Biology-driven Selection of Optimal Systemic Therapy of Primary Breast Cancer

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KEY POINTS

1. Combined modality therapy is the therapeutic approach of choice for the management of early breast cancer.
2. Systemic treatments are estimated to reduce annual odds of recurrence by 50% to 60% and annual odds of death by about 40% to 50%.
3. Breast cancer includes at least five discrete, molecularly defined subgroups with distinct natural histories, drug sensitivities and specific molecular therapeutic targets.
4. Patients with hormone receptor-positive, HER2 negative tumors benefit from adjuvant endocrine therapy.
5. Patients with HER2-positive tumors, any ER/PR or menopausal status derive major benefit from the administration of one year of trastuzumab in combination with chemotherapy.
6. Clinical and pathological factors commonly used to determine risk of recurrence and death from breast cancer can be combined in indices, such as the on-line program, Adjuvant!Online, to obtain a more accurate prediction of outcome for individual patients.

Combined modality therapy is the therapeutic approach of choice for the management of early breast cancer. Systemic therapies, surgical resection and radiotherapy all have important functions in this strategy. Systemic therapy includes endocrine treatments, chemotherapy and HER-2-targeted therapies. Whether administered before optimal local-regional treatments or following local therapy, systemic treatments are estimated to reduce annual odds of recurrence by 50% to 60% and annual odds of death by about 40% to 50%. While endocrine therapy is unarguably the oldest of all systemic treatments, wide acceptance of adjuvant endocrine therapy did not occur until the mid to late 1980s. Combination chemotherapy was the first successful and fully validated adjuvant systemic intervention. Initial regimens included variations of cyclophosphamide, methotrexate and fluorouracil (CMF). CMF-type regimens are clearly effective, regardless of age, menopausal status and nodal status. In subsequent generations of adjuvant therapy regimens, anthracyclines were substituted for methotrexate, with a 20% to 30% improvement in outcomes compared to CMF-like regimens. The introduction of taxanes produced another incremental improvement in relapse-free and overall survival. Chemotherapy research over the past decade has focused on issues of dose, dose-density and scheduling, with varying degrees of success. The initial endocrine adjuvant therapies were designed for unselected patients with primary breast cancer, since the estrogen receptor was only discovered in the 1960s. By the mid-1980s, there was fairly compelling evidence that tamoxifen, administered for several years, reduced significantly the risk of recurrence, and in some trials, the risk of death, especially in postmenopausal women. Subsequent clinical trials established that around five years of adjuvant tamoxifen were optimal. Clinical trials conducted in the same era,
also demonstrated that for hormone receptor-positive tumors, the combination of tamoxifen and chemotherapy was more effective than either component, and this approach was eventually adopted as the standard of care. The initial trials of adjuvant ovarian ablation were underpowered, and accrual to such trials was quite challenging. Definitive evidence of the therapeutic activity of ovarian ablation/suppression was provided by the Oxford meta-analysis in the early 1990s. It was also the meta-analysis that provided definitive support for the effectiveness of adjuvant tamoxifen in the management of premenopausal patients with breast cancer, and that the expression of the estrogen receptor in tumor tissue was the most effective predictor of benefit from endocrine therapy; conversely, the evidence also indicated that patients with estrogen receptor-negative tumors did not benefit from hormonal therapy. Progress during the 1990s was incremental in nature: the development of adjuvant selective aromatase inhibitors (AIs) and the introduction of taxanes. AIs are clearly more effective than tamoxifen, and considered to be the first choice for adjuvant endocrine therapy of postmenopausal women with hormone receptor-positive breast cancer. In fact, the AIs are now the subject of intensive investigation in the prevention of breast cancer in women at high risk of developing this disease. The recent presentation of the first analysis of the BIG1-98 trial suggested that the administration of adjuvant AIs up front was the best strategy, and performed better than a sequential tamoxifen-to-AI (or AI to tamoxifen) sequential strategy for most risk-defined groups. Ongoing clinical trials will soon establish the optimal duration of adjuvant endocrine therapy for postmenopausal women. While there is considerable uncertainty and ongoing controversy about optimal endocrine therapy for premenopausal women with hormone receptor-positive breast cancer several well-designed clinical trials (SOFT and TEXT) to define the best strategy are approaching completion. Clinical trials have clearly established that ovarian ablation or suppression (using gonadotropin analogs) has equivalent therapeutic activity to some first-generation chemotherapy regimens (CMF). Trials have also suggested that, for patients with hormone receptor-positive tumors, ovarian ablation/suppression might have superior activity to that of CMF. However, these answers provide incomplete guidance for optimal management of premenopausal women with hormone-responsive breast cancer. The endocrine therapy and chemotherapy used in the relevant clinical trials are now of historical interest only, since they have largely been replaced by more effective regimens. Thus, the optimal integration of aromatase inhibitors into the management of premenopausal women has not been determined, and no endocrine therapy has been directly compared with modern chemotherapy regimens (TAC, dose-dense AC+T, etc.). Even more importantly, the most pressing question is not whether endocrine therapy is better or worse than chemotherapy, but whether and what combination of endocrine and chemotherapy will offer the highest probability of long-term disease control to both premenopausal and postmenopausal women with hormone-sensitive breast cancer.

The incorporation of taxanes into adjuvant and neoadjuvant therapy was accomplished in a relatively short time interval. It is now generally accepted that the optimal schedule of administration for paclitaxel is the weekly schedule, while the 3-weekly schedule appears to have the best therapeutic index for docetaxel. Nab-paclitaxel is currently under evaluation in the adjuvant and neoadjuvant settings. Retrospective analyses suggest that the incremental benefit of adjuvant taxanes is greater for patients with hormone receptor-negative tumors than for hormone receptor-positive breast cancer. This observation has not been reported for docetaxel-based regimens, so there is substantial uncertainty about the relevance of the initial reports to clinical practice. Perhaps a more important line of investigation is to determine whether there are subsets...
of hormone receptor positive tumors that derive little or no benefit from chemotherapy. For premenopausal women, these issues are somewhat more complicated, because chemotherapy affects ovarian function, and therefore, has endocrine effects for some, but perhaps not all premenopausal women. This observation explains, at least in part, why combinations of endocrine therapy and chemotherapy do not provide the same magnitude of additive benefit observed in postmenopausal patients. This is particularly true for ovarian ablation added to chemotherapy. Retrospective analyses suggest, but do not establish, that the benefit of ovarian ablation after chemotherapy might be limited to those premenopausal women whose menses persist during and after adjuvant chemotherapy.

