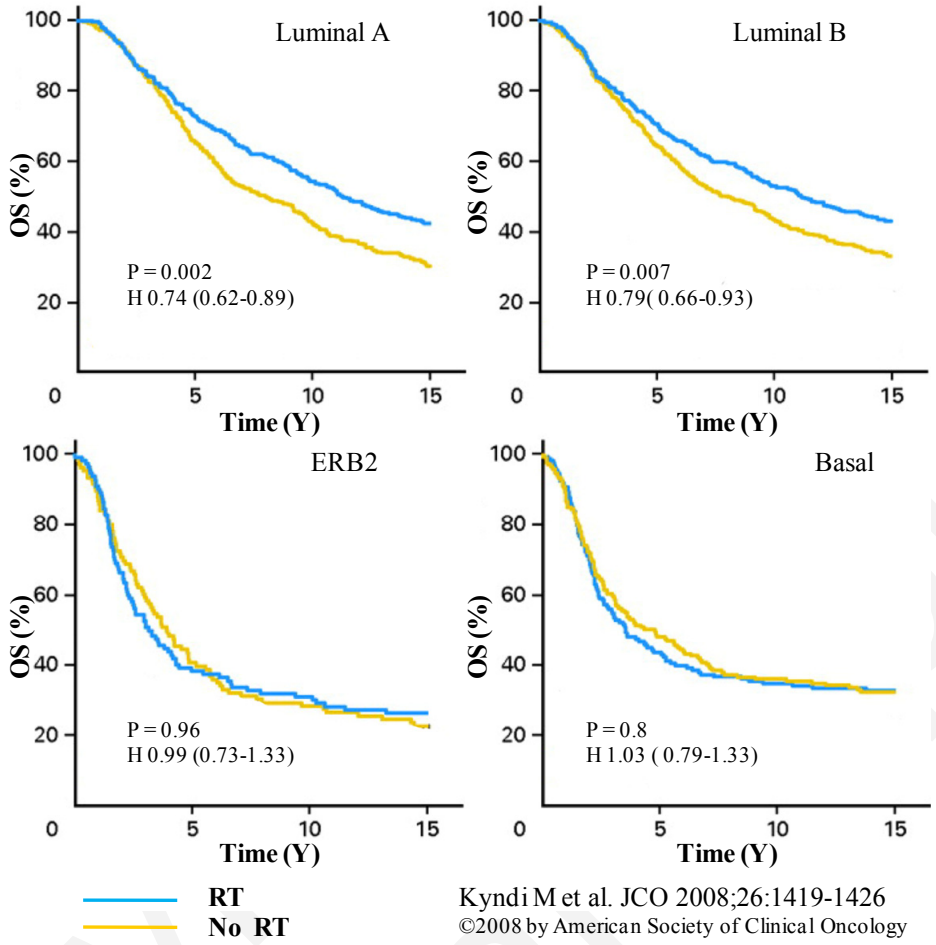


Figure 1.6: Overall survivals (OS)% of different molecular subtypes of breast cancer patients after receiving post mastectomy radiation therapy (RT). P values and 95% CI of Hazard (H) ratios are shown

1.6.3 Chemotherapy and molecular targeted-therapy

Chemotherapeutic drugs are applied in neoadjuvant settings to shrink the size of tumor that has metastasized and also in adjuvant settings to delay the further growth and spread of the tumor. It is found that combinations of drugs are more effective than just one drug alone for breast cancer treatment. The most common drugs recommended to be used in combination in early breast cancer are cyclophosphamide, methotrexate, 5-fluorouracil (CMF combinations), doxorubicin (Adriamycin), epirubicin, paclitaxel (Taxol), and docetaxol (Taxotere). Although the benefit and clinical outcome of chemotherapy is dependent on clinical and histopathological parameters, but there are a percentage of cases that behave in an unexpected manner, even if the clinical and pathological parameters indicate the opposite (Gonzalez-Angulo et al., 2007). The introduction of