Two other important development in the 1990s were not incremental, but paradigm changing. The discovery and validation of HER2 amplification/overexpression as an adverse prognostic factor, and the development of a monoclonal antibody to the HER2 cell surface oncoprotein, and more recently small molecule tyrosine kinase inhibitors with similar (although not identical) effects, opened entirely new avenues of therapeutic research. Six large, prospective randomized trials documented the marked antitumor efficacy of these drugs, both in the metastatic and the adjuvant settings.

Simultaneously with these developments, technological advances made possible the simultaneous evaluation of not 2 or 3, but thousands of genes (the entire human genome, in fact) on the same tissue. Our increased understanding of the heterogeneity of primary breast cancer, and the identification of discrete, molecularly defined subgroups of breast cancer with distinct natural histories, drug sensitivities and specific molecular therapeutic targets has revolutionized our conceptual and therapeutic approach to breast cancer. Thus, it is apparent today, that luminal, basal, HER2-like and perhaps other, smaller molecular subsets can be reproducibly identified by microarray technology. Somewhat more simplistically (and less accurately), the use of three immunohistochemical assays (estrogen receptor [ER], progesterone receptor [PR] and HER2) defines similar, although not identical groups of tumors. These three markers are today considered an integral component of the diagnosis of breast cancer, and represent prognostic indicators as well as selectors of optimal therapy for individual patients. We no longer design clinical trials for “breast cancer”; instead, clinical trials focus on HER2-positive tumors, or hormone receptor-positive/HER2-negative breast cancer, or “triple-negative” malignancies. Increasingly, as part of therapeutic trials, we incorporate biological correlative studies in an attempt to identify within relatively homogeneous populations the operative mechanisms of resistance. The challenge of future drug development will be to generate compelling biological and clinical evidence of safety and efficacy in populations of smaller and smaller size.

Another important collateral benefit of multigene assays is the ability to identify genetic “profiles” or “signatures” associated with improved or adverse prognosis or response to therapies. One such example is the Oncotype Dx assay. This is an RT-PCR-based assay that measures the expression of 21 genes: 16 related to the estrogen signaling pathway, proliferation markers, invasion and metastasis and HER2. The other five are “housekeeping genes”. Retrospective analyses of paraffin-embedded tumor samples of patients with estrogen receptor-positive tumors have shown that the Recurrence Score, derived from Oncotype Dx, is linearly associated with the risk of recurrence, whether the patient received tamoxifen or not, and regardless of nodal status. Additional analyses provide preliminary evidence suggesting that patients with low Recurrence Score tumors might not benefit from adjuvant chemotherapy, while those with high Recurrence Scores might not benefit from tamoxifen, despite a positive estrogen receptor assay. A large prospective validation trial is ongoing and should provide more
compelling answers to these and potentially other outstanding questions. Another is being planned for patients with ER-positive, lymph node-positive breast cancer. The Recurrence Score also predicts the probability of achieving a pathological complete remission after neoadjuvant chemotherapy. Other genomic assays (Mammaprint, PAM50 and others) are also available for more accurate determination of prognosis and are under evaluation to predict therapeutic benefit. Modern technology should provide us with better and better methods to select the most appropriate therapies for individual patients and thus increase efficacy, while limiting toxicity. The era of personalized medicine is upon us, although the validation of these intuitively attractive concepts will take a good part of the next decade.

Today, the aggregate available evidence suggests the following:

1) Patients with hormone receptor-positive, HER2 negative tumors:
   a. Premenopausal women benefit from adjuvant or neoadjuvant ovarian ablation/suppression or tamoxifen; chemotherapy (CMF, FAC/FEC, AC+T, TAC, etc.) provides incremental benefit above that achieved by endocrine therapy for many patients.
   b. Postmenopausal women benefit from adjuvant or neoadjuvant aromatase inhibitors (AI, alone or followed by tamoxifen); chemotherapy of the same type shown for premenopausal women provides incremental benefit, although to a lesser extent than for premenopausal women;

2) Patients with HER2-positive tumors, any ER/PR or menopausal status: the administration of one year of trastuzumab in combination with chemotherapy is associated with about a 50% reduction in odds of recurrence and about a 30% reduction in odds of death. The optimal timing and duration of trastuzumab is under investigation, although trastuzumab has been given in the adjuvant and neoadjuvant situations with apparently similar benefits. Whether other molecular markers can identify those patients with HER2-positive tumors that will benefit from trastuzumab, and what the role of lapatinib is in the management of primary breast cancer is also under investigation.

3) Preliminary evidence from three adjuvant trials (HERA, N9831 and PACS) suggests that simultaneous administration of chemotherapy and trastuzumab is more effective than sequential use of chemotherapy followed by trastuzumab.

4) Because of the increased cardiac toxicity observed with simultaneous or sequential combinations of an anthracycline and trastuzumab, some have proposed that anthracyclines have limited or no role in the management of primary breast cancer. This concept is being hotly debated; there is no reliable or reproducible marker of anthracycline benefit that would serve to identify the population most and least likely to benefit from this group of drugs.

5) Patients with “triple-negative” breast cancer: chemotherapy with an anthracycline, cyclophosphamide and a taxane is the treatment of choice for patients with HR-negative, HER2-negative tumors; platinum-based, non-anthracycline-containing regimens are under evaluation; bevacizumab is active in the metastatic setting in this group, and is under evaluation in clinical trials in the adjuvant and neoadjuvant settings. The recent and very promising results of PARP-inhibitors combined with chemotherapy in the metastatic setting suggest that similar combinations are likely to be effective in the triple-negative population of patients with primary breast cancer.

6) There is much interest in identifying those patients who will benefit more from anthracyclines than other agents, and those who need a taxane for optimal results.
Topoisomerase II amplification has been proposed as a maker for anthracycline sensitivity, as have a number of other molecular markers.

7) The incremental benefit of chemotherapy for women with high HR content is under renewed investigation. Molecular indices (Oncotype DX, Mammaprint, GGI, PAM50, SET index, and others) are currently under critical evaluation for this purpose.

8) Clinical and pathological factors are commonly used to determine risk of recurrence and death from breast cancer.(7) These factors are reasonably accurate in predicting prognosis for groups of patients, but much less so for individual patients. An on-line program, Adjuvant!Online considers multiple clinical and pathological factors to predict risk of recurrence and mortality.(8) In addition, this program incorporates the effect of comorbid conditions in the determination of prognosis and benefit from various therapeutic interventions. This program is available on-line at no cost to the user. Adjuvant!Online has been independently validated by Canadian investigators, and the concordance with actual recurrence and mortality rates was within 1% of predictions based on this model.(9)

9) Multigene predictors of prognosis and responsiveness to therapy are currently under development and clinical validation.(10;11) The Oncotype Dx assay seems to be most advanced in validation trials and has been used in over 100,000 patients in the practice setting.(12) Mammaprint requires fresh or fresh-frozen tumor samples; others can be performed on paraffin-embedded archival material, increasing the possibility of general use in the community. Preliminary analyses suggest that combined use of the Oncotype DX assay and Adjuvant!Online provides even more accurate prognostic information than each component alone.

10) The results of current trials will determine whether more precise determination of prognosis and identification of patients most likely and least likely to benefit from specific therapies can improve the efficacy and reduce the toxicity of systemic treatments. As individual tumors are molecularly characterized and molecularly targeted therapies are clinically validated, “personalized” adjuvant therapy will become a reality in the not too distant future.(13)

Reference List


Pathologic Response Following Neoadjuvant Chemotherapy As An Outcome For Clinical And Translational Research.

W. Fraser Symmans, M.D.
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Keypoints:

1. The definition of pathologic complete response (pCR) should be the absence of any residual invasive cancer in the breast and absence of any metastatic cells in the regional lymph nodes.

2. Neoadjuvant chemotherapy trials provide a valid clinical model in which to test for further improvements in adjuvant treatment.

3. Residual disease encompasses a broad spectrum of actual responses, and so evidence-based stratification of this group can further refine the prognostic utility of pathologic response following chemotherapy.

4. Efforts to standardize gross description, sampling and section codes, and reporting of residual disease after neoadjuvant chemotherapy should be practical and support evidence-based systems that evaluate pathologic response as a clinical outcome.
   a. If minimal residual disease has identical prognosis as pCR, do we really need to exhaustively sample the residual tumor bed to find a last remaining cancer cell?

5. Successful adoption of point 4 would improve the knowledge that is gleaned from clinical trials, help to identify at-risk patients for additional post-surgical systemic therapy (currently in clinical trials), and provide meaningful information in the usual pathology report.

1. Background

A central tenet of neoadjuvant clinical trials is that tumor response, as a surrogate endpoint, should be strongly correlated with long-term patient survival. Pathologic complete response (pCR) is associated with long-term survival, and has been adopted as the primary endpoint for neoadjuvant trials. While it is generally held that a definition of pCR should include patients without residual invasive carcinoma in the breast (pT0), the presence of nodal metastasis, minimal residual cellularity, and residual in situ carcinoma are not consistently defined as pCR or residual disease (RD). When there is no residual invasive cancer in the breast, the number of involved axillary lymph nodes is inversely related to survival. Conversely, patients who convert to node-negative status after treatment have excellent survival, even if there is residual disease in the breast. Consequently, the combination of tumor size and nodal status after neoadjuvant treatment is prognostic.

Alternatively, the Miller and Payne classification ignores tumor size and nodal status altogether, and estimates only the decrease in cancer cellularity after treatment. However, the reduction in cellularity is often greatest when the residual tumor is small, suggesting a relationship between residual size and cellularity. Other systems, such as those reported by Honkoop, Chevallier and Sataloff, incorporate pathologic evidence of treatment response (using different criteria) to stratify patients with residual disease. While microscopic residual disease, altered cytologic appearance, and estimated tumor volume <1 cm^3 also indicate good response, these tend to be descriptive parameters and are also difficult to apply to tumor beds with dispersed microscopic foci of carcinoma. Finally, there is no evidence that residual in situ carcinoma alone increases risk of future distant relapse.

*Therefore, the definition of pathologic complete response (pCR) should be the absence of any residual invasive cancer in the breast and absence of any metastatic cells in the regional lymph nodes.*
2. Improvements in Pathologic Complete Response Translates To Predicts Improved Survival

Patients who achieve pathologic complete response (pCR) from neoadjuvant (pre-operative) systemic therapy have excellent 5-year overall survival that is independent of treatment regimen or tumor phenotype. Furthermore, Table 1 illustrates how improvement in pCR observed in a neoadjuvant trial anticipated a survival difference in a phase III adjuvant trial for three recent treatment advances: addition of a taxane to anthracycline-based chemotherapy (white), more frequent paclitaxel dosing schedule (gray), and the addition of trastuzumab (Herceptin) to sequential anthracycline-taxane chemotherapy (blue). Therefore, neoadjuvant chemotherapy trials provide a valid clinical model in which to test for further improvements in adjuvant treatment.

3. The Prognostic Importance of Residual Cancer Burden (RCB) After Neoadjuvant Treatment

Residual disease (RD) after neoadjuvant treatment includes a broad range of actual responses from near-pCR to frank resistance. We developed a method to measure RD by combining histopathologic components of residual disease (cellularity, overall diameter, number and extent of nodal involvement) into a numerical index of residual cancer burden (RCB). Minimal RD (RCB-I) in 17% of patients carried the same prognosis as pCR, even in hormone receptor-negative breast cancers (Figure 1A). Furthermore, extensive RD (RCB-III) in 13% of patients was associated with poor prognosis (Figure 1). Even for ER-positive breast cancer, patients with RCB-III had a 5-year distant relapse rate of 40% despite ongoing treatment with adjuvant hormonal treatment (Figure 1B). This identifies an important subset of patients with either combined insensitivity to chemotherapy and hormonal therapy, or with residual disease (after surgery) that is too extensive to be controlled by hormonal therapy alone, and illustrates how identification of the subset of receptor-positive patients who might correctly be spared (denied) adjuvant chemotherapy despite consensus treatment recommendations will require very careful selection based on the tumor’s predicted chemosensitivity and the predicted endocrine sensitivity. In summary, RCB incorporates the information from pCR, represents the extent of residual disease, more strongly predicts distant relapse-free survival, and can define clinically relevant subsets with near-pCR (RCB-I) or resistance (RCB-III).