hormonal receptor status to the classical clinical parameters improved the clinical outcome (Goldhirsch et al., 2003). The chemotherapeutic drugs are designed to target the specific molecular markers (molecular targeted therapy) overexpressed in cancer tissues. The presence of ER is correlated with a better prognosis, predicting response to hormonal therapies such as tamoxifen and aromatase inhibitors. But still 15-20% of breast cancer patients with ER+ have recurrent disease. It's the luminal B subgroup of previously classified ER+ tumor that is irresponsive to tamoxifen treatment as they co-express EGFRs and shows poor relapse-free survival (RFS) and over-all survival (OS). Thus over-simplified classification based on ER status required additional molecular makers for sub-classification for optimal treatment. The molecular portraits based on gene profiling divides breast carcinomas into luminal (A and B), basal, HER-2 and normal like. Basal and HER-2 types normally overexpress EGFR and HER-2 respectively. EGFR and HER-2 is overexpressed in 17-30% and 20-30% respectively in breast cancer. Both EGFR and HER-2 is associated with poor prognosis and worse clinical outcome. Basal like subtypes are more aggressive and less responsive to conventional chemotherapy and expected to benefit from EGFR-targeted therapies. Tyrosine kinase inhibitors (TKI) (ZD1839, ZD6474) in combined with anthracyclines (doxorubicin, epirubicin) or taxanes based regimens will improve the clinical outcome of the basal subtypes. HER-2 might serve as a marker for tissue HER-2 status, especially for the prediction of benefit from trastuzumab and/or chemotherapy regimens (anthracyclines) (Sandri et al., 2004). Although the molecular profile of the tumor is a major determinant of disease progression and response to treatment, other factors including chemo- sensitvity or resitivity may be of considerable importance. It is found that for 100 node-negative, premenopausal women receiving chemotherapy according to standard criteria, at 5 years 3 are cured by chemotherapy, 83.50 would have been alive without chemotherapy and 13.50 die despite chemotherapy. With application of molecular profiling to predict the outcome (for the same 100 people), the number treated would be reduced to 39.05 (allowing for a false-positive rate equivalent to that seen in the van 't Veer study) (van 't Veer et al., 2002), resulting in an increase in the proportion cured (from 3 out of 100 to 3 out of 39 or 8%). If it were possible to predict chemo-responsiveness, it is possible that the number receiving chemotherapy would reduce further from 39.05 to 29.20 (allowing for a false-

positive rate equivalent to that seen in the van't Veer study). In this scenario, the proportion cured by chemotherapy would be 3 out of 29.20 (10.16%) (>3-fold increase in survival rate using chemotherapy), and the number of women treated has been reduced by 70.80%. Thus it is found that molecular profiling will enhance the survival benefit of chemotherapeutic regimens, which will be further improved applying the knowledge of chemo-responsiveness as shown in Fig. 1.7. If accurate determination of chemo-sensitivity were achieved by observing the set of genes responsible for treatment response, the overall number receiving cytotoxic treatment unnecessarily would decrease, and the overall survival benefit derived, per person treated, increase accordingly, as shown in Fig 1.7. However, the absolute survival benefit of patients diagnosed with breast cancer would be unaffected and would be improved with more molecular subtypes along with the development of specific agents targeting particular biomarkers (molecular targeted therapy).

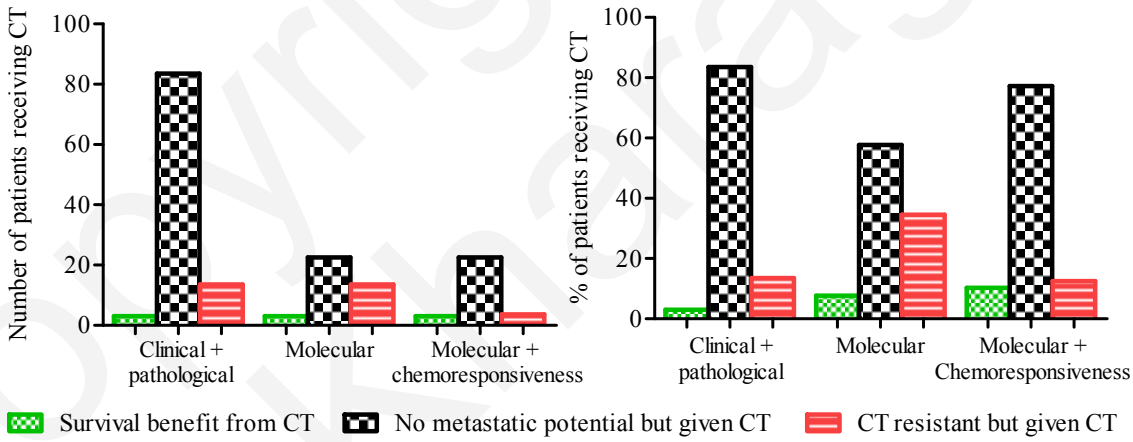


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Figure 1.7: Model for the effect of molecular profiling on breast cancer. The data shows numbers of premenopausal women with node negative breast cancer receiving chemotherapy (CT), and associated benefit at 5 years. 100 node-negative, premenopausal women receiving chemotherapy according to standard criteria, at 5 years showed survival benefit, no benefit and breast cancer specific death. The two bar graph represents absolute survival benefit and % survival benefit of breast cancer patients receiving chemotherapy. Note that in neither figure has consideration been given to the false-negative rate inherent in molecular profiling. It has been assumed that all deaths occurring were breast cancer related.

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