### Table 1. Changes in Pathologic Complete Response in Neoadjuvant Trials Predicted Survival Difference in Adjuvant Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment Arms</th>
<th>N</th>
<th>pCR (%)</th>
<th>P</th>
<th>Trial</th>
<th>Treatment Arms</th>
<th>N</th>
<th>5 yr DFS</th>
<th>P</th>
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<td>NSABP-B27</td>
<td>AC + Tam</td>
<td>802</td>
<td>13%</td>
<td>&lt;0.0001</td>
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<td>AC + Tam</td>
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<td></td>
<td>AC / Dx4 + Tam</td>
<td>803</td>
<td>26%</td>
<td></td>
<td></td>
<td>AC / Dx4 + Tam</td>
<td>803</td>
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<td>NSABP-B28</td>
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<td>1529</td>
<td>72%</td>
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<td>(0.83)</td>
<td>AC / Tx4 + Tam</td>
<td>1531</td>
<td>76%</td>
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<td></td>
<td>AC / Tx4</td>
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<td>65%</td>
<td>0.002</td>
<td>(0.83)</td>
<td>AC / Tx4</td>
<td>1570</td>
<td>70%</td>
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<td>CALGB-9344</td>
<td>AC</td>
<td>1253</td>
<td>76.9%</td>
<td>0.006</td>
<td>(0.79)</td>
<td>weekly Tx12 / AC</td>
<td>1231</td>
<td>81.5%</td>
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<tr>
<td></td>
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<td>weekly Tx12 / AC</td>
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<td>E1199</td>
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<td>1253</td>
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<td>28%</td>
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<td>weekly Tx12 / AC</td>
<td>1231</td>
<td>81.5%</td>
<td>0.79</td>
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<td>MDACC</td>
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<td>1672</td>
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4. Detailed Pathology Methods For Using Residual Cancer Burden

Residual cancer burden (RCB) is estimated from routine pathologic sections of the primary breast tumor site and the regional lymph nodes after the completion of neoadjuvant therapy. Six variables are included in a calculation formula. The calculated RCB index value can also be categorized as one of four RCB classes. The calculation formula and detailed description can be found at a dedicated website http://www.mdanderson.org/breastcancer_RCB.

Relevant information can be included within a pathology report (diagnoses or comment) without need for reporting calculated RCB index results. An example of relevant information from a report would be:

- Residual invasive carcinoma with chemotherapy effect.
- Residual carcinoma measures 2.4 x 1.8 cm and contains approximately 10% cancer cellularity.
- Residual intraductal carcinoma, solid type with necrosis, comprising 5% of the residual carcinoma.
- Metastatic carcinoma involving three of fourteen axillary lymph nodes (3/14).
- The largest metastasis measures 4 mm in greatest dimension.

From the results above, one could calculate RCB using these results: \(d_1 = 24\) mm, \(d_2 = 18\) mm, \(\%CA = 10\%\), \(\%CIS = 5\%\), \(LN = 3\), \(d_{\text{met}} = 4\) mm.

**Primary Tumor Bed:** In general terms, pathologic evaluation of the primary tumor bed in the breast requires that the pathologist make three judgments about the primary tumor bed:

i. Identify the cross-sectional dimensions of the residual tumor bed \(d_1\) and \(d_2\),
ii. Estimate of the proportion of that residual tumor bed area that is involved by cancer (%CA), and
iii. Estimate the proportion of the cancer that is in situ component (%CIS).

**Defining the Tumor Bed.**
In cases of multicentric disease, the RCB measurements are from the largest residual tumor bed. In cases where the extent of residual cancer under the microscope does not correlate with the gross measurement of the residual tumor bed, the tumor bed dimensions can be revised according to the microscopic findings (Figure 1).

![Figure 2. Diagrams to illustrate how gross residual tumor bed dimensions are first estimated from the gross findings (pink area) but may be revised after review of the slides from the gross tumor bed area according to the extent of residual cancer (blue).](image)

In these diagrams, the macroscopic tumor bed dimensions in examples A, C, D also define the final dimensions of the residual tumor bed after microscopic review. However, the macroscopic tumor bed dimensions in example B overestimate the extent of residual cancer, and so the dimensions of the residual tumor bed ($d_1$ and $d_2$) would be revised after microscopic evaluation of the extent of residual cancer in the corresponding slides from the gross tumor bed. In a different example (E), microscopic residual cancer extends beyond the confines of the macroscopic tumor bed. Again, the dimensions of the residual tumor bed ($d_1$ and $d_2$) would be revised after microscopic evaluation of the recognizable extent of residual cancer beyond the macroscopic tumor bed.

This approach accounts for differences in the concentration and distribution of residual cancer within a tumor bed. In the illustration above, the estimated %CA in example A would be high (in a small area), whereas the estimated %CA for examples C and D would be lower (in a larger area). In examples C and D, the estimated %CA would likely be similar, even though the distribution of cancer within the residual tumor bed is different in those two examples.

**Estimating Cellularity within the Tumor Bed**
The proportion of cancer (%CA) and the proportion of in situ component (%CIS) are estimated from microscopic evaluation of the slides from the residual tumor bed area. The most effective way to obtain this
information is to measure and submit for histology the largest cross-sectional area of residual tumor bed, and to designate in the report which slides represent the cross section of tumor bed. After reviewing those slides, the pathologist can estimate the average cellularity in the tumor bed on each slide in order to estimate the overall average cellularity of the tumor bed area (illustrated below).

The key is to simply:

i. Define the gross tumor bed as the largest cross-sectional area
ii. Submit sections representing that tumor bed area as individual slides
iii. Review those slides to estimate the $%CA$ and $%CIS$ within the residual tumor bed

![Pathology Protocol Diagram]

Figure 3. Illustrated summary of the pathology protocol to record the dimensions, section, and evaluate the primary tumor bed after neoadjuvant chemotherapy.

A practical way to estimate $%CA$ in a slide is to encircle with ink dots the tumor bed on each slide from the grossly defined residual tumor bed (e.g. slides A1-A5 in the example above). Then use the microscope to estimate the cellularity in each microscopic field across the area of tumor bed. In each microscopic field, $%CA$ can be estimated by comparing the proportion of residual tumor bed area containing cancer (invasive or in situ). Estimate an average of the readings for $%CA$ in the cross-sectional area. The same can be done for in situ component ($%CIS$). Estimates are to the nearest 10%, but include 0%, 1%, and 5% for areas with low cellularity. The average cellularity within the tumor bed from each slide across the tumor bed can then be estimated (illustrated above). The website contains computer-generated diagrams of % cellularity per area to assist pathologists to estimate accurately the cellularity of a microscopic field. Those diagrams are appended at the end of this document.

**Regional Lymph Nodes:** Pathologic evaluation of the primary tumor bed in the breast requires that the pathologist make two judgments:

i. Count the number of positive lymph nodes ($LN$),
ii. Measure the diameter of the largest nodal metastasis ($d_{met}$).
5. Special Circumstances With Relevance For Assessment of RCB

**Inoperable or Progressive Disease**

The RCB index cannot be accurately calculated for patients whose disease remains inoperable at the completion of the neoadjuvant treatment course (e.g. requiring subsequent additional treatments before surgical resection is possible), or those who experience disease progression and so do not undergo surgical resection at the completion of the neoadjuvant treatment course. For those patients, RCB is assigned as extensive, i.e. RCB-III.

**Internal Mammary Lymph Node Metastasis**

There were no examples of internal mammary nodal metastasis in the published study that evaluated the prognostic value of RCB. However, it is reasonable to include internal mammary nodes with the other regional (axillary) nodes in the assessment of RCB.

**Pre-treatment Sentinel Lymph Node Biopsy**

Surgical excision of a positive sentinel lymph node before the neoadjuvant treatment would invalidate the accuracy of measuring RCB after the treatment to assess response. If all sentinel lymph nodes were negative before treatment began, this would not affect the assessment of RCB after treatment ended.

6. Validation of Pathologic Response and Survival Risk

Independent validation is eventually required of any prognostic or predictive tool. The dichotomous pCR versus residual disease has been extensively validated, but other systems have only recently been validated for prognostic utility.

The Chevallier and Sataloff systems have recently been validated and compared in a retrospective study of 710 subjects. It should be noted that Chevallier classes 1 and 2 are both included in the current definition of pCR (see section 1), and that combined classes 1 and 2 have significantly better prognosis than combined classes 3 and 4 (residual disease). The authors also reported that class 4 had worse survival than other classes combined (DFS, p = 0.01; OS, p = 0.07). Sataloff class T-A (cancer cells absent or comprising < 5% of the residual tumor bed area) was significantly different from more extensive residual disease in the breast (DFS, p = 0.005; OS, p = 0.006). There was no difference in DFS or OS between partial response classes T-B (> 50% therapeutic effect) and class T-C (< 50% therapeutic effect in the primary tumor), but the authors reported that class T-D (no therapeutic effect in the primary tumor) had worse survival than other classes combined (DFS, p = 0.01; OS, p = 0.07). Although this system has four classes of nodal status, only node-negative versus node-positive status had prognostic import, and this held in the subset with class T-A. It is not reasonable to compare the Kaplan Meyer survival plots from this study with those from the RCB studies because the treatments were very different, as well as other cohort differences. Nevertheless, at some time it might be advantageous for a future study to directly compare different systems in a single cohort of patients who received a current standard therapy.

A study of 45 cases of locally advanced or inflammatory breast cancers determined that RCB score was significantly prognostic in univariate (HR 1.57; 95% CI 1.04 to 2.38; p = 0.018) and in multivariate (HR 1.59; 95% CI 1.04 to 2.43; p = 0.033) Cox regression analyses of event-free survival, whereas pCR was not. Recently, the prognostic utility of RCB categories has been demonstrated in two other study cohorts (323 patients at MDACC who received T/FAC (Hatzis et al ASCO, 2008) and 200 patients in the iSPY trial who received AC/docetaxel or AC/paclitaxel (Esserman et al ASCO, 2009), each with 3 years median follow-up. Additional validation cohorts and longer follow-up from these studies is desirable.

7. Breast Cancer Phenotype

The data are currently limited, but the evaluation of all 564 cases from MDACC shows that RCB (as a measure of pathologic response) is prognostic for each of the three main phenotypic groups of breast cancer (HER2+, ER+/HER2-, and ER-/HER2-). The survival curves for ER+/HER2- breast cancers are similar to those for ER+ (Figure 1). Of note, approximately 20% of ER+/HER2- subjects with RCB-III after chemotherapy still have an approximate 30-40% risk of distant relapse within 5 years, despite ongoing endocrine therapy. Also, the curves for ER-/HER2- breast cancer are similar to those of ER- breast cancer (Figure 1). Of note, the prognosis of RCB-I is the same as for pCR, and the patients with RCB-III have a very high probability of early distant relapse. The analysis of the iSPY trial showed a similar result.
Although RCB after chemotherapy is also prognostic in HER2+ breast cancer, the new standard of HER2-targeted therapy with chemotherapy now renders that result obsolete. There are only limited data for RCB after concurrent chemotherapy and trastuzumab for HER2-positive breast cancer, in which the frequency of pCR or RCB-I was 70%, irrespective of ER-status. However, this study is small in number and there is currently insufficient follow up of those patients to evaluate the prognostic relevance of RCB following trastuzumab.

8. Reproducibility of Residual Cancer Burden Assessments

We have preliminary evidence that more detailed assessments of response (e.g. RCB) can be reproducible among pathologists. In a pilot study we asked 3 pathologists to evaluate RCB in 100 cases from the original study cohort with residual disease (in situ, invasive, or nodal), and included the RCB assessments as a fourth reading. Correlation of 100 RCB measurements was high among these 4 pathologists (Pearson coefficient 0.92-0.96, Spearman coefficient 0.94-0.96). Perhaps more importantly, the survival analyses using the results from each pathologist all showed strong prognostic differences between the classes of RCB.

9. Future Directions

It is likely that neoadjuvant studies will become more common, and thereafter, trials of additional post-surgical treatments for patients who have a significant amount of residual disease at the completion of neoadjuvant treatment. An example of such a trial opened at M.D. Anderson Cancer Center in 2009. In that trial, patients with RCB-III, or RCB-II if ER-negative, after neoadjuvant chemotherapy are randomized to receive post-surgical ixabepilone, versus placebo. This approach contrasts with trials that include any residual disease by concentrating on those at greater residual risk of relapse.

Response measurements should be improved if better methods can be developed to more accurately measure pre-treatment tumor burden. When we combined the cellularity from the core biopsy with the radiologists’ measurement of the pre-treatment dimensions we found no significant improvement in the prognosis (beyond RCB alone), except for the subset of RCB-II patients. This suggests that improvements would be likely, but are probably currently hampered by limitations to the accuracy of information about the extent of tumor when using standard breast imaging of mammography and ultrasound.

There is interest in the imaging professions to develop methods to study tumor response in vivo, and also to develop better methods to direct post-treatment surgical planning.

There is current controversy about whether sentinel lymph node sampling should be performed to stage the axilla before neoadjuvant treatment or after the treatment has been completed. Is it more useful prognostic information to know what the patient began with, or what was left after the chemotherapy? At MDACC we prefer post-treatment SLN evaluation because it reduces the number of surgeries and we believe it has stronger prognostic value, but there are surgical concerns in the other camp that question the accuracy of sampling at that time. We do note that RCB measurements might be unreliable if a positive SLN was excised prior to the chemotherapy. The issue remains controversial and will likely be the subject of a prospective randomized trial.

10. Summary of Key Points For Pathologic Assessment of the Pathologic Resection Specimen

1. **GROSS.** Identify the probable tumor bed and describe this macroscopic finding
   a. Report the measurements of the largest gross dimensions (prefer 3 dimensions, but minimum is 2 dimensions).
   b. Submit the largest cross-sectional area for histology and specifically describe those blocks in the Section Code
      i. Try to indicate how they are oriented by photography, radiography, photocopy, or intelligent description (e.g. “sections B1 – B7 cross section of tumor bed in rows from antero-superior to postero-inferior”).
      ii. If additional sections are from surrounding tissues, then describe those as well
      iii. Five representative sections from a big, obvious tumor bed should be sufficient

2. **MICROSCOPY.** Review the slides that correspond to the tumor bed (+/- surrounding tissues)
   a. Estimate the extent of spread of residual cancer relative to the gross tumor bed
i. If similar to the gross description, then keep the original measurements.
ii. If obviously different, then revise the dimensions of the tumor bed based on the microscopic review of the tumor bed.
iii. Suggestion: dotting the perimeter of cancer in each slide can be helpful to reconstruct the tumor extent across multiple slides (see point 1-b-i).

b. Using the microscope, make visual snapshots of cancer cellularity as you go from field to field across the defined tumor bed from one end to the opposite (e.g. left to right, then top to bottom) to estimate the:
   i. Average cancer cellularity (%) across the entire tumor bed. This is all cancer, whether invasive or in situ.
   ii. Average percent of the cancer within the tumor bed that is in situ.
   iii. Cellularity estimates are to the nearest 10%, with additional selections of 1% and 5% for very low cellularity. For reference there are images of computer-generated examples linked to our website http://www.mdanderson.org/breastcancer_RCB.
   iv. The usual misunderstanding is to only make estimates in foci of the tumor bed that contain lots of cancer. The estimated cancer cellularity should represent the average across the entire residual tumor bed area.

3. REPORTING. There are many different formats for the diagnosis in pathology reports, and for making additional comments in the report. Furthermore, many pathologists would prefer not to report calculated indices such as residual cancer burden. However, it is nearly impossible for a clinician or clinical investigator to calculate RCB from usual pathology reports, if they wish to do so. We now encounter this situation when patients participate in some clinical trials. One option is to provide the relevant data in the text of the diagnosis or comment, or in a synoptic report. An illustrative example is as follows:
   a. Residual carcinoma involves a tumor bed that measures 37 x 25 mm in greatest dimensions and contains approximately 20% average cancer cellularity by area, of which 10% is carcinoma in situ.
   c. The largest metastasis measures 4 mm in greatest dimension.

A clinician or investigator can readily obtain RCB from this information, as below:

*Values must be entered into all fields for the calculation results to be accurate.

(1) Primary Tumor Bed

<table>
<thead>
<tr>
<th>Primary Tumor Bed Area:</th>
<th>37 (mm) x 25 (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Cancer Cellularity (as percentage of area):</td>
<td>20 (%)</td>
</tr>
<tr>
<td>Percentage of Cancer That Is in situ Disease:</td>
<td>10 (%)</td>
</tr>
</tbody>
</table>

(2) Lymph Nodes

<table>
<thead>
<tr>
<th>Number of Positive Lymph Nodes:</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter of Largest Metastasis:</td>
<td>4 (mm)</td>
</tr>
</tbody>
</table>

Residual Cancer Burden: 3.329
Residual Cancer Burden Class: RCB-III
REFERENCES


Modern classification of breast cancer—should we stick with morphology or convert to molecular profiles?

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Introduction

The future role of Pathology will to improve personalisation of care for breast cancer patients. In the past the importance of the Pathology Laboratory in the field of tumour pathology has been under-estimated and under-utilised, the clinician wanting (and receiving) only a one-line report stating the diagnosis. It has, however, now become widely accepted that more information can be gleaned from the histopathological appearance of a tumour and that this may be used to predict the biological behaviour and clinical outcome in many malignancies, including breast cancer. In addition, the use of other techniques, such as immunohistochemistry and molecular examination, has been expanded in the search for features of the tumour which can predict reliably not only the prognosis of the patient but also the potential for response to a given treatment.

PROGNOSTIC FACTORS

Prognostic factors, although not specific predictors of response to a therapy, can be used for appropriate treatment selection of patients with malignancies; those patients who have an extremely good prognosis after tumour excision may not warrant toxic adjuvant therapies which themselves carry a significant morbidity, but those with a poor prognosis may benefit from an aggressive adjuvant approach. Identifying the prognostic features of an invasive breast carcinoma for these reasons is particularly important as the disease has a markedly variable course; a group of women with “curable” carcinomas who do not receive significant benefit from adjuvant therapy can be identified, whilst others will succumb relatively rapidly.
to the disease. Because of this widely differing clinical outcome and because breast carcinoma is common, prognostic factors, and more recently predictive factors, in this malignant disease are probably the most widely studied.

PREDICTIVE FACTORS

In breast cancer oestrogen receptor (ER) and HER 2 are the best, and at present the only widely applied example of specific tests used to predict response to a specific therapy in breast cancer management. They are not in our hands of independent significance in predicting prognosis in breast cancer patients due to their close relationship with histological grade. We nevertheless assess ER and HER2 status routinely on patients with invasive breast carcinoma as a predictive factor to assist in selection of appropriate treatment.

FUTURE PREDICTIVE MARKERS

With expanding knowledge of molecular biology of cancer and the availability of the Human Genome Project we are now experiencing a rapid increase in potential molecular targets for drug development. It is inevitable that pathology laboratories will play a pivotal role in developing methods to assess 1) potential efficacy based on signalling pathway changes, 2) identify surrogate endpoints for early clinical trials based on biomarker change, 3) identify markers predictive of response, 4) identify and understand mechanisms of response and failure to respond and 5) integrate diagnostic and predictive testing into routine cancer management.

FUTURE CLASSIFICATION

Recent high-throughput genomic studies have offered the opportunity to challenge the molecular complexity of breast cancer and have provided evidence for an alternative method for classifying breast cancer into biologically and clinically distinct groups based on gene expression patterns. Such new molecular taxonomies have identified many genes, some of which are being proposed as candidate genes for sub-grouping breast cancer. Such studies have been applied on a relatively small number of tumours and require validation in large series and comparison with traditional classification systems prior to acceptance in clinical practice. This has partly been achieved using using high throughput tissue screening tissue microarray (TMA) technology. These studies have examined expression of proteins known
to be of relevance in breast cancer and have resulted in recognition of classes of breast cancer broadly similar to those identified by gene expression studies. Of note is the recognition of the importance of luminal or basal epithelial differentiation as well as hormone receptor and HER 2 expression. Basal epithelial differentiation or HER 2 expression being associated with an adverse outcome when compared to tumours showing luminal epithelial differentiation and hormone receptor expression.
Modern Classification of Breast Cancer

Should we stick with morphology or convert to molecular profiles?

Ian Ellis

Molecular Medical Sciences, University of Nottingham
Department of Histopathology, Nottingham University Hospitals NHS Trust

Time — Prognosis — Intrinsic

How long the tumour has been there
Stage

The nature of the tumour
Biology

Traditional Prognostic Factors

- Histological grade
- Histological type
- Lymph node stage
- Tumour size
- Vascular invasion

Nottingham Prognostic Index

Grade + LN Stage + (0.2 x Size)

1-3 1-3 cm

What Would Your Treatment Strategy Be For This Patient?

- Age: 61
- ER: 95%
- PR: 95%
- Tumor Type: IDC
- Tumor Size: 0.6 cm*
- Tumor Grade: 2
- HER-2 neu Neg (FISH)

*Additional 6 mm on re-excision

**Histological grade**

![Graph showing survival percentages and histological grades](image)

- Survival %
- Years
- Grade 1
- Grade 2
- Grade 3

90% of Events

<table>
<thead>
<tr>
<th></th>
<th>Gr I</th>
<th>Gr II</th>
<th>Gr III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to LR/RR</td>
<td>100</td>
<td>82</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>106</td>
<td>88</td>
<td>56</td>
</tr>
<tr>
<td>Time to Death</td>
<td>336</td>
<td>150</td>
<td>90</td>
</tr>
</tbody>
</table>

**Tumour Size**

Most studies have found a significant association between tumour size and prognosis

- Fisher et al, 1969
- Elston et al, 1982
- Haybittle et al, 1982
- Neville et al, 1990

Patients with small tumours have a longer survival than those with large tumours

![Graph showing tumour size distribution](image)

- 0-9mm
- 10-14mm
- 15-19mm
- 20-24mm
- 25mm or more

**Time to Death**

![Graph showing time to death](image)
Time to death by Size

Lymph Node Stage

Survival by LN Stage

Lymph Node Involvement

Sentinel node biopsy
Vascular Invasion
Prognostic significance

Close correlation with loco-regional lymph node status –
Correlates with early recurrence in lymph node negative patients –
Rosen et al, 1983; Bettelheim et al, 1984; Neville et al, 1992

Vascular Invasion
Prognostic significance

Predicts for long term survival, independent of nodal status
Roses et al, 1982; Pinder et al, 1994
Predicts for local recurrence following breast conserving surgery
Fourquet et al, 1989; Borger et al, 1994; Pinder et al, 1994; Sundquist et al, 2000
Predicts for local recurrence after mastectomy
O'Rourke et al, 1994; Sundquist et al, 2000

Progress to systemic metastatic disease

- 173 women who developed metastatic disease after a previous breast cancer.
- 72% had nodal metastases
- 59% had definite vascular invasion
- 84% had either lymph node metastases or vascular invasion or both.
- Consistently present whatever the histological grade of the primary tumour.
- Absence of VI and nodal involvement indicated a low risk of subsequent metastatic disease.  
  (Evans 2001)

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  (Evans 2001)

LVI for LN neg

LVI contribution and nodal status contribution to hazard

Cumulative Proportion Surviving (Kaplan-Meier)
Complete  Censored
LVInegLNneg  LVIposLNneg
 one  two  three  fourplus

WWW = 18513.  Sum = 1229E5
Var = 2419E4
Test statistic = 3.764129  
p = .00017
Merging LVI pos 1 and 2

Cumulative Proportion Surviving (Kaplan-Meier)

Complete  Censored

LVIneg LNneg

three

twoplus

LVIpos 1 and 2

0 50 100 150 200 250 300

Time

0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

Cumulative Proportion Surviving

Chi-Square

0

EPG

GPG

MPG I

MPG II

PPG

The Need

Many Questions

NICE - UK

NIH - USA

ESMO - EU

ST Gallen - International consensus

Others - other national and organisations

Up to 2005

Risk was the major determinant

"Average" the best for all

From 2005

The major determinant is the target

Risk is not a target

St. Gallen 2007 Treatment Choice

Recommendations

<table>
<thead>
<tr>
<th>Highly endocrine responsive</th>
<th>Incompletely endocrine responsive</th>
<th>Endocrine non-responsive</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2-negative</td>
<td>ET (consider adding CT according to risk)</td>
<td>ET+ (consider adding CT according to risk)</td>
</tr>
<tr>
<td>HER2-positive</td>
<td>ET + Trastuzumab + CT</td>
<td>ET + Trastuzumab + CT</td>
</tr>
</tbody>
</table>

ET= endocrine therapy; CT= chemotherapy

Prognostic Factor:

Altered natural history

Predictive Factor:

Resistance or sensitivity to therapy
**ER Immunohistology**

Cut off points for treatment

<table>
<thead>
<tr>
<th>Score treatment</th>
<th>Effect of Endocrine Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No effect</td>
</tr>
<tr>
<td>2 - 3</td>
<td>Small (20%) chance</td>
</tr>
<tr>
<td>4 - 6</td>
<td>Even (50%) chance</td>
</tr>
<tr>
<td>7 - 8</td>
<td>Good (75%) chance</td>
</tr>
</tbody>
</table>


**Her-2 status**

**Predictive assays**

- **ER & PR**
  - Presence of target protein

- **HER 2**
  - Presence and overexpression
  - Gene amplification

- **EGFR**
  - ? Target protein
  - ? Gene copy number
  - ? Gene mutation
A signature to rule them all?

**Gene-expression profiles to predict distant metastasis of lymph-node-negative primary breast cancer**

**Oncotype DX™ 21-Gene Recurrence Score (RS) Assay**

16 Cancer and 5 Reference Genes From 3 Studies

**RS** = +0.47 x HER2 Group Score - 0.34 x ER Group Score +1.04 x Proliferation Group Score +0.10 x Invasion Group Score +0.05 x CD68 -0.08 x GSTM1 -0.07 x BAG1

**Onco type DX™ Clinical Validation:**

RS as Continuous Predictor

My RS is 30. What is the chance of recurrence within 10 years?

95% CI
Meta-Analysis – Gene signatures

Blue dots: good prognosis
Red dots: poor prognosis

Take home message

- Prognostic gene signatures
  - Correlate with proliferation (and grade!)
    - Ki-67?
  - Good discriminatory power
    - ER positive disease
  - Limited value for ER negative disease
  - Cannot be readily applied to FFPE samples
  - Complementary to histopathology

Breast Cancer is a Family of Diseases

- Convergence of clinical and genomic data
- Unclear how many distinct members of this family
- At a minimum:
  - HER-2 +
  - Basal-like or triple negative
  - ER + (luminal A)
  - ER + (luminal B)

"Basal-like" ER/PR-negative HER2-negative
HER2-positive ER-positive Luminal B
ER-positive Luminal A

Luminal / ER positive/ basal negative group (group 1)
Basal positive luminal /ER negative (group 5)

Other candidates:
BRCA 1  17q  Medullary
BRCA 2  13q  Tub & Lob
1q 3p 11q 13q 17q  Tubular
**Luminal Subtypes**

- Luminal A/B - generally carry a good prognosis \(^{(1)}\)
- Luminal A better prognosis than B \(^{(1)}\)
- Expect better response to ET in luminal subtypes

\(^{(1)}\) Sorlie et al PNAS 2003: 100: 8418 - 23,
\(^{(2)}\) Rouzier et al Human Cancer Biology 2005: 11: 5678-85
A case of tubular carcinoma

<table>
<thead>
<tr>
<th>Microdissected Lesions</th>
<th>MGMA Expression</th>
<th>Genome Plot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Columnar Cell Lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ductal Carcinoma In Situ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive Tubular Carcinoma (at centre)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive Tubular Carcinoma (at periphery; solid)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A Cases of Invasive Lobular Carcinoma
Basal Breast Cancer

- The concept of BP has been known for some time
- First described using electron microscopy >30 years ago
- Its potential poor survival first reported by Dairkee et al in 1987
Definition of basal-like

- No internationally accepted definition!
- Triple negative phenotype (ER-ve, PR-ve, HER2-ve)
- Rakha/ Ellis/ Nottingham
  - Expression of high mol wt cytokeratins (Ck 5/6, Ck 14, Ck 17)
- Nielsen
  - ER-ve, HER2-ve
  - Expression of Ck 5/6 and/or EGFR

Breast Cancer Subtypes, Race and Age

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Basal</th>
<th>HER2+</th>
<th>Luminal A</th>
<th>Luminal B</th>
<th>Unclass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal African-American</td>
<td>99</td>
<td>39%</td>
<td>9%</td>
<td>36%</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>Premenopausal non African-American</td>
<td>164</td>
<td>16%</td>
<td>6%</td>
<td>51%</td>
<td>18%</td>
<td>10%</td>
</tr>
<tr>
<td>Postmenopausal African-American</td>
<td>99</td>
<td>14%</td>
<td>7%</td>
<td>59%</td>
<td>16%</td>
<td>4%</td>
</tr>
<tr>
<td>Postmenopausal non African-American</td>
<td>136</td>
<td>16%</td>
<td>6%</td>
<td>58%</td>
<td>16%</td>
<td>4%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>496</td>
<td>20%</td>
<td>7%</td>
<td>51%</td>
<td>16%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Adapted from Carey LA et al, ASCO 04

P=0.0001

Basal-like Breast Cancer and Chemotherapy (MDACC)

Gene expression array subtyping and pathologic complete response to neoadjuvant chemotherapy with T-FAC (n=83)

<table>
<thead>
<tr>
<th>Molecular classification</th>
<th>Residual Disease</th>
<th>Pathologic complete response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal</td>
<td>93% [78-99]</td>
<td>7% [1-22]</td>
</tr>
<tr>
<td>Normal breast</td>
<td>100% [29-100]</td>
<td>0% [0-31]</td>
</tr>
<tr>
<td>HER2+</td>
<td>55% [32-77]</td>
<td>45% [23-68]</td>
</tr>
<tr>
<td>Basal subtype</td>
<td>55% [32-76]</td>
<td>45% [24-66]</td>
</tr>
</tbody>
</table>

Chi square: P=0.001

Rouzier R et al, SABCS 2004

Treatment Approaches of Interest for Triple Negative Disease

- Angiogenesis inhibitors
- EGFR inhibitors
- PARP inhibitors (particularly in setting of BRCA1 and 2 mutant tumors)
- Platinum salts
  - Take advantage of inability of BLC to repair double strand DNA breaks
  - Similarities between sporadic basal-like cancers and BRCA1 associated tumors

Familial Breast Cancer

- BRCA 1 Prediction
- BRCA 1 - basal phenotype
  - Ck 5/6&14 +ve - 44% of all BRCA 1 carriers
  - Ck 5/6&14 +ve - < 2% sporadic cancers

Time — Prognosis — Intrinsic

How long the tumour has been there
The nature of the tumour

Lakhani Clin Cancer Res
What Would Your Treatment Strategy Be For This Patient?

- Age: 61
- ER: 95%
- PR: 95%
- Tumor Type: IDC
- Tumor Size: 0.6 cm*
- Tumor Grade: 2
- HER-2 neu Neg (FISH)

*Additional 6 mm en re-excision

Recurrence Score: 36
Average Rate of Distant Recurrence at 10 Yrs: 25%

Results

CLINICAL EXPERIENCE

Future Classification of Breast Cancer

Emerging classification system with clinical relevance based on:
- morphology
- phenotype
- molecular genetics

Routine provision of prognostic and predictive information
Identification of key therapeutic targets
Linked development of theranostics with drug development

Future Classification of Breast Cancer

Translation of research techniques / methods to routine clinical practice
Robust validated & standardised routine methods
Quality assurance integrated into service provision
Pathology has a central role - analytical & coordination
Decision making support systems will be essential